Analysis of antibacterial agents in clinical and preclinical development

Overview and analysis 2025

World Health Organization

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Contents

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Abbreviations

3GCRE	3rd generation cephalosporin-resistant Enterobacterales
AFB	acid-fast bacillus
ALT	alanine aminotransferase
AP	acute pyelonephritis
ARDS	acute respiratory distress syndrome
AST	aspartate transaminase
AUC	area under concentration–time curve
BDQ	bedaquiline
BLI	β-lactamase inhibitor
BPP	bacterial priority pathogen
BPPL	bacterial pathogens priority list
BSI	bloodstream infection
CABP	community-acquired bacterial pneumonia
CDI	*Clostridioides difficile* infection
CF	cystic fibrosis
CFU	colony-forming unit
CI	confidence interval
cIAI	complicated intra-abdominal infection
Cmax	mean maximum concentration
CoNS	coagulase-negative staphylococci
CPP	critical priority pathogen
CRE	carbapenem-resistant Enterobacterales
CREC	carbapenem-resistant *Escherichia coli*
CRKP	carbapenem-resistant *Klebsiella pneumoniae*
CRPA	carbapenem-resistant *Pseudomonas aeruginosa*
cUTI	complicated urinary tract infection
DBO	diazabicyclooctane
DFI	diabetic foot infection
DFO	diabetic foot osteomyelitis

DS-TB	drug-sensitive tuberculosis
EBA	early bactericidal activity
EMA	European Medicines Agency
EOT	end of treatment
ESBL	extended-spectrum beta-lactamase
EU	European Union
GARDP	Global Antibiotic Research and Development Partnership
HABP	hospital-acquired bacterial pneumonia
ICU	intensive care unit
IM	intramuscular
IMP	imipenemase
iMPV	inhaled murepavadin
IND	investigational new drug
ITT	intent-to-treat
iv	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
LMICs	low- and middle-income countries
MAA	marketing authorization application
mAb	monoclonal antibody
MAD	multiple ascending dose
MBL	metallo-β-lactamase
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
micro-ITT	microbiologic intent-to-treat
MITT	modified intent-to-treat
MOA	mode of action
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NBTI	novel bacterial topoisomerase inhibitor
NCR	no known cross-resistance
NDA	new drug application
NDM	New Delhi metallo-β-lactamase
NTM	non-tuberculosis mycobacterium
PBP2	penicillin-binding protein 2
PIP	paediatric investigational plan
PJI	prosthetic joint infection

PK	pharmacokinetic
PO	oral
PTA	probability of target attainment
QIDP	Qualified Infectious Disease Product
R&D	research and development
rCDI	recurrent *Clostridium difficile* infection
RR-TB	rifampicin-resistant tuberculosis
SAD	single ascending dose
SAE	serious adverse event
SBL	serine β-lactamase
SI	selective index
SOC	standard of care
TB	tuberculosis
TEAE	treatment emergent adverse events
TOC	test-of-cure
TTP	time to positivity
US-FDA	United States Food and Drug Administration
uUTI	uncomplicated urinary tract infection
VABP	ventilator-associated bacterial pneumonia
vHABP	ventilated hospital-acquired bacterial pneumonia
VRE	vancomycin-resistant *enterococci*
WBA	whole blood activity
WBC	white blood cell

1

Introduction

1. Introduction

Antimicrobial Resistance (AMR) is one of the most urgent global health threats and development challenges, causing over a million deaths annually. Without intensified action, it is estimated that 39 million deaths will be attributable to AMR by 2050 *(1)*.

To address this growing threat, the World Health Organization (WHO) published the updated priority list of bacterial pathogens (WHO BPPL) in 2024 to guide research and development (R&D) of new antibacterial agents *(2)*. Importantly, WHO continues to review both the clinical and the preclinical antibacterial pipelines on an annual basis to assess how the pipeline and the R&D ecosystem are addressing the WHO BPPL.

The 2025 WHO update of antibacterial agents in clinical and preclinical development targeting WHO bacterial priority pathogens (BPPs) is based on a review conducted by the WHO pipeline team between 31 December 2023 and 15 February 2025. This update follows the methodology described in the WHO report *2023 Antibacterial agents in clinical and preclinical development (3)* published in June 2024. Since that previous report, rifampicin-resistant *Mycobacterium tuberculosis* has been designated a critical priority pathogen by WHO. However, for this report anti-tuberculosis (TB) agents are listed in a stand-alone table (Table 4).

This review covers new chemical entities, traditional antibiotics (i.e. direct-acting small molecules) and new biological entities, non-traditional antibacterial agents (e.g. peptides, antibodies, anti-virulence agents, bacteriophages and phage-derived enzymes, oligonucleotides, and microbiome-modulating agents) in clinical (Phase 1, 2, 3 and new drug application (NDA)/marketing authorization application (MAA)) and preclinical development worldwide that do not have marketing authorization for human use anywhere in the world, as well as antibacterial agents that were approved since the WHO 2023 report was developed and published. The review is restricted to antibacterial agents that could potentially be used to treat serious systemic bacterial infections caused by the WHO BPPs, *Clostridioides difficile* and *Helicobacter pylori*.

2

Clinical pipeline

2. Clinical pipeline

Key messages from the 2025 clinical pipeline update

- **Overview.** As of 15 February 2025, there are a total of 90 antibacterials and/or combinations that include at least one new therapeutic entity targeting the WHO BPPs, or *Clostridioides difficile* and *Helicobacter pylori*, in the clinical pipeline from Phase 1 to the NDA/MAA stage worldwide. Of these, 50 are traditional antibacterial agents and 40 are non-traditional agents (Fig. 1).
- **New products in clinical development.** Between December 2023 and February 2025, one new traditional agent targeting the WHO BPP *M. tuberculosis* entered the clinical pipeline. Additionally, one new non-traditional agent targeting *Pseudomonas aeruginosa*, and three new non-traditional agents targeting *C. difficile* began their clinical development.
- **Changes since last report: new authorizations or discontinuations.** Between December 2023 and February 2025, four agents, three traditional and one non-traditional drugs, were approved (4/97, 4.1%), one agent entered the NDA/MAA stage (1/97, 1%), and ten agents (10/97, 10.3%) were withdrawn from clinical development.
    - Among the recently authorized traditional agents: the β-lactam/β-lactamase inhibitor combination, cefepime/enmetazobactam, was approved by both the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) for use in adults with complicated urinary tract infections (cUTIs) including pyelonephritis. Cefepime/enmetazobactam was also approved in the European Region for the treatment of hospital-acquired bacterial pneumonia (HABP) in adults, including ventilator-associated bacterial pneumonia (VABP). The thiopenem, sulopenem (an oral carbapenem), was approved in the United States for the treatment of adult patients with cUTI. Both antibiotics are active against 3rd generation cephalosporin-resistant Enterobacterales. The ketolide, nafithromycin, active against the WHO high priority pathogen macrolide-resistant *Streptococcus pneumoniae*, was approved in India for the treatment of community-acquired bacterial pneumonia (CABP). None of the three approved traditional agents may be considered innovative based on the WHO criteria (see Methods section).
    - The non-traditional anti-virulence agent Ftortiazinon (fluorothiazinone) was approved in the Russian Federation for cUTI caused by *Escherichia coli*, *Klebsiella pneumoniae* and *P. aeruginosa*. Ftortiazinon is the first non-traditional agent targeting a WHO priority pathogen to be approved.
    - One agent entered the regulatory review (NDA/MAA) stage, solithromycin (T-4288) a semi-synthetic 2-fluoroketolide that is being evaluated by the the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).
    - Among the ten agents withdrawn from clinical development since the previous report, three are traditional antibacterials, none of them considered potentially innovative according to the WHO criteria (see Methods section) and seven are non-traditional agents. None of the withdrawn agents targets *M. tuberculosis*. The withdrawal rate for products in Phase 1 of development is higher for non-traditional agents compared to traditional ones (3/10, 30% vs 2/16, 12.5%). In Phase 1/2 to Phase 2, 11% (1/9) of traditional agents were withdrawn from clinical development compared to 7.4% (2/27) of non-traditionals. Additionally, two non-traditional agents were discontinued during Phase 3 development (2/5, 40%), compared to one traditional agent (1/16, 6%).
- **Number of agents against critical priorities.** The total number of antibiotics approved against WHO critical priority pathogens (CPPs; carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant Enterobacterales (CRE), 3rd generation cephalosporin-resistant Enterobacterales (3GCRE), and rifampicin-resistant *M. tuberculosis*] and *P. aeruginosa* [a critical priority pathogen until 2024), since the first release of the WHO BPPL in 2017, has increased from seven to nine compared to the 2023 WHO antibacterial pipeline analysis.

- **Innovation.** Five traditional agents out of 27 (19%) show no known cross-resistance and are thus considered potentially innovative according to the WHO criteria for innovation. Ten additional agents (37%) do not presently have sufficient published data to support the absence of cross-resistance; however, they fulfil at least one of the WHO surrogate predictors for the absence of cross-resistance. Six of them belong to a new chemical class, of which two also hit a new target and have a new mechanism of action, and one also has a new mechanism of action. Of note, only five of these potentially innovative products are active against WHO CPPs.

  The TB pipeline looks more innovative with six agents out of 18 (33%) with no known cross-resistance, and three products (17%) with insufficient published data for a sound evaluation of no cross-resistance that meet at least one of the WHO surrogate predictors for the absence of cross-resistance. Two of them belong to a new chemical class, hit a new target and have a new mechanism of action, whereas one has both a new target and new mechanism of action.

- **Paediatric development.** The number of antibacterials in paediatric trials is slowly increasing.

  Among the antibiotics in clinical development, the β-lactamase inhibitor funobactam had its paediatric investigation plan (PIP) approved by the EMA in September 2023, although no dedicated clinical trial has been registered thus far. Overall, of the 13 products in Phase 2 development or later, six have an approved/amended PIP, whereas seven have presented no PIP as yet. This number has remained stable since the 2023 analysis. The agents in clinical development with an approved/amended PIP are: solithromycin (2016), cefepime + taniborbactam (2020), cefepime + zidebactam (2021), zoliflodacin (2022), gepotidacin[1] (2022) and funobactam (XNW4107) + imipenem + cilastatin (2023). Among the 16 approved antibiotics, the β-Lactam/β-lactamase inhibitor combinations imipenem-cilastatin-relebactam (2025), sulbactam-durlobatam (2025), and meropenem-vaborbactam (2024), along with eravacycline (2025), omadacycline (2024), and cefiderocol (2024), have newly registered clinical trials in paediatric patients.

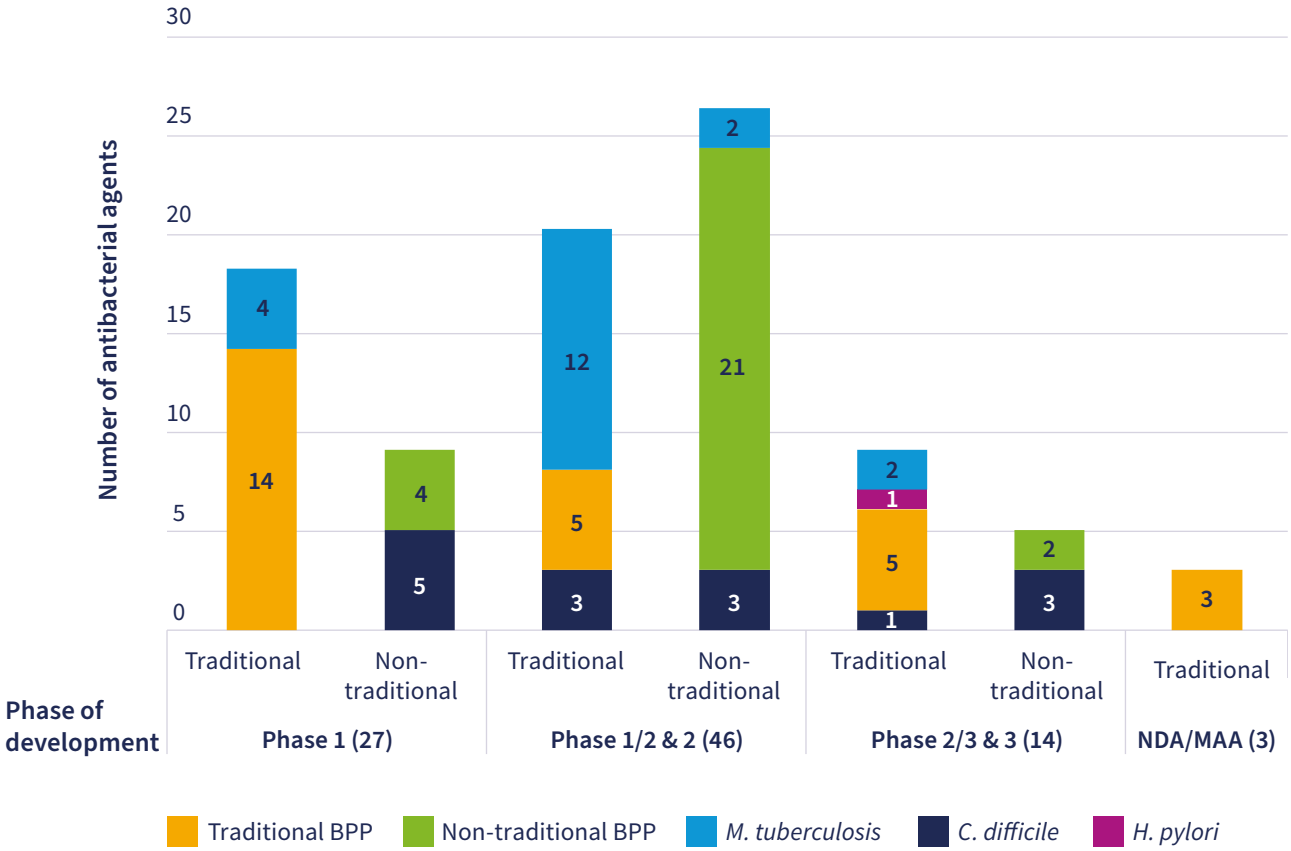
The only authorized antibiotic with a paediatric study is pretomanid, and that was present in the WHO 2023 pipeline. Overall, out of 16 authorized antibiotics, seven (44%) have ongoing paediatric studies, three (19%) are fluoroquinolones not recommended/contraindicated in children, and one, plazomicin, has an old PIP that, due to the antibiotic limited availability worldwide, will probably result in no studies.

In the 2025 clinical pipeline there is still a substantial imbalance in the availability of antibacterial agents with paediatric indications and/or formulations against the WHO BPPs as compared to those for adults.

Overall, the antibacterial agents, especially the innovative ones, in the clinical pipeline combined with those approved in the last seven years are still insufficient to tackle the ever-growing threat of the emergence and spread of drug-resistant infections.

[1] Post-review update: as of 25 March 2025, gepotidacin (Blujepa) has been approved by the US FDA for treatment of uncomplicated urinary tract infections (uUTIs) in female adults and paediatric patients 12 years of age and older *(4)*.

Fig. 1. Number of traditional and non-traditional antibacterials by clinical development phase (Phases 1–3 and NDAs/MAAs)

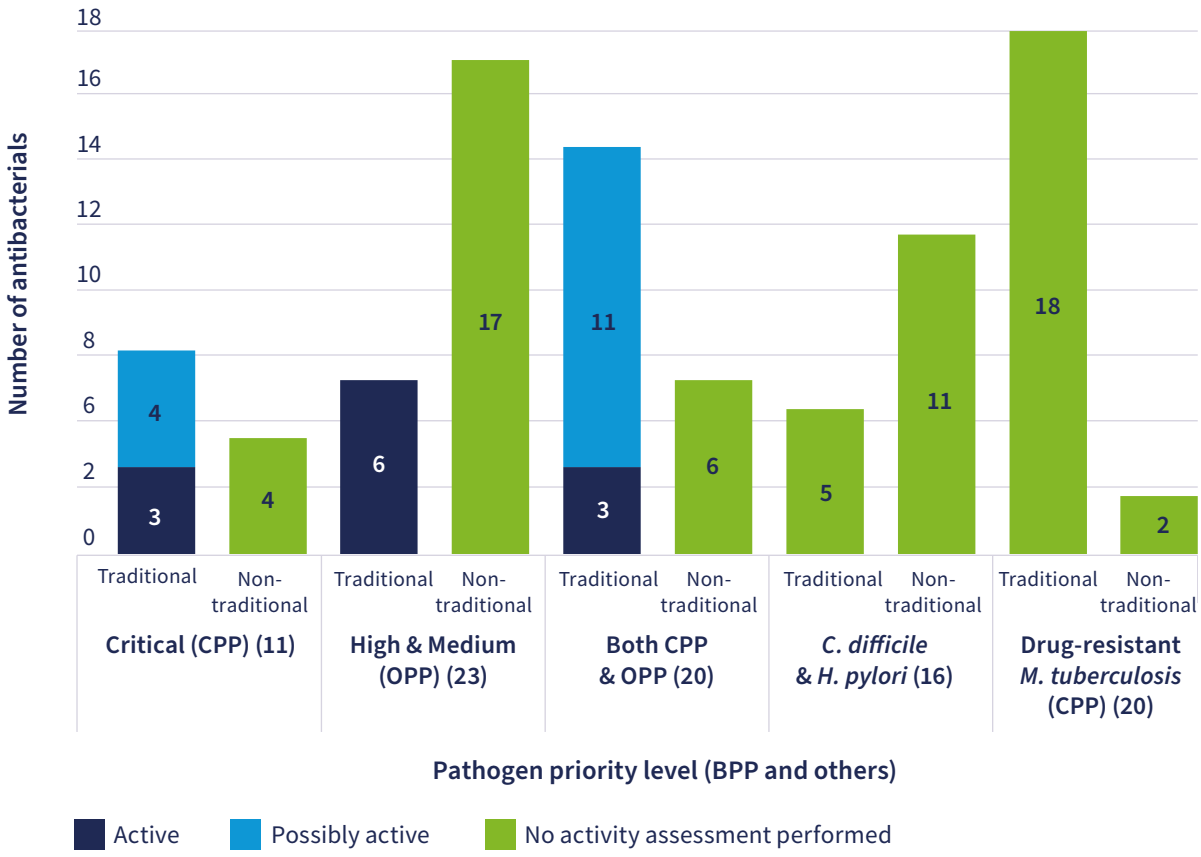


BPP: bacterial priority pathogen; NDA: new drug application; MAA: marketing authorization application.

Key updates on traditional antibacterial agents in clinical development

Of the 50 traditional antibacterial agents in the 2025 WHO clinical pipeline, 45 (90%) target WHO BPPs, including 18 (40%) focused on drug-resistant *M. tuberculosis*. Additionally, four (8%) traditional agents are being developed for *C. difficile*, and one (2%) for *H. pylori* (Fig. 2).

Fig. 2. Number of traditional and non-traditional antibacterials in clinical development (Phases 1–3 and NDAs/MAAs) by intended target



CPP: critical priority pathogen; OPP: other priority pathogen.

Note: The category 'Both CPP & OPP' refers to agents active against pathogens in both critical and other priority groups (i.e. high and medium). Agents that are considered possibly active and indicated with a question mark (?) in Table 2 are included in this count.

The following changes have occurred in the clinical pipeline of traditional antibacterials targeting WHO BPPs during 2024:

- One antibacterial, gepotidacin, has entered the regulatory approval process in United States for the indication of uncomplicated urinary tract infection (uUTI) in adult patients.[2]
- Non-clinical in vitro and in vivo data on the novel bacterial topoisomerase inhibitor, BWC0977, have also been published showing activity against the WHO critical pathogens CRE, 3GCRE and CRAB, and in vitro data against the high priority pathogen carbapenem-resistant *P. aeruginosa* (CRPA).

  Data on BWC0977 has recently been published showing the lack of known cross-resistance, raising the total number of potentially innovative antibacterials with respect to no known cross-resistance to 11 out of 45 agents in development (24%).

- Four agents, one (OMN6) targeting *A. baumannii* and three (TBAJ-876, TBI-223 and TBD09) targeting *M. tuberculosis* have completed Phase 1 development and are moving to Phase 2.

The number of agents in the clinical pipeline with insufficient published activity data continues to be high, preventing a sound assessment of their potential against WHO BPPs.

- Excluding the products targeting *M. tuberculosis*, more than half (14/27, 52%) of agents targeting WHO BPPs lack sufficient published evidence to assess their activity against at least one WHO BPP.

WHO reiterates its recommendation for developers to publish in vitro and in vivo activity data on candidate antibacterials, including against drug-resistant isolates, to facilitate the evaluation of the clinical need for new efficacious drugs.

[2] Post-review update: as of 25 March 2025, gepotidacin (Blujepa) has been approved by the US FDA for treatment of uUTIs in female adults and paediatric patients 12 years of age and older (4).

The following changes have occurred in the clinical pipeline of traditional antibacterials targeting *C. difficile* during 2024:

- One agent targeting *C. difficile*, the first-in-class compound, ibezapolstat, has published evidence of no cross resistance with the currently approved treatments for *C. difficile* (i.e. metronidazole, vancomycin and fidaxomicin) in 2024. This increases the number of potentially innovative agents with no known cross-resistance targeting *C. difficile* to three out of four (75%).

Key updates on non-traditional antibacterials in clinical development

- Of the 40 non-traditional agents, 29 target WHO BPPs, including two agents against *M. tuberculosis* and 11 agents against *C. difficile* infections. The only non-traditional product included in the 2023 WHO clinical pipeline against *H. pylori* is no longer in clinical development in 2024.
- A new bacteriophage cocktail for inhalation, TP-122A, targeting *P. aeruginosa* infections in patients with VABP has entered Phase 1/2a clinical development in 2024, raising the total number of bacteriophages under development to 14 candidates, six of which target *P. aeruginosa*. Bacteriophages continue to represent the most prevalent type of non-traditional agent in the clinical pipeline.
- Four non-traditional agents are advancing in their clinical development: the bacteriophage cocktail BX004a against *P. aeruginosa* and SNIPR-001 against carbapenem-resistant *E. coli*, the monoclonal antibody RESP-X against *P. aeruginosa*, and the anti-virulence agent ALS-4 targeting *Staphylococcus aureus*. BX004a is moving to Phase 2b, RESP-X entered Phase 2, SNIPR-001 entered phase 1b/2a, and ALS-4 completed its Phase 1 trial. As a result, the number of non-traditional drugs in the 2025 WHO clinical pipeline that have successfully completed Phase 1 development has increased to 15 (37.5%).
- One non-traditional agent, the live biotherapeutic product VE303, intended for faecal microbiota transplant in recurrent *C. difficile* infections, has progressed to Phase 3. The proportion of non-traditional agents in Phase 3 development in the 2025 WHO clinical pipeline has increased to 12.2% (5/41).

Potential label extensions and/or marketing authorizations in additional countries

Several antibiotics are currently undergoing development and expansion of their approved indications:

Meropenem-vaborbactam (Vabomere), currently approved for cUTI in adults, is expanding through two paediatric studies. A Phase 1 dose-finding, pharmacokinetics, safety and tolerability study (clinicaltrials.gov: NCT02687906; TANGOKIDS) focuses on patients from birth to 18 years with serious bacterial infections (running until June 2025), while a Phase 2 multicentre, open-label, single-arm, pharmacokinetics, safety and tolerability study (clinicaltrials.gov: NCT06672978; not yet recruiting) will investigate it as an intravenous (iv) infusion treatment in children 3 months to 12 years with cUTI including acute pyelonephritis (AP).

Eravacycline (Xerava), approved for complicated intra-abdominal infections (cIAI), is being investigated in a new observational study (clinicaltrials.gov: NCT06223100; not yet recruiting) in immunocompromised patients with multidrug-resistant bacterial infections, scheduled from February 2024 to December 2025. The goal of the study is to explore treatment modes and clinical outcomes, evaluate efficacy and safety of eravacycline in addition to standard of care (SOC) combined therapy, and generate reference data for treating immunocompromised populations.

Omadacycline (Nuzyra), which is approved for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infection (ABSSSI), is under investigation in a pharmacokinetic study (clinicaltrials.gov: NCT05217537) of its iv and oral forms in children and adolescents with confirmed bacterial infections. It was initially estimated to be completed in September 2024.

Cefiderocol (Fetroja) is a siderophore cephalosporin antibiotic that was initially approved for treating cUTI and HABP/VABP caused by Gram-negative bacteria in patients with limited treatment options. A registered clinical trial (clinicaltrials.gov: NCT05314764) evaluating cefiderocol pharmacokinetics in adult patients with cystic fibrosis was completed in June 2023. There are no publicly available results as yet.

Potential marketing authorizations in additional countries:

Tebipenem pivoxil hydrobromide (TBP-PI-HBr), which has been approved in Japan since 2009 for the treatment of bacterial pneumonia, otitis media and sinusitis in children, is being investigated in a global, randomized, double-blind Phase 3 trial (clinicaltrials.gov: NCT06059846; PIVOT-PO) for cUTI/AP treatment. The trial, projected to run from December 2023 to November 2025, aims to enrol approximately 2648 adult patients, to compare oral tebipenem HBr with iv imipenem-cilastatin, assessing the overall response, which includes clinical cure and microbiological eradication, at a specific visit post-treatment. This study could make it the first oral broad-spectrum carbapenem therapy available in the United States for cUTI.

Contezolid (MRX-I, oral) and contezolid acefosamil (MRX-4, iv), novel oxazolidinone antibiotics, approved by the National Medical Products Administration of China for the treatment of complicated skin and soft tissue infections (cSSTI), including, but not limited to, methicillin-susceptible *S. aureus*, methicillin-resistant *S. aureus* (MRSA), *Streptococcus pyogenes* and *Streptococcus agalactiae*, have received US FDA Qualified Infectious Disease Product (QIDP) and Fast

Track designations for the treatment of moderate to severe diabetic foot infection (DFI) without concomitant osteomyelitis. A Phase 3 multicentre, randomized, double-blind, safety and efficacy study (clinicaltrials.gov: NCT05369052) comparing the iv/oral forms with linezolid in the treatment of DFI, administered for a total of 14 to 28 days in adult subjects with moderate or severe DFI, is anticipated to complete by the end of June 2026.

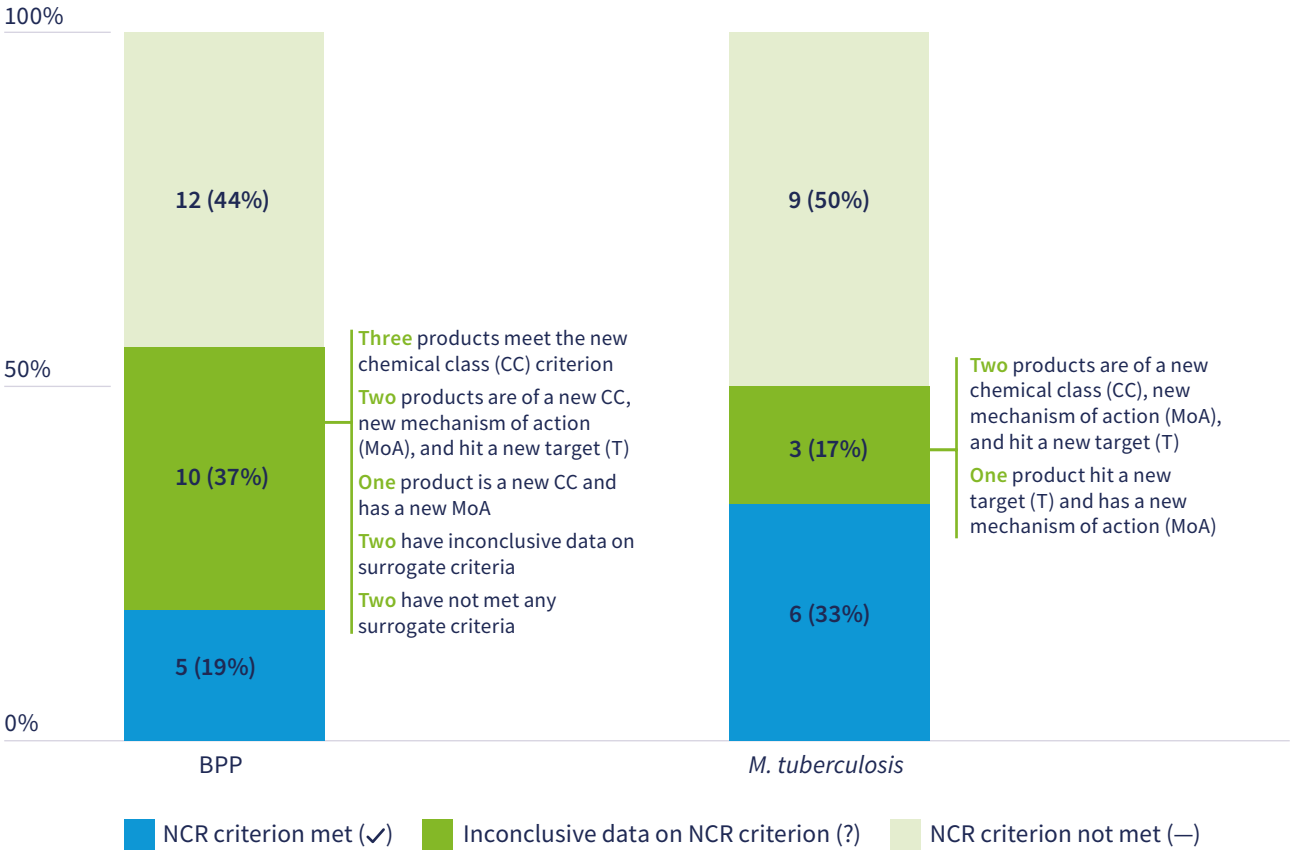
Clinical overview

The below analysis shows the decrease in the number of clinical candidates from 97 agents in 2023 to 90 agents by February 2025. The approval of an additional four agents against WHO BPPs and the discontinuation of 10 agents versus four in the previous report.

Each agent, in clinical development or recently approved, was evaluated against the four WHO innovation criteria (see Methods section). Fig. 3 is an outline of the potential innovation in the clinical pipeline as it relates to traditional agents in the clinical pipeline active against WHO BPPs and *M. tuberculosis*. Of the 27 traditional BPP agents, five (19%) show no known cross-resistance (NCR), and are deemed potentially innovative by WHO. Ten additional BPP agents (37%) lack sufficient data to meet the NCR criterion; however, six (60%) meet at least one of the surrogate criteria for innovation (see further details in Fig. 3).

In the TB pipeline, 33% of 18 traditional TB agents show no known cross-resistance and three (17%) have insufficient data to meet NCR criteria but meet some of the WHO surrogate predictors of innovation.

Fig. 3. WHO innovation assessment of traditional agents active against BPP and *M. tuberculosis* in the clinical antibacterial pipeline



BPP: bacterial priority pathogen.

Table 1 shows new traditional (Table 1a) and non-traditional (Table 1b) antibacterial agents authorized from 1 July 2017 to 15 February 2025.

Table 1a. Traditional antibacterial agents that gained market authorization between 1 July 2017 and 15 February 2025

Name (trade name)	Marketing authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication(s)	WHO EML & AWaRe classification[a]	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Cefepime (EXBLIFEP) + enmetazobactam (AAI-101)	Allecra Therapeutics	EMA (01/2024); US FDA (02/2024)	β-lactam (cephalosporin) + Boronate BLI	IV (copackaged)	cUTI including pyelonephritis (US-FDA); cUTI including pyelonephritis,HABP/ VABP and associated bacteraemia (EMA)	WHO EML: not yet evaluated AWaRe: not yet classified	X	X	X	● [b]	-	-	-	-
Sulopenem; Sulopenem Etzadroxil/ Probenecid (ORLYNVAH)	Iterum Therapeutics	US-FDA (10/2024)	β-Lactam (thiopenem)	PO	uUTI	WHO EML: not yet evaluated AWaRe: not yet classified	X	X	X	● [b]	-	-	-	-
Nafithromycin (WCK-4873)	Wockhardt	CDSCO, India 2/2025	Macrolide/ketolide	PO	CABP	WHO EML: not yet evaluated AWaRe: not yet classified	/	/	/	●	?	-	-	-
Sulbactam + durlobactam (Xacduro)	Innoviva (former Entasis Therapeutics)	US FDA (05/2023)	BLI/PBP1,3 binder + DBO-PBP2 binder	IV	HABP/VABP	WHO EML: not yet evaluated AWaRe: not yet classified'	●	X	X	/	-	-	-	-
Delafloxacin (Baxdela / Quofenix)	Melinta Therapeutics (USA) (Menarini, EU)	US FDA (6/2017 ABSSSI, 10/2019 CAP), EMA (12/2019 ABSSSI, 02/2021 CAP)	Fluoroquinolone	IV	ABSSSI, CABP	WHO EML: no, AWaRe: Watch	X	X	X	● [c]	-	-	-	-

Table 1a (continued). Traditional antibacterial agents that gained market authorization between 1 July 2017 and 15 February 2025

Name (trade name)	Marketing authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication(s)	WHO EML & AWaRe classification[a]	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Meropenem + vaborbactam	Melinta Therapeutics (United States) (Menarini, EU)	US FDA (8/2017) EMA (11/2018)	β-lactam (carbapenem) + Boronate BLI	IV	cUTI, (cUTI, cIAI, HABP/VABP in EU)	WHO EML: yes AWaRe: Reserve	X	X	●[d]	/	?[e]	✓	-	-
Plazomicin (Zemdri)	Achaogen (Cipla (United States)/ QiLu Antibiotics, (China))	US FDA (8/2018)	Aminoglycoside	IV	cUTI	WHO EML: yes AWaRe: Reserve	X	X	●	/	-	-	-	-
Eravacycline (Xerava)	Tetraphase Pharmaceuticals (La Jolla Pharmaceutical Company, Everest Medicines)	US FDA (8/2018) EMA (9/2018)	Tetracycline	IV	cIAI	WHO EML: no, AWaRe: Reserve	?	X	●	/	-	-	-	-
Omadacycline (Nuzyra)	Gurnet Point Capital and Novo Holdings	US FDA (10/2018)	Tetracycline	IV & PO	CABP (iv), ABSSSI (iv, oral)	WHO EML: no, AWaRe: Reserve	X	X	X	●[f]	-	-	-	-
Imipenem / cilastatin (Recarbrio) + Relebactam	Merck Sharp & Dohme	US FDA (7/2019 cUTI/ cIAI, 7/2020 HAP/VAP), EMA (2/2020 G-ve)	β-lactam (carbapenem)/ degradation inhibitor + DBO-BLI	IV	cUTI, cIAI, HABP/ VABP	WHO EML: no, AWaRe: Reserve	X	?	●[d]	/	-	-	-	-

Table 1a (continued). Traditional antibacterial agents that gained market authorization between 1 July 2017 and 15 February 2025

Name (trade name)	Marketing authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication(s)	WHO EML & AWaRe classification[a]	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Lefamulin (Xenleta)	Nabriva (Sunovion Pharmaceuticals Canada)	US FDA (8/2019) EMA (7/2020)	Pleuromutilin	IV & PO	CABP	WHO EML: not yet evaluated AWaRe: Reserve	/	/	/	●[g]	?	✓[h]	-	-
Pretomanid (Dovprela)	TB Alliance (Viatris)	US FDA (8/2019) EMA (8/2020) CDSCO (7/2020)	Nitroimidazole	PO	XDR-TB	WHO EML:yes AWaRe: not yet classified	/	/	/	●[i]	-	-	-	-
Lascufloxacin (Lasvic)	Kyorin Pharmaceutical	PDMA (8/2019)	Fluoroquinolone	IV & PO	CABP, otorhinolaryn-gological	WHO EML: not yet evaluated AWaRe: Watch	X	X	X	●[g]	-	-	-	-
Cefiderocol (Fetroja)	Shionogi	US FDA (11/2019 cUTI, 9/21 HAP/ VAP), EMA (4/2020)	Siderophore β-lactam (cephalosporin)	IV	cUTI, HABP/VABP, aerobic G-ve j	WHO EML: yes AWaRe: Reserve	●	●	●	/	-	-	-	-

Table 1a (continued). Traditional antibacterial agents that gained market authorization between 1 July 2017 and 15 February 2025

Name (trade name)	Marketing authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication(s)	WHO EML & AWaRe classification[a]	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Levonadifloxacin (Emrok); alalevonadifloxacin (Emrok-O)	Wockhardt	CDSCO (1/2020)	Fluoroquinolone	IV & PO	ABSSSI	WHO EML: not yet evaluated. AWaRe: Watch & not yet classified respectively k	X	X	X	●[l]	-	-	-	-
Contezolid (Youxitai); contezolid acefosamil	MicuRx	NMPA (6/2021)	Oxazolidinone	IV & PO	cSSTI	WHO EML: not yet evaluated AWaRe: not yet classified	/	/	/	●[l]	-	-	-	-

Pathogen activity: ● active; ? possibly active; X not or insufficiently active; / activity not assessed, as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods. Agents not active against CPP were assessed for activity against OPP, which includes the WHO high and medium priority pathogens.

Innovation assessment: ✓ criterion fulfilled; ? inconclusive data; - criterion not fulfilled.

ABSSSI: acute bacterial skin and skin structure infection; AWaRe: Access Watch Reserve; CABP: community-acquired bacterial pneumonia; CC: new chemical class; cIAI: complicated intra-abdominal infection; CRAB: carbapenem-resistant *A. baumannii*; CRE: carbapenem-resistant Enterobacterales; CRPA: carbapenem-resistant *P. aeruginosa*; cSSTI: complicated skin and soft tissue infection; cUTI: complicated urinary tract infection; CDSCO: Central Drugs Standard Control Organization of the Government of India; EMA: European Medicines Agency; EML: WHO Essential Medicines List; G-: Gram-negative; HABP: hospital-acquired bacterial pneumonia; IV: intravenous; KPC: *K. pneumoniae* carbapenemase; MBL: metallo-β-lactamase; MDR: multidrug-resistant; MoA: new mode of action; N/A: not applicable; NCR: no cross-resistance to other antibiotic classes; NMPA: China National Medical Products Administration; OPP: other priority pathogens; PDMA: Pharmaceuticals and Medical Devices Agency (Japan); T: new target; TB: tuberculosis; US FDA: United States Food and Drug Administration; VAP: ventilator-associated pneumonia; XDR-TB: extensively drug-resistant TB.

[a] For inclusion in the WHO EML: no = evaluated and not recommended and yes = evaluated and included on list.
[b] Active against 3GCRE.
[c] Active against MRSA in ABSSI including fluoroquinolone-nonsusceptible strains.
[d] Active against KPC, but not MBL-producing Enterobacterales.
[e] New reports suggest that cross-resistance can be obtained when the porin OmpK35-36 level is varied *(5)* and for overproduction of KPC-3 associated with increased gene dosage *(6)*.
[f] Active against MRSA in ABSSSI; active against macrolide-resistant *Streptococcus pneumoniae* in CABP.
[g] Active against MRSA and macrolide-resistant *Streptococcus pneumoniae*.
[h] First systemic formulation of this class, which was previously used in animals and topically in humans.
[i] Approved for the treatment of XDR-TB or treatment-intolerant/non-responsive MDR-TB, in combination with bedaquiline and linezolid.
[j] The EMA approved cefiderocol for the treatment of infections due to aerobic Gram-negative bacteria in adults with limited treatment options, which is broader than the US FDA approval.
[k] Only levonadifloxacin has been classified under AWaRe (Watch). Alalevonadifloxacin has yet to be classified under AWaRe.
[l] Active against MRSA.

Table 1b. Non-traditional antibacterial agents that gained market authorization between 1 July 2017 and 15 February 2025

Name (trade name)	Marketing authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication/s	Pathogen	Reference (product information)
SER-109 (VOWST (fecal microbiota spores, live-brpk)	Seres Therapeutics	US-FDA 04/2023	Live biotherapeutic product	PO	Recurrent/ refractory diarrhoea prevention [a]	*C. difficile*	Vowst
BB128 (Biomictra faecal microbiota)	BiomeBank	TGA (Aus) 11/2022	Live biotherapeutic product	Endoscopic delivery or enema	Recurrent/ refractory diarrhoea prevention [a]	*C. difficile*	Biomictra
RBX2660 (Rebyota (fecal microbiota, live-jslm)	Ferring Pharmaceuticals	US-FDA 11/2022	Live biotherapeutic product	Enema	Recurrent/ refractory diarrhoea prevention [a]	*C. difficile*	Rebyota
Ftortiazinon (fluorothyazinone) (to be administered with cefepime)	Gamaleya Research Institute of Epidemiology and Microbiology	Ministry of Health Russian Federation, 2024	Anti-virulence (thyazinone type III secretion system inhibitor)	PO	cUTI	*E. coli*, *K. pneumoniae* and *P. aeruginosa*	Ftortiazinon

TGA - Therapeutic Goods Administration

[a] Prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Table 2 shows traditional antibacterial agents in clinical development from Phase 1 to the marketing authorization application (MAA)/new drug application (NDA) stage.

Table 2. Antibacterial agents being developed against WHO priority pathogens

International nonproprietary name (company code)	Phase	Trial registration code	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment	Expected activity against priority pathogens					Innovation			
							CRAB	CRE	3GCRE	CRPA	OPP[a]	NCR	CC	T	MoA
Solithromycin (T-4288)	NDA	NCT02628769	Macrolide/ketolide	IV/PO	Fujifilm Toyama Chemical		/	/	/	/	●	-	-	-	-
Cefepime + Taniborbactam (VNRX-5133)	NDA	NCT03840148	β-lactam (cephalosporin) + Boronate BLI	IV	Venatorx Pharmaceuticals/ GARDP/Everest Medicines		X	●	●	●	/	?	✓	-	-
Zoliflodacin	3	NCT03959527	Spiropyrimidene-trione (novel bacterial topoisomerase inhibitor)	PO	Innoviva (former Entasis Therapeutics)/ GARDP		/	/	/	/	●	✓[b]	✓	-	✓
Gepotidacin	NDA for uUTIs 10/ 2024	NCT04020341 (cUTI)	Triazaacenaphthylene (novel bacterial topoisomerase inhibitor)	IV/PO	GSK		/	?[c]	?[c]	/	●	?	✓	-	✓
Cefepime + Zidebactam (WCK 5222)[d]	3	NCT04979806	β-lactam (cephalosporin) + DBO-BLI/PBP2 binder	IV	Wockhardt		?[e]	●	●	?[e]	/	-[f]	-	-	-
Cefepime+ Nacubactam (OP0595)[d]	3	NCT05887908	β-lactam (cephalosporin) + DBO-BLI/PBP2 binder	IV	Meiji Seika		/	●	●	?	/	-	-	-	-
Aztreonam+ Nacubactam (OP0595)[d]	3	NCT05887908	β-lactam (monobactam) + DBO-BLI/PBP2 binder	IV	Meiji Seika		/	●	●	X	/	-	-	-	-

Table 2 (continued). Antibacterial agents being developed against WHO priority pathogens

International nonproprietary name (company code)	Phase	Trial registration code	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment	Expected activity against priority pathogens					Innovation			
							CRAB	CRE	3GCRE	CRPA	OPP[a]	NCR	CC	T	MoA
Funobactam (XNW4107) + Imipenem + Cilastatin	3	NCT05204368	DBO-BLI + β-lactam (carbapenem) + degradation inhibitor	IV	Evopoint Bioscience		?[g]	?[h]	?[i]	X	/	-	-	-	-
Benapenem	2	NCT04505683	β-Lactam (carbapenem)	IV	Xuanzhu Biopharm[j]		X	X	?	X	/	-	-	-	-
Afabicin (Debio-1450)	2	NCT03723551	Pyrido-enamide (FabI inhibitor)	IV/PO	Debiopharm		/	/	/	/	●	✓	✓	✓	✓
TNP-2092	2	NCT03964493	Rifamycin-quinolizinone hybrid	IV/PO[k]	TenNor Therapeutics		/	/	/	/	●	-	-	-	-
Recce-327 (R327)	1, 2	ACTRN-12621001313820	Synthetic (acrolein) polymer	IV/Topical	Recce Pharmaceuticals.		?	?	?	?	?	?	?	?	?
OMN6	2	NCT06087536	Insect host defence peptide	IV	Omnix Medical		●	?	/	?	?	?	✓	✓	✓
Murepavadin (POL7080, iMPV)	1	NOT registered	Macrocyclic peptidomimetic compound	Inhaled[l]	Spexis AG		X	X	X	●	/	?	✓	✓	✓
Ceftibuten + ledaborbactam (VNRX-7145)	1	NCT05488678	β-lactam (cephalosporin) + Boronate-BLI	PO	Venatorx Pharmaceuticals		X	●	●	X	/	?	✓	-	-
Xeruborbactam (QPX7728) + β-lactam (S-649228)	1	NCT05072444 NCT04380207	Boronate-BLI + undisclosed IV β-lactam	IV	Qpex Biopharma/ Shionogi		●	●	●	●	/	?	-	-	-

Table 2 (continued). Antibacterial agents being developed against WHO priority pathogens

International nonproprietary name (company code)	Phase	Trial registration code	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment	Expected activity against priority pathogens					Innovation			
							CRAB	CRE	3GCRE	CRPA	OPP[a]	NCR	CC	T	MoA
Upleganan (SPR-206)	1	NCT4865393	Polymyxin	IV	Spero Therapeutics/ Pfizer		●	●	●	●	/	-	-	-	-
MRX-8	1	NCT04649541	Polymyxin	IV	MicuRx		●	●	●	●	/	-	-	-	-
QPX9003	1	NCT04808414	Polymyxin	IV	Brii Biosciences		●	?	?	●	/	? [m]	-	-	-
Zifanocycline (KBP-7072)	1	NCT05507463	Tetracycline (aminomethylcycline)	IV/PO	KBP BioSciences		●	?	?	X	●	✓	-	-	-
Apramycin (EBL-1003) [n]	1	NCT05590728	Aminoglycoside	IV	Juvabis		●	●	?	?	/	-	-	-	-
TXA709	1	Not registered	Difluorobenzamide (FtsZ inhibitor)	PO	TAXIS Pharmaceuticals		X	X	X	X	●	✓	✓	✓	✓
Zosurabalpin (RG6006)	1	NCT04605718	Macrocyclic peptide	IV	Roche		● [o]	X	X	X	X	?	?	?	?
BWC0977	1	NCT05088421	Pyrazino-oxazinones (novel bacterial topoisomerase inhibitor)	IV/PO	Bugworks Research		●	● [p]	●	?	?	✓ [q]	✓	?	✓
Ertapenem + Zidebactam [d]	1	NCT05645757	β-lactam (carbapenem) + DBO-BLI/PBP2 binder	IV	Wockhardt/NIAID		X	●	●	?	/	-	-	-	-

Table 2 (continued). Antibacterial agents being developed against WHO priority pathogens

International nonproprietary name (company code)	Phase	Trial registration code	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment	Expected activity against priority pathogens					Innovation			
							CRAB	CRE	3GCRE	CRPA	OPP[a]	NCR	CC	T	MoA
Meropenem + ANT3310	1	NCT05905913	β-lactam (carbapenem) + DBO-BLI/PBP2 binder	IV	Antabio SAS		●	●	●	?	/	-	-	-	-
Meropenem + KSP-1007 (MEROPEN)	1	NCT05226923	β-lactam (carbapenem) + Boronate BLI	IV	Sumitomo Dainippon Pharma		?	?	?	?	/	?	✓	-	-

Strength of Activity: Peer-reviewed data. Not-peer-reviewed data. In vitro data. In vivo data.

Activity Assessment: ● Active; ? Possibly Active; X Not Active; / Not Tested

Innovation Assessment: ✓ Criterion fulfilled; ? Inconclusive data; - Criterion not fulfilled

3GCRE: 3rd generation cephalosporin-resistant Enterobacterales; BLI: β-lactamase inhibitor; CC: chemical class; CRAB: carbapenem-resistant *A. baumannii*; CRE: carbapenem-resistant Enterobacterales; CRPA: carbapenem-resistant *P. aeruginosa*; ESBL: extended-spectrum β-lactamase; FabI: enoyl-acyl carrier protein reductase; DBO: diazabicyclooctane; FtsZ: filamenting temperature-sensitive Z; GARDP: Global Antibiotic Research and Development Partnership; iv: intravenous; KPC: *K. pneumoniae* carbapenemase; MOA: new mode of action; OPP: other priority pathogens; NCR: no cross-resistance; NDA: new drug application; NIAID: National Institute of Allergy and Infectious Diseases; OPP: other priority pathogens; PBP2: penicillin-binding protein 2; PO: oral administration; T: new target; uUTI: uncomplicated urinary tract infection.

[a] OPP target pathogens – solithromycin: *S. pneumoniae*; nafithromycin: *S. aureus* and *S. pneumoniae*; zoliflodacin, gepotidacin: *N. gonorrhoeae* and MRSA; afabicin, TNP-2092, and TXA709: MRSA; Zifanocycline (KBP-7072): MRSA and vancomycin-resistant (VR) *E. faecium*; BWC0977: VR *E. faecium*; MRSA, fluoroquinolone-resistant (FQR) *N. gonorrhoeae*, VR *E. faecium*, macrolide-resistant Pneumococco, macrolide-resistant group A Streptococci, FQR non-typhoidal *Salmonella*.
[b] The GyrB D429N substitution reduces susceptibility to zoliflodacin. The GyrB D429N substitution can be acquired by *N. gonorrhoeae* in the presence of ciprofloxacin, resulting in increased ciprofloxacin MIC, at least in some backgrounds *(7)*.
[c] Non-clinical data available only against ESBL and NDM-1-producing *E. coli*.
[d] The DBO-BLIs zidebactam, OP0595 (nacubactam) and ETX0282 also have some antibacterial activity and have been classified as β-lactam enhancers.
[e] Limited animal data obtained with human simulated regimens suggest possible activity. See product profile for details.
[f] Activity against aztreonam-avibactam resistant NDM-like producing *E. coli* shown in one paper *(8)*.
[g] Activity towards OXA-23, -27 and -51 -producing CRAB, but susceptibility rate 57.5%; No activity vs MLB *(9)*.
[h] Activity towards KPC-producing CRKP; NOT against CR-EC *(10)*.
[i] Active against 3GCR-*K. pneumoniae* but insufficient data against 3GCR-*E. coli* *(9,10)*.
[j] Xuanzhu Biopharm is a subsidiary of Sichuan Pharmaceutical Holdings but possesses fully independent intellectual property rights.
[k] No clinical data are available for the POS formulation.
[l] Previously tested as IV in HAP and VAP in 2 phase 3 trials terminated in 2019 due to safety concerns *(11)*.
[m] Activity at higher doses against colistin-resistant strains *(12)*.
[n] Previously used as an antibacterial treatment in animals *(13)*.
[o] Activity against Colistin resistant CRAB *(14)*.
[p] Only in the in vivo E.coli model, a bacterial strain with MIC90 for BWC0977 was used.
[q] No data are available on activity against moxifloxacin-resistant bacteria.

Table 3 shows the activity of different β-lactams and β-lactam/β-lactamase inhibitor (BLI) combinations approved since 2017 or currently in development against the most clinically relevant β-lactamases, including carbapenemases.

Table 3. The activity of different β-lactams and β-lactam/BLI combinations approved since 2017 or currently in development against the most clinically relevant β-lactamases, including carbapenemases

		CRE				CRAB	
		A	A	D	B		
		ESBL	KPC	OXA	MBL		
Reference	β-lactams and β-lactam/BLI combination	(CTX-M)	(KPC-2,-3)	(OXA-48)	(NDM)	OXA	CRPA
Approved	Vaborbactam + Meropenem	●	●	●	X	X	X
Approved	Relebactam + Imipenem + Cilastatin	●	●	●	X	X	?
Approved	Cefiderocol	●	●	●	●	●	●
Approved	Sulbactam+ Durlobactam (ETX-2514)	X	X	X	X	●	X
Approved	Cefepime + Enmetazobactam (AAI-101)	●	?	X	X	X	X
NCT05584657	Sulopenem	●	X	X	X	X	X
NCT03840148	Cefepime+ Taniborbactam (VNRX-5133)	●	●	●	? [a]	-	●
NCT04505683	Benapenem	X	X	X	X	X	X
NCT04979806	Cefepime + Zidebactam	●	●	●	?	? [b]	?
NCT05072444	Xeruborbactam (QPX7728) + beta-lactam (S-649228)	●	●	●	●	●	●
NCT05204368	Funobactam (XNW4107) + Imipenem + Cilastatin	●	●	?	X	?	X
NCT05488678	Ceftibuten + Ledaborbactam (VNRX-7145)	●	●	● [d]	X	X	X

Table 3 (continued). The activity of different β-lactams and β-lactam/BLI combinations approved since 2017 or currently in development against the most clinically relevant β-lactamases, including carbapenemases

		CRE				CRAB	
		A	A	D	B		
		ESBL	KPC	OXA	MBL		
Reference	β-lactams and β-lactam/BLI combination	(CTX-M)	(KPC-2,-3)	(OXA-48)	(NDM)	OXA	CRPA
NCT05645757	Ertapenem + Zidebactam	●	●	● [e]	● [e]	X	?
NCT05887908	Cefepime+ Nacubactam (OP0595)	●	●	X	?	X	?
NCT05887908	Aztreonam + Nacubactam (OP0595)	●	●	●	●	X	X
NCT05905913	Meropenem + ANT3310	●	●	●	/	●	X
NCT05226923	Meropenem + KSP-1007(MEROPEN)	●	●	?	?	?	?

Pathogen activity: ● active; ? possibly active; X not active; / not tested.

CRAB: carbapenem-resistant *A. baumannii*; CRPA: carbapenem-resistant *P. aeruginosa*; CTX-M: CTX-M-type β-lactamase; ESBL: extended-spectrum β-lactamase; KPC: *K. pneumoniae* carbapenemase; MBL: metallo-β-lactamase; NDM: New Delhi metallo-β- lactamase; OXA: oxacillinase.

Grey shading: Market authorized as of July 2017.

[a] Heteroresistance described *(15)*.
[b] MICs for CRAB isolates *(16)* expressing OXA23,24 and 58 clustered around 8–16 mg/L, compared with 64 mg/L for cefepime alone and >128 mg/L for zidebactam alone *(16)*.
[c] Not active in vivo against IMP6 producing-KP. See product profile for details.
[d] Loss of activity if co-production of class C and class D (OXA48-like) SBL *(17)*.
[e] Active against MBL-producing *E. coli*, but not *K. pneumoniae*; not active against Enterobacterales with the combination of MBL+OXA48 *(18)*.

Table 4 shows agents (traditional and non-traditional) under clinical development for the treatment of multidrug-resistant *M. tuberculosis* while Table 5 shows traditional (Table 5a) and non-traditional (Table 5b) antibacterials in clinical development for the treatment of *C. difficile* and *H. pylori*.

Table 4. Antimicrobial agents for the treatment of *Mycobacterium tuberculosis* in clinical development

Name (synonym)	Trial registration code	Phase	Antibiotic class	Route of administration	Developer	Innovation			
						NCR	CC	T	MoA
Traditional agents									
Sudapyridine (WX-081)	Phase 3: NCT05824871	3	Mycobacterial ATP synthase inhibitor (respiratory chain inhibitor)	PO	Shanghai Jiatan Biotech	-	-	-	-
TBAJ-876	Phase 1: NCT04493671, Phase 2: NCT06058299 (NC-009)	2	Diarylquinoline (bedaquiline analogue; respiratory chain inhibitor)	PO	TB Alliance	-	-	-	-
Telacebec (Q203)	NCT03563599	2	Imidazopyridine amide (respiratory chain inhibitor)	PO	Qurient / Infectex / TB Alliance	✓	✓	✓	✓
BTZ-043	NCT05382312, NCT06114628 (PARADIGM4TB), NCT05807399 (PanACEA), NCT05926466 (DECISION)	2	Benzothiazinone (DprE1 inhibitor)	PO	University of Munich / Hans Knöll Institute, Jena / German Center for Infection Research	✓	✓	✓	✓
Quabodepistat (OPC-167832)	NCT05971602	2	3,4-Dihydrocarbostyril (DprE1 inhibitor)	PO	Otsuka Pharmaceutical	✓	✓	✓	✓
TBA-7371	NCT04176250	2	Azaindole (DprE1 inhibitor)	PO	TB Alliance / Gates MRI / Foundation for Neglected Diseases Research	✓	✓	✓	✓
Macozinone (PBTZ-169)	Phase 1a in EU: NCT03776500; Phase 2a in the Russian Federation and Belarus: NCT0333473	1/2	Benzothiazinone (DprE1 inhibitor)	PO	Innovative Medicines for Tuberculosis / Nearmedic Plus	✓	✓	✓	✓

Table 4 (continued). Antimicrobial agents for the treatment of *Mycobacterium tuberculosis* in clinical development

Name (synonym)	Trial registration code	Phase	Antibiotic class	Route of administration	Developer	Innovation			
						NCR	CC	T	MoA
Sutezolid (PF-2341272, PNU-100480)	NCT05971602, NCT03959566 (SUDOCU), NCT05686356 (panTB-HM), NCT06192160 (A5409/RAD-TB), NCT05807399 (PanACEA)	2/3	Oxazolidinone (protein synthesis inhibitor)	PO	TB Alliance / Gates MRI / Aurum Institute	-	-	-	-
Delpazolid (RMW2001, LCB01-0371)	NCT04550832 (DECODE)	2	Oxazolidinone (protein synthesis inhibitor)	PO	LigaChem Biosciences / Haihe Biopharma	-	-	-	-
TBI-223	Phase 1: NCT03758612, NCT06192160 (A5409/RAD-TB)	2	Oxazolidinone (protein synthesis inhibitor)	PO	TB Alliance / Institute of Materia Medica	-	-	-	-
Ganfeborole, GSK3036656 (GSK070)	NCT06354257, NCT05382312 (EBA), NCT03557281	2	Oxaborole (LeuRs inhibitor; protein synthesis inhibitor)	PO	GlaxoSmithKline	✓	✓	✓	✓
SQ109	NCT01785186 (PanACEA MAMS-TB)	2	Ethylenediamine (inhibits micolic acid assembly by targeting MmpL3)	PO	Sequella	?	-	✓	✓
Pyrifazimine (TBI-166) a	NCT04670120 (EBA)	2	Riminophenazine (clofazimine analogue)	PO	Institute of Materia Medica / TB Alliance / Chinese Academy of Medical Sciences / Peking Union Medical College	-	-	-	-
Sanfetrinem cilexetil (GV118819)	NCT05388448	2	Tricyclic β-lactam	PO	GSK	-	-	-	-
TBAJ-587	NCT04890535	1	Diarylquinoline (bedaquiline analogue; respiratory chain inhibitor)	PO	TB Alliance/ University of Auckland	-	-	-	-

Table 4 (continued). Antimicrobial agents for the treatment of *Mycobacterium tuberculosis* in clinical development

Name (synonym)	Trial registration code	Phase	Antibiotic class	Route of administration	Developer	Innovation			
						NCR	CC	T	MoA
TBD09 (MK7762)	NCT05824091	1	Oxazolidinone (protein synthesis inhibitor)	PO	Gates MRI / Merck & Co. Inc / NIAID	-	-	-	-
GSK2556286 (GSK286)	NCT04472897	1	Adenylyl cyclase Rv1625c agonist (inhibitor of micobacterial cholesterol)	PO	GlaxoSmithKline / TB Drug Accelerator	?	✓	✓	✓
TBD11	NCT06707142	1	Adenylyl cyclase Rv1625c agonist (inhibitor of micobacterial cholesterol)	PO	Gates MRI	?	✓	✓	✓
Non-traditional agents									
Alpibectir (BVL-GSK098) + ethionamide	Phase 2: NCT05473195	2	Amido piperidine (inactivation of TetR-like repressor EthR2; ethionamide enhancer) spiroisoxazoline	PO	BioVersys / GSK	NA	NA	NA	NA
Dovramilast (CC-11050, AMR-634)	Phase 2: NCT02968927	2	PDE4 inhibitor (host immune response)	PO	Medicines Development for Global Health / Aurum Instiitute	NA	NA	NA	NA

Innovation assessment: ✓ criterion fulfilled; ? Inconclusive data; - criterion not fulfilled.

CC: chemical class; DprE1: decaprenylphosphoryl-β-D-ribose 2′-epimerase; LeuRS: leucyl-tRNA synthetase; MOA: new mode of action; NCR: no cross-resistance; T: new target; TB: tuberculosis.

[a] The lead drug clofazimine is approved to treat leprosy and has been used off-label for TB.

Table 5a. Traditional antibacterials in clinical development for the treatment of *C. difficile* and *H. pylori*

Name (synonym)	Phase	Antibiotic class	Route of administration	Developer	Pathogen	Innovation			
						NCR	CC	T	MoA
Ridinilazole	3 [a]	Bis-benzimidazole	PO, not absorbed	Summit Therapeutics	*C. difficile*	✓	✓	✓	✓
CRS3123	2	Diaryldiamine	PO, not absorbed	Crestone/NIAID	*C. difficile*	✓	✓	✓	✓
Ibezapolstat (ACX-362E)	2	DNA polymerase IIIC inhibitor	PO, not absorbed	Acurx Pharmaceuticals	*C. difficile*	✓	✓	✓	✓
MGB-BP-3	2	Distamycin (DNA minor groove binder)	PO, not absorbed	MGB Biopharma	*C. difficile*	?	✓	✓	✓
Rifasutenizol (TNP-2198)	3	Rifamycin- nitroimidazole conjugate	PO, not absorbed	TenNor Therapeutics	*H. pylori*	-	-	-	-

Innovation assessment: ✓ criterion fulfilled; ? Inconclusive data; - criterion not fulfilled.

CC: chemical class; CDIs: *C. difficile* infections; iv: intravenous; MoA: new mode of action; NCR: no cross-resistance; NIAID: National Institute of Allergy and Infectious Diseases; T: new target.

[a] Following negative results from the phase 3 study NCT04802837, the ongoing study in adolescents was terminated in alignment with corporate decision to pursue further development of drug candidate with a partner.

Table 5b. Non-traditional antibacterials in clinical development for the treatment of *C. difficile*

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Pathogen
Antibodies	NCT06469151	AZD5148	1	mAb	IV	AstraZeneca	rCDI	*C. difficile*
	NCT04121169	IM-01	2	Chicken egg-derived anti-*C. difficile* polyclonal antibody	PO	ImmuniMed	CDI	*C. difficile*
Microbiome-modulating agents	NCT06306014	EXL01	1/2	Live biotherapeutic product	PO	Hospices Civils de Lyon, Exeliom Biosciences	rCDI	*C. difficile*
	NCT06237452	VE303	3	Live biotherapeutic product	PO	Vedanta Biosciences	rCDI	*C. difficile*
	NCT02865616	MET-2	1	Live biotherapeutic product	PO	NuBiyota/Takeda	rCDI	*C. difficile*
	NCT02981316	RBX7455	1	Live biotherapeutic product	PO	Ferring Pharmaceuticals (Rebiotix)	rCDI	*C. difficile*
	NCT04692181	SYN-004 (ribaxamase)	1b/2a	Antibiotic inactivator	PO	Theriva Biologics [a]	Prevention of CDI in allogeneic HCST	*C. difficile*
	NCT05911997	MTC01	1	Live biotherapeutic product	Endoscopic	Icahn School of Medicine at Mount Sinai	rCDI	*C. difficile*
	NCT04891965	ADS024 (formerly ART24)	1	Live biotherapeutic product	PO	Adiso Therapeutics [b]	rCDI	*C. difficile*
	NCT05201079	MBK-01	3	Live biotherapeutic product	PO	Mikrobiomik Healthcare Company	rCDI	*C. difficile*

Table 5b (continued). Non-traditional antibacterials in clinical development for the treatment of *C. difficile*

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Pathogen
Bacteriophages and phage-derived enzymes	NCT05330182	LMN-201	2/3	Phage endolysin and three toxin-binding proteins (5D, E3 and 7F)	PO	Lumen Bioscience	rCDI	*C. difficile*

Microbiome-modulating agents

Bacteriophages and phage-derived enzymes

Antibodies

Miscellaneous

Immune modulating agents

rCDI: recurrent *Clostridium difficile* infection.

[a] Formerly Synthetic Biologics.

[b] Formerly Artugen Therapeutics and Bacainn Therapeutics.

Table 6 describes different types of non-traditional antibacterial agents in clinical development against the WHO bacterial priority pathogens, while Table 7 describes discontinued agents.

Table 6. Non-traditional antibacterial agents in clinical development

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Priority pathogen(s)
Antibodies	NCT03816956	Salvecin (Tosatoxumab; AR-301)	3	mAb, antivirulence *S. aureus* (α-toxin)	IV	Aridis Pharmaceuticals	VABP	*S. aureus*
	NCT05331885	Suvratoxumab (AR-320)	3	mAb, antivirulence *S. aureus* (α-toxin)	IV	Aridis Pharmaceuticals [a]	Prevention of pneumonia in high-risk patients	*S. aureus*
	NCT05339802	9MW1411	2	mAb, antivirulence *S. aureus* (α-toxin)	IV	Mabwell (Shanghai) Bioscience	ABSSSI	*S. aureus*
	NCT05355207 NCT06621251	Calpurbatug (TRL1068)	2a	mAb biofilm disruption (DNABII protein)	IV	Trellis Bioscience	PJI	Gram-positive and Gram-negative pathogens
	NCT06159725	CMTX-101	1b/2	mAb biofilm disruption (DNABII protein)	IV	Clarametyx Biosciences	CF patients with chronic *P. aeruginosa* infection	Gram-positive (MRSA) and Gram-negative pathogens
	ISRCTN17978477	RESP-X (INFEX702)	2a	mAb, antivirulence *P. aeruginosa* (type III secretion system)	IV	Infex Therapeutics	Chronic *P. aeruginosa* lung infection in non-CF bronchiectasis patients (NCFB)	*P. aeruginosa*
Antivirulence	NCT05138822	GSK3882347	1b	Anti-virulence (type 1 fimbrin D-mannose-specific adhesin, FimH inhibitor)	PO	GlaxoSmithKline	uUTI	*E. coli*
	NCT05274802	ALS-4	1	Anti-virulence (staphyloxanthin biosynthesis inhibition)	PO	Aptorum Group	MRSA ABSSSI	*S. aureus*

Table 6 (continued). Non-traditional antibacterial agents in clinical development

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Priority pathogen(s)
Bacteriophages and phage-derived enzymes	NCT06370598	TP-122A	1/2a	Bacteriophage	inhalation	Technophage	VABP	*P. aeruginosa*
	NCT05616221 (Tailwind)	AP-PA02	2	Bacteriophage	inhalation	Armata Pharmaceuticals	Chronic *P. aeruginosa* lung infection in non-CF	*P. aeruginosa*
	NCT04596319 (SWARM-Pa)		1b/2a	Bacteriophage	inhalation	Armata Pharmaceuticals	Chronic *P. aeruginosa* lung infection in CF	*P. aeruginosa*
	NCT04684641	YPT-01	1/2	Bacteriophage	inhalation	Yale University	Chronic *P. aeruginosa* lung infection in CF	*P. aeruginosa*
	NCT05010577	BiomX Phagebank: BX004-A	2b	Bacteriophage	Inhalation	BiomX	Chronic *P. aeruginosa* lung infections in CF	*P. aeruginosa*
	NCT05488340 (ELIMINATE trial)	LBP-EC01	2	CRISPR-Cas3 enhanced phage	irrigation/iv	Locus Biosciences	Recurrent uUTI caused by MDR *E. coli*	*E. coli*
	NCT05277350	SNIPR001	1b/2a	CRISPR-Cas3 enhanced phage	PO	SNIPR Biome	Prevention of BSI in patients with haematologic malignancy	*E. coli*
	NCT05177107 (DANCE)	BiomX Phagebank: BX211	2b	Bacteriophage	iv and topical	BiomX	Diabetic Foot osteomyelitis	*S. aureus*
	NCT05453578 (WRAIR-PAM-CF1)	WRAIR-PAM-CF1	1b/2	Bacteriophage	IV	NIAD/BiomX	Chronic *P. aeruginosa* lung infection in CF	*P. aeruginosa*

Table 6 (continued). Non-traditional antibacterial agents in clinical development

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Priority pathogen(s)
Bacteriophages and phage-derived enzymes	NCT06605651	Phages: PP1493 and PP1815	2	Bacteriophage	intra-articular	PHAXIAM	Knee/hip PJI with the indication of DAIR and SAT	*S. aureus*
	NCT03808103	EcoActive	1/2a	Bacteriophage	PO	Intralytix	Crohn's disease	*E. coli*, AIEC
	NCT05182749	ShigActive	1/2a	Bacteriophage	PO	Intralytix	Shigellosis	*Shigella* spp.
	NCT05715619	VRELysin	1/2a	Bacteriophage	PO	Intralytix	VRE colonization and associated bacteraemia	VRE
	NCT05184764	AP-SA02	1b/2a	Bacteriophage	IV	Armata Pharmaceuticals	Bacteraemia	*S. aureus*
Immune-modulating agents	NCT05947955 (ARDS); NCT03466073 (CABP)	Rhu-pGSN (rhu-plasma gelsolin)	2	Rhu-pGSN protein	IV	BioAegis Therapeutics	Hospitalized patients with acute CABP and ARDS	Gram-positive and Gram-negative pathogens (activity: pneumococcus and *P. aeruginosa* in vivo. *E. coli* in vitro)
Microbiome-modulating agents	NCT04995653	SER-155	1b	Microbiome modulator (fermented microbiome, commensal bacteria)	PO	Seres Therapeutics	Reduce GvHD and infections in patients undergoing HSCT	Gram-positive and Gram-negative pathogens

Table 6 (continued). Non-traditional antibacterial agents in clinical development

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Priority pathogen(s)
Miscellaneous	NCT05137314	PLG0206	1	Anti-biofilm (eCAPs)	irrigation	Peptilogics	PJI	Gram-positive and Gram-negative pathogens
	NCT05776004	CAL02	2	Broad-spectrum anti-toxin liposomal agent and nanoparticle	IV	Eagle Pharmaceuticals [e]	CABP	*S. pneumoniae*
	NCT03669614	AR501 (Panaecin)	1/2a	Anti-iron (gallium citrate solution)	inhalation	Aridis Pharmaceuticals	*P. aeruginosa* pneumonia	*P. aeruginosa*
	NCT03822455 completed no results	Oligo G	2b	Anti-biofilm (alginate oligosaccharide, G-block fragment)	Inhalation	AlgiPharma	Chronic *P. aeruginosa* lung infection in CF	*P. aeruginosa*

Microbiome-modulating agents

Antivirulence

Bacteriophages and phage-derived enzymes

Antibodies

Miscellaneous

Immune modulating agents

mAB: monoclonal antibody; CF: cystic fibrosis; CABP: community-acquired bacterial pneumonia; VABP: ventilator-associated bacterial pneumonia; ABSSSI: acute bacterial skin and skin structure infection; PJI: periprosthetic joint infection; uUTI: uncomplicated urinary tract infection; MRSA: methicillin-resistant *S. aureus*; ARDS: acute respiratory distress syndrome; GvHD: graft versus host disease; HSCT: haematopoietic stem cell transplant.

[a] Licensed from AstraZeneca.

[b] Terminated: Enrollment into this study was terminated by the sponsor prior to completion for strategic reasons.

[c] Withdrawn: business decision before FPFV; not related to any safety concerns.

[d] Licensed from iNtRON.

[e] Licensed from Combioxin.

Table 7. Agents not under active development by year of activity last reported

Name (synonym)	Phase	Antibiotic class	Pathogen activity	Developer	Year activity last reported
GSK-3342830	1	Siderophore-cephalosporin	Gram-negative	GSK	2017
AIC-499 + unknown BLI	1	β-Lactam + BLI	Gram-negative	AiCuris	2017
DS-2969	1	GyrB inhibitor	*C. difficile*	Daiichi Sankyo	2017
514G3 (omodenbamab)	1/2	Anti-*S. aureus* IgG mAb	*S. aureus*	Xbiotech	2017
SPR-741 + β-lactam	1	Polymyxin (potentiator) + β-lactam	Gram-negative	Spero Therapeutics / Everest Medicines	2018
Cefilavancin (TD-1792, RD-1792)	3	Glycopeptide-cephalosporin hybrid	*S. aureus*	R-Pharm / Theravance Biopharma	2018
Ramoplanin	2	Lipodepsipeptide	*C. difficile*	Nanotherapeutics	2018
Ancremonam (BOS-228, LYS-228)	2	Monobactam	CRE	Boston Pharmaceuticals	2018
Cadazolid	3	Oxazolidinone-quinolone hybrid	*C. difficile*	Actelion Pharmaceuticals	2019
RC-01 (T 1228)	1	LpxC inhibitor	Gram-negative	Recida Therapeutics / Fujifilm Toyama Chemical	2019
GT-1	1	Siderophore-cephalosporin	Gram-negative	Geom Therapeutics	2019
MK-3866	1	BLI	Gram-negative	Merck Sharp & Dohme	2019
AR-105 (Aerucin)	2	Anti-*P. aeruginosa* fully human IgG1 mAb	*P. aeruginosa*	Aridis Pharmaceuticals (Serum Institute of India)	2019
BCM-0184	1	Undisclosed (likely peptide)	*S. aureus*	Biocidium Pharmaceuticals	2019
Iclaprim	3	DHFR inhibitor	*S. aureus*	Motif Bio	2020
MEDI-3902 (gremubamab)	2	Anti-*P. aeruginosa* IgG mAb	*S. aureus*	AstraZeneca (MedImmune)	2020
OPS-2071	2	Quinolone	*C. difficile*	Otsuka	2020
AR-101 (Aerumab, KPBA-101)	2	mAb	*P. aeruginosa* LPS serotype O11	Aridis Pharmaceuticals / Kenta Biotech	2020
DSTA4637S	1	Anti-*S. aureus* IgG mAb / rifamycin conjugate	*S. aureus*	Genentech (Roche)	2021
KB109	N/A	Synthetic glycan	Gram-positive and Gram- negative	Kaleido Biosciences	2021

Table 7 (continued). Agents not under active development by year of activity last reported

Name (synonym)	Phase	Antibiotic class	Pathogen activity	Developer	Year activity last reported
TP-271	1	Tetracycline	*S. aureus* and *S. pneumoniae*	La Jolla Pharmaceutical Company (Tetraphase Pharmaceuticals)	2021
TP-6076	1	Tetracycline	*A. baumannii*	La Jolla Pharmaceutical Company (Tetraphase Pharmaceuticals)	2021
DAV132	2	Antibiotic inactivator and protective colon-targeted adsorbent	*C. difficile*	Da Volterra	2022
CP101	2	Live biotherapeutic product	*C. difficile*	Finch Therapeutics	2023
Bacteriophage	3	Phage	Gram-positive and Gram-negative	Tashkent Pediatric Medical Institute	2023
NC™-M3 (VP20621)	2	Live biotherapeutic product	*C. difficile*	Destiny Pharma, Sebela Pharmaceuticals	2023
SVT-1C469	1	Live biotherapeutic product	*H. pylori*	Servatus	2023
Oxaquin (DNV3837, MCB-3837; prodrug of MCB3681)	2	Oxazolidinonequinolone hybrid	*C. difficile*	Deinove	2023
Exebacase (CF-301)	3	Phage endolysin	*S. aureus*	ContraFect	2023
LSVT-1701, N-Rephasin (SAL200, Tonabacase)	2	Phage endolysin	*S. aureus*	Roivant Sciences/iNtRON Biotechnology/Basilea Pharmaceutica	2021
Reltecimod (AB103)	3	Synthetic peptide antagonist of both superantigen exotoxins and the CD28 T-cell receptor	*S. aureus*	Atox Bio	2022
Nacubactam + meropenem	1	β-lactam (carbapenem) + DBO-BLI/PBP2 binder	CRE, 3GCRE	Meiji Seika	2020
ETX0282 + Cefpodoxime proxetil	1	β-lactam (cephalosporin) + DBO-BLI/PBP2 binder	CRE, 3GCRE	Entasis Therapeutics Inc.	2020
APT Phages	1	Bacteriophages	Gram + and Gram - PJI intrarticular	APT Phage bank	2023
APT Phages	2	Bacteriophages	Gram + and Gram - PJI intrarticular	APT Phage bank	2023

CRE: carbapenem-resistant Enterobacterales; 3GCRE: 3rd generation cephalosporin-resistant Enterobacterales; PJI: periprosthetic joint infection.
Underlined: New chemical class.
BLI: β-lactamase inhibitor; CRE: carbapenem-resistant Enterobacterales; 3GCRE: third generation resistante cephalosporins; GyrB: DNA gyrase subunit B; IgG: immunoglobulin G; mAb: monoclonal antibody

3

Preclinical pipeline

3. Preclinical pipeline

Key messages from the 2024 preclinical pipeline update

The WHO fifth global review of antibacterial agents in preclinical development based on publicly available data captures 232 products in development targeting the WHO BPPs:

- 148 individual groups are progressing 232 programmes worldwide.
- The European Region and the Region of the Americas host the majority of groups (45.3% and 41.2% respectively).
- Only 75 agents (32.3%) target a single pathogen, continuing a downward trend in this area.
- 92 products (39.7%) are classified as non-traditional, including phages, virulence inhibitors, immunomodulatory compounds and potentiator agents, among others.

The 148 institutions progressing preclinical programmes worldwide are classified as either academic universities, companies, or foundations/non-profits. Most institutions are commercial companies (n=118, 79.7%), followed by academic institutions (n=23; 15.6%) and foundations (n=7, 4.7%). The dominance of commercial companies performing antibacterial product development has remained stable over the years of analysis (Fig. 4). Of the 118 commercial institutions, most were privately owned (n = 102, 86.4%) and a significant proportion (n=107, 90.7%) of all companies contain <50 employees, with a large number (n=73, 61.9%) having <10 employees (Fig. 5).

Fig. 4. Categorization of groups with preclinical pipeline programmes by type

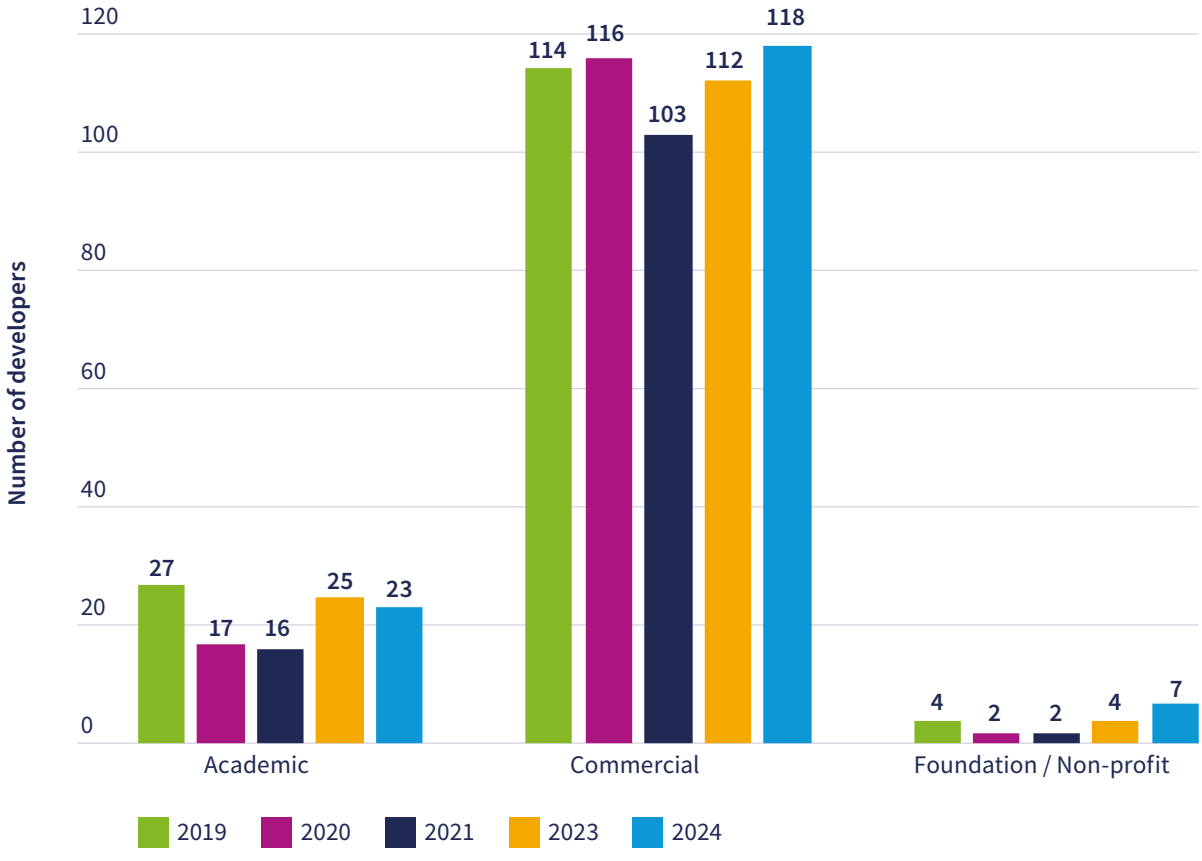


Fig. 5. Categorization of companies with preclinical pipeline programmes by ownership and size

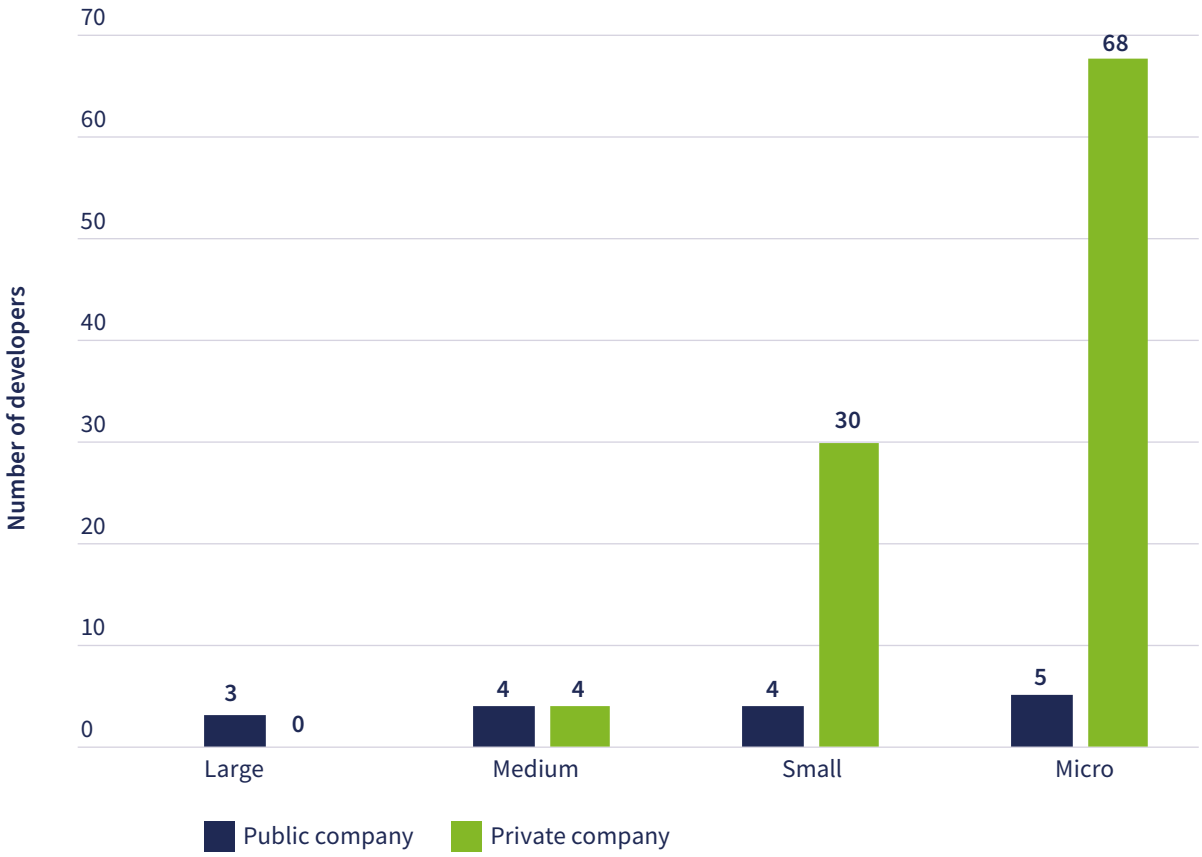


Table 8. Distribution of preclinical programmes by antibacterial agent category

Product type	2024 (number)	2024 (%)
Small molecule - direct acting	109	47.0
* Small molecule - indirect acting	30	12.9
Peptide - direct acting	28	12.1
* Peptide - indirect acting	3	1.3
* Large molecule - direct acting	15	6.5
* Large molecule - indirect acting	5	2.2
* Bacteriophage/bacteriophage products	22	9.5
* Biologic (antibody or other biotherapeutic)	7	3.0
* Nucleic acid-based product	2	0.9
* Immunomodulators	5	2.2
* Microbiome-modifying agents	3	1.3
Decolonization agents	3	1.3
Total	**232**	**100.0**

46 of the 141 developers (32.6%) from the 2023 analysis were excluded from the 2024 pipeline review as the programmes could not be verified.

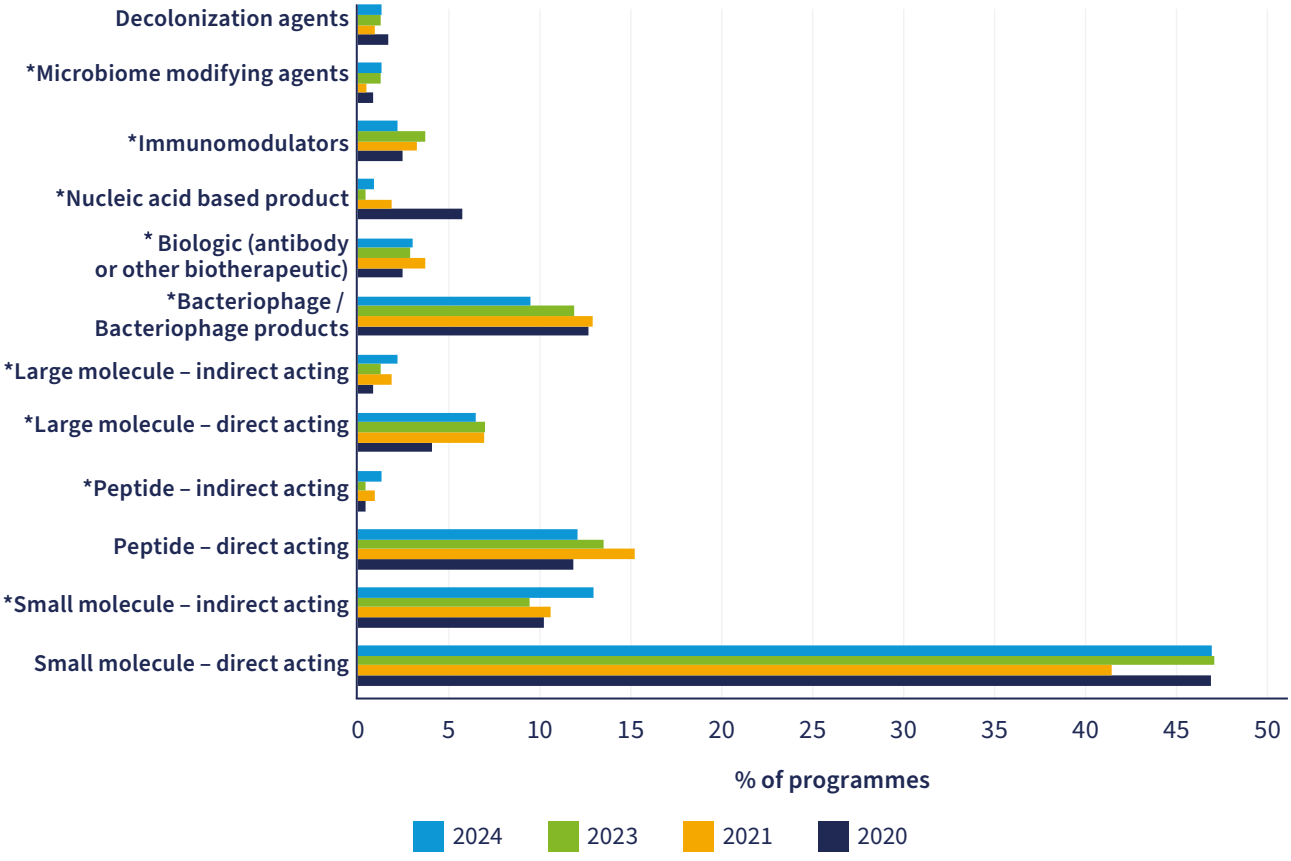
Categorization of preclinical agents

The review reveals a large variety of different agents in preclinical development. Most of the programmes were focused on direct-acting small molecules (n = 109; 47.0%) (Table 8). There were also many direct-acting peptide programmes (n = 28; 12.1%). There were 92 non-traditional products, representing 39.7% of the preclinical pipeline with the largest contributing groups being indirect-acting small molecules (n = 30; 12.9%) and bacteriophage programmes (n = 22; 9.5%).

A total of 178 (76.7%) programmes were developing single agents, while 44 (19%) programmes involved a combination of agents. Only 10 programmes (4.3%) were focused on developing a novel combination with an unapproved partner agent. A comparison of the relative percentages of the preclinical pipeline from earlier analyses, categorized by these different modalities, indicated the relative stability of the pipeline composition, despite the turnover of developers and programmes (Fig. 6). Note that data from 2019 was not included here due to differences in the way programmes were categorized.

The general composition of the preclinical pipeline has remained relatively constant over the years, with between 40 and 50% of the pipeline focused on direct-acting small molecules since 2020. The proportion of non-traditional agents has consistently ranged between 38 and 42.5% of the total pipeline (Fig. 6).

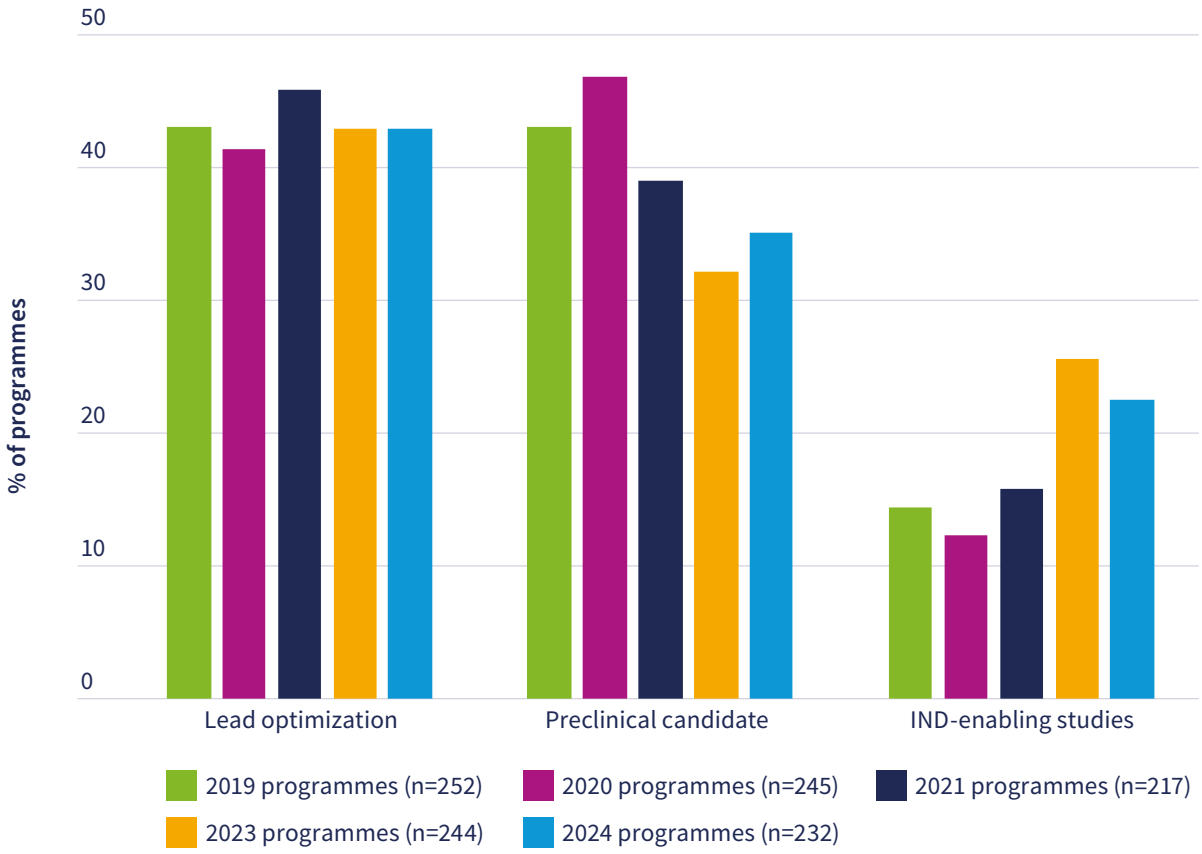
Fig. 6. Categorization of preclinical pipeline projects by biological modality over the last three pipeline reviews



Note: Non-traditional modalities are shown with an asterisk *.

To understand the dynamics of the ecosystem, several analyses of the progression of the preclinical pipeline in 2024 were performed and compared to past analyses. The programmes were grouped by their self-declared preclinical development stage and compared to data collected in previous years (Fig. 7). The proportions of programmes in each stage of development have remained relatively constant over the 6-year period, suggesting that, as projects either fail or progress into clinical development, they are replaced by new programmes.

Fig. 7. Categorization of programmes by stage of preclinical development across five consecutive analyses



IND: investigational new drug.

In the 2024 analysis, 52 programmes (22.4%) were listed as being in the investigational new drug (IND)-enabling phase of preclinical development. It should be noted that 34 of these were also listed in the same phase in 2023, and some even longer, suggesting limited progress due to either scientific reasons or inadequate funding to implement the programme. Given that this phase of experimentation does typically take longer than 12 months depending on the molecule, this will be an important metric to follow year-on-year to appropriately assess the progression of the preclinical antibacterial pipeline. Of the remaining 18 programmes listed in the IND-enabling phase, 12 were new additions and six had transitioned from earlier stages in the 2023 analysis. In 2023, there was a notable increase in this later IND-enabling phase, which has been fairly well maintained in 2024. This suggests the importance of focusing investments and resources in this phase of development as it represents the launching pad for new clinical development programmes.

Five of the programmes listed as IND-enabling in 2023 have initiated clinical studies and three were deemed out of scope due to the updated BPPL. There were eight programmes whose parent company were either liquidated or exited the AMR therapeutic area, and while two of those programmes have been acquired and are still ongoing, the status of the remainder is unknown.

> The high turnover (approx. 33%) of antimicrobial developers underscores the ongoing fragility of the therapeutic R&D ecosystem.

Table 9 shows the 232 products categorized by their antibacterial mode of action (MoA) and self-declared preclinical development stage. Overall, the large number of direct-acting peptide and bacteriophage programmes has resulted in a significant number of products with a direct membrane effect (n = 55; 23.7%). For 19 (8.1%) products, no information on the MoA was available (either unknown or not disclosed).

Table 9. Distribution of programmes by mode of action and preclinical development stage

Mode of action category	Total number (%)	Development stage		
		Lead optimization	Preclinical candidate	IND-enabling
Anti-virulence	20 (8.6)	13	5	2
Cell wall synthesis - β-lactam/β-lactamase inhibitor	5 (2.2)	1	0	4
Cell wall synthesis - other	34 (14.7)	14	13	7
Central metabolism	7 (3.0)	1	4	2
Direct membrane effect	55 (23.7)	16	26	13
DNA replication/synthesis	20 (8.6)	8	2	10
Protein synthesis	18 (7.8)	8	5	5
RNA synthesis	6 (2.6)	5	0	1
Immunomodulation	11 (4.7)	2	6	3
Other cellular function	20 (8.6)	9	8	3
Potentiator or enabling agent	15 (6.5)	10	5	0
Not disclosed	11 (4.7)	7	4	0
Unknown	8 (3.4)	5	1	2
Decolonization	2 (0.9)	0	2	0
Total	**232 (100)**	**99**	**81**	**52**

IND: investigational new drug.

Spectrum of activity

Examination of the preclinical pipeline projects indicated that a substantial number of products (n=75; 32.3%) target a single pathogen, reinforcing the trend towards more targeted therapies rather than broader spectrum agents. However, this relative percentage appears to be decreasing slightly over time (see below). A total of 35 species-specific programmes targeted CPPs, including 21 against *M. tuberculosis* (Table 10). There were 39 programmes directed against high-priority pathogens, driven largely by 22 specifically targeting *P. aeruginosa*, along with eight products directed against both *S. aureus* and *N. gonorrhoeae* (Table 10). This strong emphasis on anti-*P. aeruginosa* programmes likely stems from its designation as a CPP in the original 2017 BPPL. The impact of its repositioning as a high priority pathogen in 2024 on the preclinical pipeline will likely take some time to become apparent, even though investment should not be de-prioritized for this clinically relevant pathogen in hospital-acquired infections.

Table 10. Distribution of species-specific programmes by WHO bacterial priority pathogens list

Organism	Total products[a]	Species-specific products	WHO BPPL
A. baumannii	76	7	Critical
E. coli [b]	90	3	
K. pneumoniae [b]	89	4	
Enterobacter spp. [b]	58	0	
M. tuberculosis	38	21	
Salmonella spp.	27	0	High
Shigella spp.	20	0	
E. faecium	42	1	
P. aeruginosa	91	22	
N. gonorrhoeae	27	8	
S. aureus	80	8	
Group A streptococci	16	0	Medium
S. pneumoniae	44	1	
H. influenzae	20	0	
Group B streptococci	13	0	
Broad G+/G- [c]	8		
Gram-negative [c]	3		
Total		**75**	

[a] Note that products with activity against multiple species will be counted against each species.

[b] Activity against CR and 3GC isolates not always disclosed and so species activity is represented.

[c] Activity against individual bacterial species was not provided.

Examination of the 75 species-specific programmes indicates that products targeting *P. aeruginosa* are distributed across various product types (Table 11) and multiple different MoAs (Table 12).

Table 11. Distribution of species-specific programmes by product type and WHO bacterial priority pathogens list

		Bacterial priority pathogen														
		CRITICAL					HIGH						MEDIUM			
Mode of action category	Total (%)	*A. baumannii*	*E. coli* [a]	*K. pneumoniae* [a]	Enterobacter spp. [a]	*M. tuberculosis*	*Salmonella* spp.	*Shigella* spp.	*E. faecium*	*P. aeruginosa*	*N. gonorrhoeae*	*S. aureus*	Group A streptococci	*S. pneumoniae*	*H. influenzae*	Group B streptococci
Anti-virulence	11		1							7	1	2				
Cell wall synthesis - Other	7	1				3				1	2					
Central metabolism	4					2				2						
Direct membrane effect	16	1	1	3					1	7		3				
DNA replication/synthesis	5	1	1	1						1		1				
Protein synthesis	1					1										
RNA synthesis	3					3										
Immunomodulation	4	1				1					2					
Other cellular function	13	2				9				1	1					
Potentiator or enabling agent	5									3	1	1				
Not disclosed	3	1				1					1					
Unknown	3					1						1		1		
Total	**75 (100)**	**7**	**3**	**4**	**0**	**21**	**0**	**0**	**1**	**22**	**8**	**8**	**0**	**1**	**0**	**0**

[a] Activity against bacteria resistant to carbapenem antibiotics and bacteria resistant to third-generation cephalosporin antibiotics is not always disclosed and so species activity is represented.

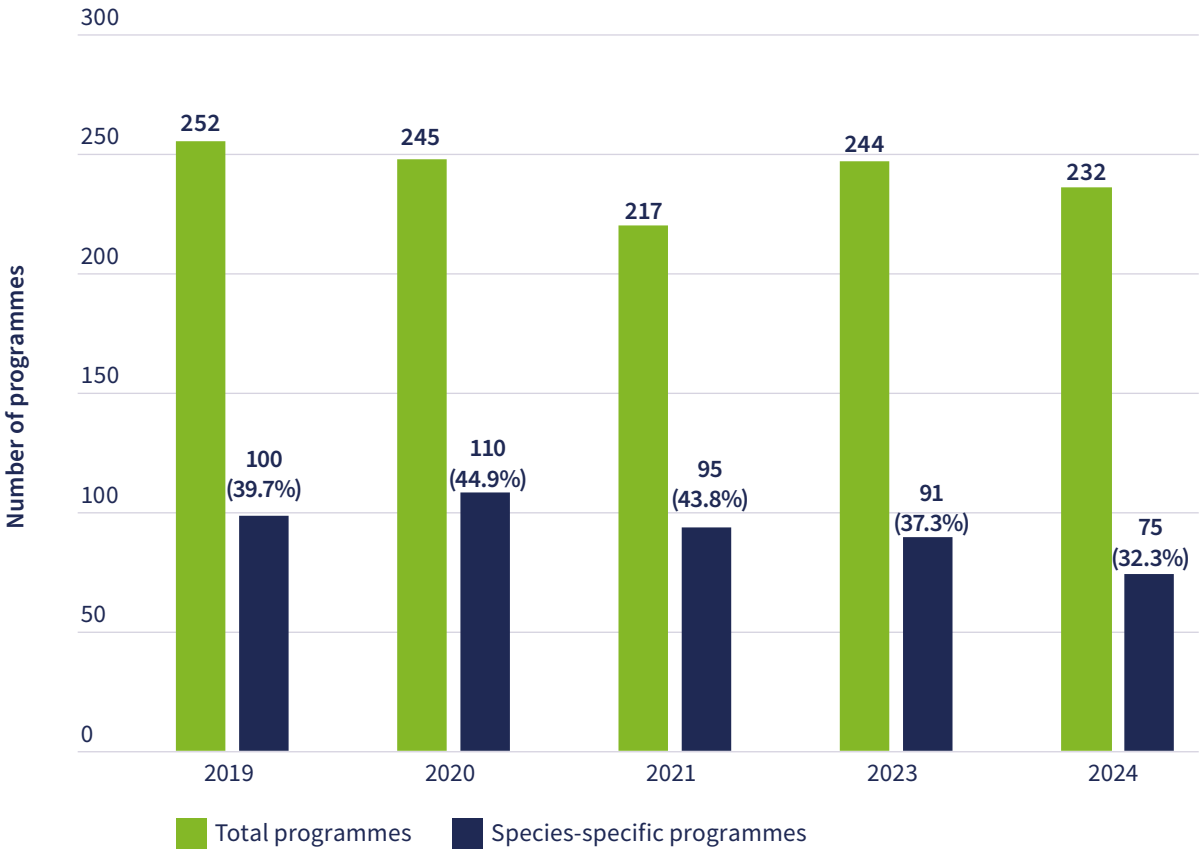
Table 12. Distribution of species-specific programmes by mode of action and WHO bacterial priority pathogen list

		Bacterial priority pathogen														
		CRITICAL					HIGH						MEDIUM			
Mode of action category	Total (%)	*A. baumannii*	*E. coli*	*K. pneumoniae*	Enterobacter spp.	*M. tuberculosis*	*Salmonella* spp.	*Shigella* spp.	*E. faecium*	*P. aeruginosa*	*N. gonorrhoeae*	*S. aureus*	Group A streptococci	*S. pneumoniae*	*H. influenzae*	*Group B* streptococci
Small molecule - direct acting	30	5				17				2	4	1		1		
Small molecule - indirect acting	16					1				10	2	3				
Peptide - direct acting	4					3				1						
Large molecule - direct acting	4			1						3						
Large molecule - indirect acting	2										2					
Bacteriophage/bacteriophage products	13	1	2	3					1	4		2				
Biologic (antibody or other biotherapeutic)	5	1	1							2		1				
Nucleic acid-based products	1											1				
Total	**75 (100)**	**7**	**3**	**4**	**0**	**21**	**0**	**0**	**1**	**22**	**8**	**8**	**0**	**1**	**0**	**0**

[a] Activity against bacteria resistant to carbapenem antibiotics and bacteria resistant to third-generation cephalosporin antibiotics is not always disclosed and so species activity is represented.

An analysis of species-specific programme trends across the five previous preclinical pipeline reviews is shown in Fig. 8. While the overall number of programmes has remained relatively stable since 2019, the last two reviews indicate a downward trend, with species-specific programmes accounting for about one third of the pipeline in 2024. Over the last five pipeline analyses, the two dominant target pathogens have remained the same. The number of products/programmes targeting *P. aeruginosa* have fluctuated between 18% in 2019 and 29.3% in 2024, whereas those for *M. tuberculosis* have shown greater variation, ranging between a high of 43% in 2019 to a low of 21.1% in 2021.

Fig. 8. Analysis of the species-specific programmes across five consecutive preclinical pipeline reviews



Geographical distribution

The number of projects and institutions in 2024 remained consistent with the previous pipeline reviews (Fig. 9), despite significant turnover of the research groups (see below). Of the 250 programmes recorded in 2019, approximately 145 did not appear in any subsequent year (Fig. 10). The 2024 preclinical pipeline analyses highlight the wide geographical distribution of developers, located across five WHO regions (Fig. 10A) and originating from 29 different countries (Fig. 10B). However, the majority of data used for the 2024 survey originated from groups in the European Region (n= 67, 45.3%) and the Region of the Americas (n=61, 41.2%). The global distribution of preclinical products has remained relatively stable across all five analyses undertaken since 2019. Of note in the African Region (AFR) and Eastern Mediterranean Region (EMR), preclinical development is minimal.

Fig. 9. Total number of preclinical programmes (green) and unique groups[3] developing the products (blue) across the five pipeline analyses performed since 2019

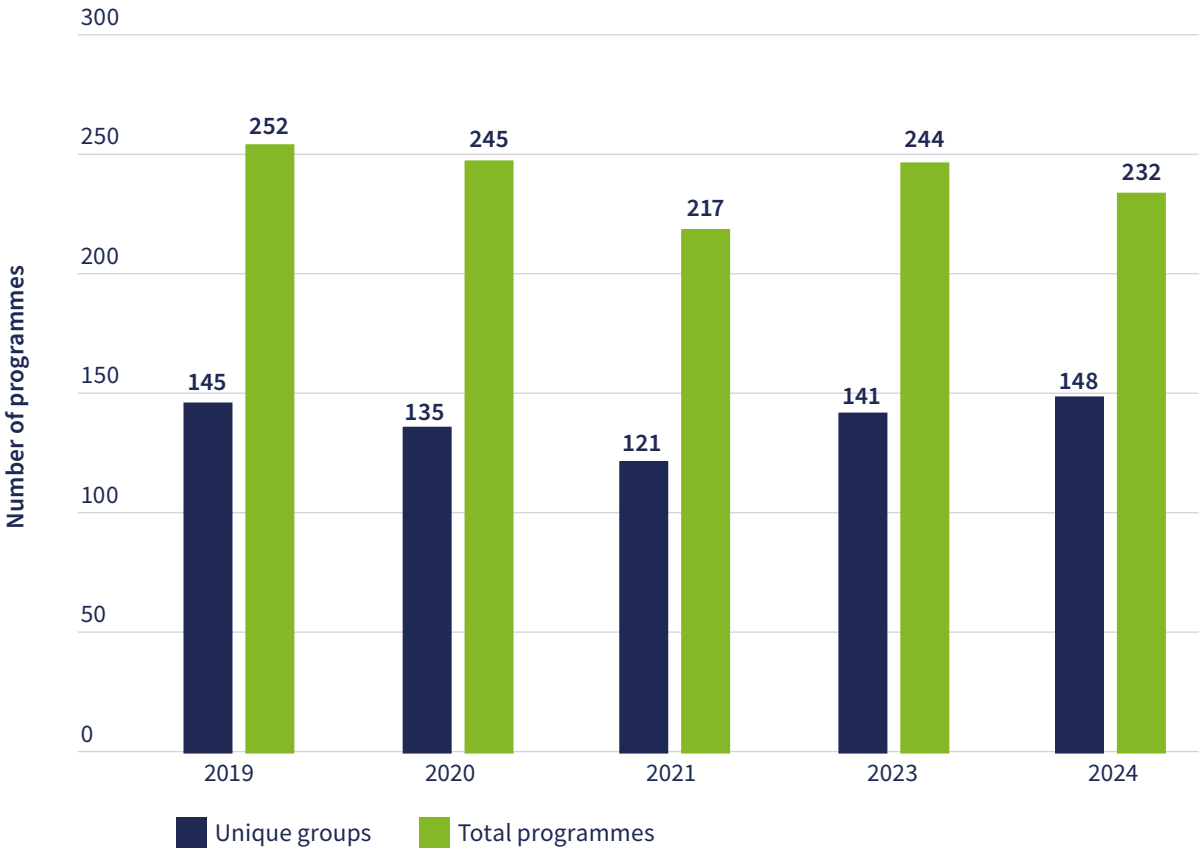
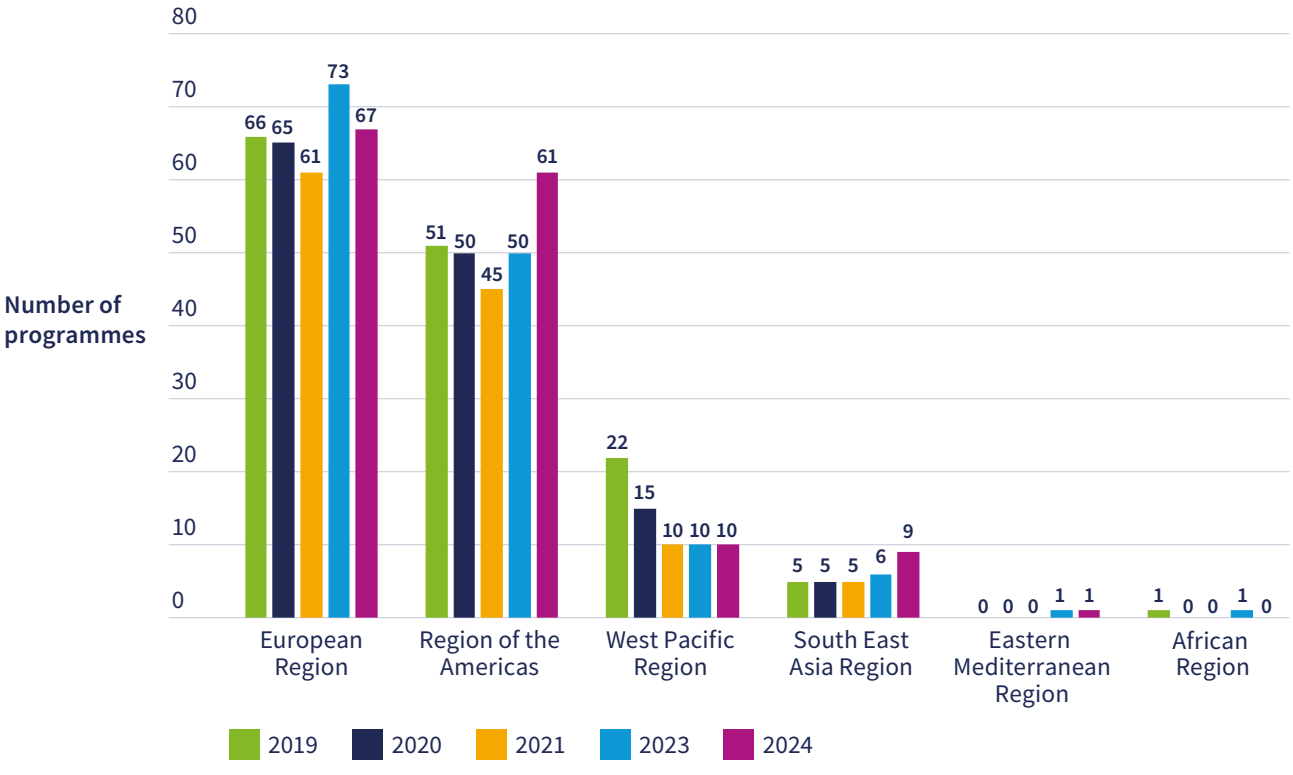
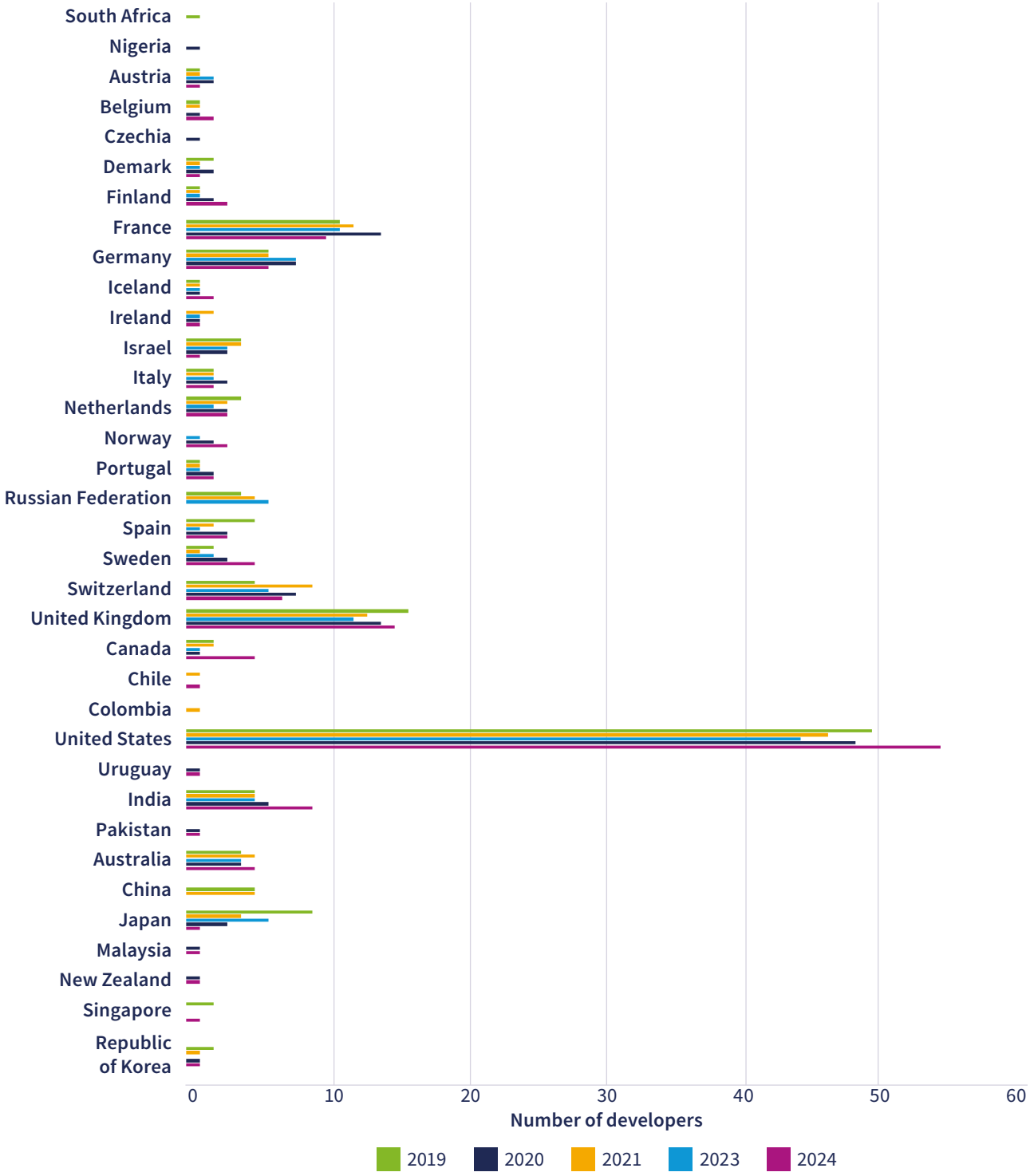


Fig. 10. Geographical distribution of the 148 institutions with preclinical pipeline projects across the 2019–2024 analysis shown by WHO geographical regions (panel A)



[3] This refers to the number of developers.

Fig. 10. Geographical distribution of the 148 institutions with preclinical pipeline projects across the 2019–2024 analysis shown by country (panel B).



Conclusion

Building upon the findings from the WHO 2023 antibacterial agents report, this current analysis underscores that there are still too few agents in clinical development capable of effectively targeting critical Gram-negative bacteria. New innovative strategies are needed to contrast the increasingly urgent global threat of drug resistance to existing antibacterial agents; however, only a limited number of products in the clinical pipeline have data showing no cross-resistance and may be considered potentially innovative. No short-term support seems to come from the development of non-traditional agents. Although the first non-traditional drug targeting WHO critical pathogens, Ftortiazinon, was recently approved in the Russia Federation, data from Phase 2/3 trials showing its efficacy and safety are at present not publicly available and thus no sound evaluation of the clinical benefit of the drug is possible, as yet.

The primary focus of the preclinical pipeline remains on Gram-negative pathogens, although the shift towards narrow-spectrum agents focusing on a single pathogen appears to have decreased slightly over the past two years. The development of species-specific agents will also likely require increased use of rapid diagnostics both for patient stratification and enrolment during clinical trials. While there is a broad geographical distribution of preclinical pipeline projects as well as a large variety of product types, these remain heavily focused toward the European Region and the United States.

4

R&D priorities to strengthen the antibacterial pipeline

4. R&D priorities to strengthen the antibacterial pipeline

During the seventh Advisory Group consultation held on 30 January 2025, experts discussed key areas to steer the R&D of novel antibacterial agents and strengthen the current pipeline. This discussion builds on the policy brief on Antibacterial pipeline trends and recommendations to enhance research and development, published in 2024 by WHO, in which each priority was described in detail *(19)*. During the intervening period, the overall R&D priorities outlined have not changed. The key priority areas identified during the consultation and based on expert opinion include (Fig. 11):

Fig. 11. Research and development priorities to strengthen the antibacterial pipeline

Notes: SMEs: small and medium enterprises; LMICs: low- and middle-income countries.

Prioritize innovation: Identifying new ways to defeat bacteria is a critical step in the fight against AMR. Bacteria keep evolving under the selective pressure of any new antibacterial agents we expose them to, and this generates new and smarter mechanisms of drug resistance. Globalization, travel, natural disasters and wars all have an impact on how quickly resistance spreads. Therefore, we must adopt a culture of continuous innovation to ensure a sustainable pipeline of innovative therapies. They should be able to overcome multiple steps of resistance, to ensure a quick and complete pathogen eradication and – ideally – with a lower propensity for selective pressure. We need substantial investments in the R&D of antibiotics targeting the most serious infections, with a strong emphasis on innovation to stay ahead of bacterial evolution. The use of combinations of single-

targeted agents, as is done with *M. tuberculosis*, HIV and hepatitis C virus, to reduce resistance selection, should be seriously explored. Additionally, investment in diagnostic solutions is essential for appropriate use in patients and to safeguard these public health goods.

Improve access: Available, affordable and effective antibiotics are crucial to our global health security agenda. For novel antibiotics, global equitable access strategies should be built within the corresponding R&D plan. Financial incentives should be sustainable, linked with innovation and be of adequate scale. To favour product introduction in low- and middle-income countries (LMICs), registration pathways within national regulatory authorities can leverage global reliance mechanisms *(20)*. Access strategies should also include stewardship considerations to safeguard antibiotic use while ensuring availability to patients.

Paediatric treatment options and oral formulations: We must also commit to delivering novel medicines and diagnostics to patients, providing long-term solutions to this crisis in a holistic fashion, that accounts for the needs of the different target populations including the most vulnerable, such as children. The availability of oral formulations for antibiotics plays a pivotal role in stepping down patients and facilitating outpatient treatment. Oral formulations in the 2025 pipeline are limited (34%; 31/91 excluding TB agents) and represent a significant unmet medical need.

Support R&D in LMICs: Over 90% of clinical programmes for antibiotics are led by developers in high-income and upper-middle-income countries. LMICs face significant challenges in antibacterial R&D due to economic constraints that limit expertise and training. Additionally, there is an urgent need for reliable post-approval usage data for newly approved antibiotics to assess their effectiveness in real-life scenarios, especially in LMICs where the impact of negative outcomes is more severe.

Expand R&D for non-traditional agents: The development of certain classes of non-traditional agents for commercial use is a relatively new endeavour and can be complicated by the lack of understanding of how these molecules perform in the standard preclinical models, and therefore the relevance to how observed effects would potentially translate clinically to humans. Bacteriophages are the most represented group among non-traditional agents. To further accumulate scientific evidence that can eventually support the integration of bacteriophages and phage-based solutions in clinical practice for large scale use, including in LMICs, the Advisory Group recommended the development of a global roadmap for bacteriophages, including a gap analysis and recommendations for R&D and access with the involvement of key implementing partners and developers.

In conclusion, to strengthen the antibacterial pipeline several areas of R&D of novel antibacterials should be enhanced. We need innovation across multiple fronts, including: drug discovery; translation (especially for non-traditional agents); access; clinical use with rapid diagnostics; and novel funding strategies to repair the broken market and provide adequate support to the SMEs that today are driving the antibiotic R&D and innovation ecosystem.

5

Next steps

5. Next steps

WHO will continue to monitor the clinical and preclinical pipeline on a regular basis and make this data available on the WHO R&D Health Observatory *(21)*.

WHO will continue to promote innovation, collaboration and transparency in the scientifically and economically challenging field of antibacterial development, to collectively move forward in developing the critically needed products to prevent and treat drug-resistant bacterial infections worldwide.

6

Methods

6. Methods

The present update adheres to the methodology described in the WHO publication 2023 Antibacterial agents in clinical and preclinical development *(3)* published in June 2024. The methodology covers the data gathering, the activity and the innovation assessment.

During the Advisory Group consultation held on 30 January 2025, the activity and innovation assessments were discussed at product level and from a methodological perspective. Therefore, a further clarification regarding the innovation assessment is reported below.

The key criterion for innovation is the demonstration of additional clinically significant benefit exerted by an individual agent. This can only be assessed when the clinical developmental programme is completed, and in some cases re-evaluated when real-world data are available. For the scope of this review, that includes candidate antibiotics in clinical development, an agent was considered potentially innovative if it had no (known) cross-resistance to existing antibacterials. Lack of cross-resistance depends upon demonstrated microbiological activity in vitro and efficacy in vivo against bacteria resistant to other antibacterials of the same or different class. Microbiological activity can be measured by in vitro susceptibility testing using diverse panels of genetically characterized isolates, combined with genetic characterization of mutants and molecular structural analysis, in addition to large-scale surveillance testing against contemporary isolates that display non-susceptibility to other antibacterial drugs.

Surrogate predictors for the absence of cross-resistance that were also assessed include the following:

- new class (new scaffold);
- new target (new molecular binding site); and
- new MoA.

Surrogate criteria for lack of cross-resistance are used as predictors of possible no cross-resistance when in vitro data on cross-resistance are still scanty, not publicly available or in case of first-in-class agents. When data on cross-resistance are available, surrogate criteria are interpreted as supporting elements that reinforce/contribute to explain the observed in vitro lack of cross-resistance.

Each agent in clinical development or recently approved was evaluated against the four innovation criteria. If products do not meet the innovation criteria, it does not necessarily mean that they do not have clinical utility for specific patients. For example, a safety profile that improves on the SOC, a less invasive route of administration (e.g. oral), less frequent administration, better clinical outcomes or increased activity against priority pathogens could provide improvements but need to be proven in clinical trials. However, pharmaceutical optimization of existing products is not reviewed in this report.

7

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8

Annexes

Annex 1
Declaration of interests of Advisory Group members

Management of conflicts of interest was a priority throughout the analysis and decision-making for the antibacterial clinical and preclinical pipeline. The declarations of interest (DOIs) were collected and thoroughly reviewed by the WHO AMR Division following WHO standard operating procedures.

Prior to the Advisory Group meeting, all the experts submitted written disclosures of competing interests that had arisen during a period of four years preceding the WHO advisory work and that were relevant for consideration before their confirmation as participants in the meeting, including employment by a commercial entity, consultancy, board or advisory board membership, lecture fees, expert witness income, industry-sponsored grants (including contracted research, patents received or pending, royalties, stock ownership or options), other personal financial interests, as well as whether the institution or employer had a financial relationship with a commercial entity that had an interest in antibacterial products evaluated by the group.

Experts were also asked to disclose academic or scientific activities that included leadership of research or grant applications, in either primary clinical studies or reviews, directly bearing on a decision about an antibacterial product. In addition, at the start of the meeting, all members were asked to provide updates about their declaration if any new conflicts had arisen in the meantime.

The experts who declared no perceived conflicts of interest were Antoine Abou Fayad, Habib Hasan Farooqui, Khalid Eljaaly, Prabha Fernandes, Stephan Harbarth, Sam Kariuki, Roman Kozlov, Christian Lienhardt, Taslimarif Saiyed, Nusrat Shafiq, Melvin Spigelman and Norio Ohmagari. These experts were allowed full participation in the meeting.

The experts who disclosed potentially significant conflicts of interest were Cesar Arias, Greg Basarab, Mark Blaskovich, Yohei Doi, Shawna McCallin, Mical Paul, John Rex, Lynn Silver, and Mo Yin.

Cesar Arias declared royalties from a book chapter related to enterococcal infections.

Greg Basarab disclosed having provided consulting services to Arrepath Inc., CARB-X, and Enable 2. He also disclosed serving in the Scientific Advisory Board of the Grand Challenges African Drug Discovery Accelerator, and GARDP.

Mark Blaskovich reported having provided consultancy in the previous four years to Lixa (SAB). He also declared honoraria for presentations on antimicrobial agents/ antibiotic research by Pfizer Australia.

Yohei Doi reported having provided consultancy in the previous four years to Shionogi, GSK, Meiji Seika Pharma, Moderna, Pfizer, and AbbVie being part of their SAB.

Shawna McCallin reported having provided consultancy, received research support, and having received travel support in the previous four years from GSK, Swiss Leading House Africa and Biotechnet.

Mical Paul reported having received research support in the previous four years from Shionogi.

John H. Rex disclosed having provided consulting services, received research grants/support, held shares or commercial interest in the previous four years from Advent Life Science, Basilea Pharmaceutica (SAB), Bugworks Research Inc. (SAB), and AMR Action Fund (SAB). He also declared shares from AstraZeneca Pharmaceuticals, F2G, and Advent Life Sciences.

Lynn Silver reported having provided consultancy, reviewed programmes or grants in the previous four years for Forge/ Blacksmith, IOI/Germinate, Novo-Repair Fund, AMED-Japan, ENABLE I and II, NIH, Uppsala, EU GNA NOW, IMI2, Dartmouth and Notre Dame.

Mo Yin reported having received in the previous four years research support from Pfizer.

Following assessment of the DOIs, Greg Basarab, Mark Blaskovich, Yohei Doi, Shawna McCallin, Mical Paul, John Rex, Lynn Silver, and Mo Yin were excluded from discussions involving products from commercial entities or other organizations listed above.

After having consulted the WHO Compliance, Risk Management and Ethics Office, Lloyd Czaplewski was invited as technical adviser. He disclosed that he provided consultancies to Clarametyx, Novo Repair Impact Fund, Novo Holdings, and Curza. He also declared a brief indirect consultancy in 2021 now ended with a tobacco company interested in diversifying interests including antibacterial therapies.

The following participants were invited as observers, no DOI was formally reviewed as such and they were granted full participation under the WHO rules of procedures governing AG meetings: Raquel Rodriguez, Radu Botgros, Martin Heidecker, François Franceschi and Lesley Ogilvie.

All reported interests were disclosed to the meeting participants by the WHO technical unit in a slide show presentation. The interests disclosed in this report will also be disclosed in subsequent relevant publications.

Annex 2
Cell wall inhibitors – β-lactams and β-lactamase inhibitors

Product name (INN or company code):	Cefepime + taniborbactam (VNRX-5133)
Pharmacology: chemical class and MoA:	β-Lactam/β-lactamase inhibitor (BLI) combination. Taniborbactam (VNRX-5133) is a boronate-based BLI with activity against Class A, C and D β-lactamases, through reversible covalent inhibition (and slow dissociation). It also exerts action on metallo-β-lactamase (MBL) through competitive inhibition. Cefepime is a fourth-generation cephalosporin.
Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.) with details of activity on carbapenems for β-lactam/BLIs:	Inhibitory activity against some CREs: Class A (ESBL CTX-M, KPC-2,-3; Class B (MBLs, especially New Delhi MBL (NDM), not universal *(3,4)*; and Verona Integron-encoded MBL (VIM), not imipenemase (IMP) *(5)*; heteroresistance described by Abbott et al. (2023) *(6)*; and Class D (OXA-48 *(1)*). Activity has been shown against carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) *(7,8)*. In vivo data are described in a neutropenic murine thigh infection model, murine cUTI model and neutropenic murine pneumonia model *(9–11)*. Cross-resistance with aztreonam-avibactam has been shown *(12)*.
Sought therapeutic indication:	Serious Gram-negative infections, including cUTI and HABP/VABP (both supported by BARDA (Biomedical Advanced Research and Development Authority) in the United States).
Pharmaceutical form, route of the administration and proposed posology:	2/0.5 g q8h iv (2 h infusion) for cUTI; a 4 h infusion is proposed for the HABP/VABP indication; however, only data from a Phase 1 trial investigating the bronchopulmonary disposition of iv cefepime-taniborbactam are currently available *(13)* (NCT03870490).
Phase of clinical development:	NDA for the indication in UTI. In February 2024, the FDA requested additional chemistry, manufacturing and controls and related data about the drug, testing methods, and manufacturing process. The companies said the FDA did not identify clinical safety or efficacy issues, nor requested any new clinical trials.

Product name (INN or company code):	Cefepime + taniborbactam (VNRX-5133)
Clinical trial(s):	• **Phase 3: A double-blind, randomized, active-controlled, non-inferiority study evaluating the efficacy, safety and tolerability of cefepime-taniborbactam, administered q8h iv over a 2 h period, compared with that of meropenem, administered q8h iv over 30 min, in adults with cUTI, including AP (NCT03840148).** – Study population: 661 adult patients diagnosed with cUTI or AP were randomized, of whom 436 patients (66.0%) infected with a Gram-negative pathogen determined to be non-resistant to study drugs were included in the microbiologic intent-to-treat (micro-ITT) population, including 42.2% with AP and 57.8% with cUTI. Patients were randomized 2:1 to cefepime-taniborbactam 2.5 g iv q8h or MEM 1 g iv q8h for 7 days or up to 14 days in patients with bacteraemia. – Time period: 7 August 2019 to 14 December 2021. – Sites: The study was conducted at 78 sites in 14 countries (Argentina, Brazil, Bulgaria, China, Croatia, Latvia, Mexico, Peru, Romania, Russian Federation, Serbia, Türkiye, Ukraine, United States). – Primary end-point: The composite successful outcome of clinical cure (i.e. symptom resolution or return to premorbid baseline of all UTI core symptoms and patient is alive, and patient has not received additional antibacterial therapy for cUTI) and microbiological eradication (defined as any Gram-negative target pathogens found at study entry ≥ 105 CFU/mL eradicated to < 103 CFU/mL) at test-of-cure (TOC) visit (after receiving three rounds of iv therapy, days 19–23). The non-inferiority margin was –15.0%, and a pre-specified test for superiority for the primary end-point was performed following confirmation of non-inferiority. – Primary efficacy evaluation was performed in the micro-MITT population, for patients infected with a Gram-negative pathogen determined to be non-resistant to study drugs. • **Phase 3: NCT06168734 a Phase 3 study to evaluate cefepime-taniborbactam compared to meropenem in adults with VABP or ventilated hospital-acquired bacterial pneumonia (vHABP).** – Study population: The study will randomize approximately 316 patients with vHABP or VABP into two groups in a 1:1 ratio (158 patients to cefepime-taniborbactam; 158 patients to meropenem). Cefepime-taniborbactam will be administered 2.5g q8h intravenously (IV) over a 4-hour period for 7 days to 14 days at the investigator's discretion. Meropenem will be administered 2g q8h iv over 4 hours for 7 days to 14 days at the investigator's discretion. – Time period: October 2024 (not yet recruiting as per 25 October) to September 2027 – Sites: not specified – Primary end-point: The primary end-point is all-cause mortality through study day 14. – Primary efficacy evaluation: The primary end-point is evaluated in the ITT population and is based on the patient's survival status through study day 14.

Product name (INN or company code):	Cefepime + taniborbactam (VNRX-5133)
Clinical study results:	In **Phase 3 trial (NCT03840148)**: Cefepime-taniborbactam met the primary efficacy end-point of statistical non-inferiority to meropenem in the micro-ITT population at TOC with composite microbiologic and clinical success occurring in 70.6% of cefepime-taniborbactam-treated patients and 58.0% of meropenem-treated patients. Cefepime–taniborbactam was statistically superior to meropenem for the primary end-point at TOC (treatment difference (cefepime-taniborbactam + meropenem), 12.6 percentage points (95% CI: 3.1–22.2; P = 0.009)). Differences in treatment response were sustained at late follow up (trial days 28–35), when cefepime-taniborbactam had higher composite success and clinical success *(14)*. – Adverse events: Treatment emergent adverse events (TEAEs) were observed in 35.5% of cefepime-taniborbactam patients and 29.0% of meropenem patients. Serious adverse events occurred in 2.0% and 1.8% of cefepime-taniborbactam and meropenem patients, respectively. The most common TEAEs were headache (cefepime-taniborbactam 6.1%, meropenem 3.7%) and diarrhoea (cefepime-taniborbactam 4.1%, meropenem 2.3%). The frequency of serious adverse events was similar in the two groups. While **in Phase 3 (NCT06168734)**: The trial met its primary end-point. Composite success occurred in 207 of 293 patients (70.6%) in the cefepime-taniborbactam group and in 83 of 143 patients (58.0%) in the meropenem group. Cefepime-taniborbactam was superior to meropenem regarding the primary outcome (treatment difference, 12.6 percentage points (95% CI: 3.1–22.2; P=0.009)). Differences in treatment response were sustained at late follow up (trial days 28 to 35), when cefepime-taniborbactam had higher composite success and clinical success. Adverse events: The frequency of adverse events was slightly greater in the cefepime-taniborbactam group (35.5%) than in the meropenem group (29.0%), with headache, diarrhoea, constipation, hypertension and nausea the most frequently reported; the frequency of serious adverse events was similar in the two groups.

Product name (INN or company code):	Benapenem
Pharmacology: chemical class and MoA:	Benapenem is a broad-spectrum β-lactam (carbapenem) that inhibits bacterial cell wall synthesis. It is structurally related to ertapenem *(15)*.
Spectrum of activity and potential resistance:	Unpublished in vitro preclinical data showed that benapenem was a time-dependent bactericidal drug and had an antibacterial spectrum similar to that of other carbapenems, with an MIC50 less than 1 mg/L to most bacteria *(16,17)*. In vivo research has shown potential for treating complicated ascending UTIs, such as AP caused by *Escherichia coli (18)*.
Sought therapeutic indication:	Treatment of cUTI or AP.
Route of administration:	Intravenous injection administered as a 1 g iv infusion over 30 min once daily for 7–14 days.
Phase of clinical development:	Completed **two Phase 1 trials and one Phase 2/3 trial** *(15)*: – a study to assess efficacy and safety intravenous benapenem in patients with cUTI or AP (NCT04505683); – a pharmacokinetic (PK) study of benapenem in subjects with renal impairment (NCT04476407); and – a single-dose PK study of benapenem in healthy subjects (NCT03588156).

Product name (INN or company code):	Benapenem
Clinical trial(s):	• **Phase 2/3 (NCT04505683):** Randomized, double-blind, positive-control, multicentre, prospective study to assess efficacy and safety of iv benapenem injection administered as a 1 g iv infusion vs ertapenem for iv injection administered as a 1 g iv infusion, in 112 participants with cUTI or AP. – Patient population: 18 to 75 year-olds with a diagnosis of cUTI or AP, with no recent antibiotic therapy more than 24 h within 72 h prior to randomization or other exclusionary diagnosis. – Time period: 13 December 2018 to 8 May 2020. – Sites: Peking University First Hospital, Beijing, China. – Primary end-point: Percentage of patients with clinical cure at TOC visit (time frame: day 7 +/– 1 day after end of treatment (EOT)). Clinical cure is defined as complete resolution of signs, symptoms and related laboratory tests of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted.
Clinical study results:	No information on the results of the Phase 2/3 trial completed in May 2020 is currently available.
Preclinical PK and safety/adverse events:	The clearance and elimination half-life (t1/2) of benapenem in rats is 0.18 L/h/kg of body weight and 2.3 h, respectively *(18)*. From published results of the first-in-human safety, tolerability and pharmacokinetics study of benapenem, there were no serious adverse events. Minor events included: white blood cell (WBC) count decreasing (two cases), alanine aminotransferase (ALT; two cases) or aspartate transaminase (AST; one case) increasing, and erythema (one case) *(17)*.

Product name (INN or company code):	Cefepime + zidebactam (WCK 5222)
Pharmacology: chemical class and MoA:	Zidebactam is a diazabicyclooctane (DBO)-type BLI with activity against *P. aeruginosa (19)*, *A. baumannii (20)* and some Enterobacterales *(21)*, due to penicillin-binding protein 2 (PBP2) inhibition and inhibition of Class A, C and some D β-lactamases. Cefepime is a fourth-generation cephalosporin, and an inhibitor of bacterial cell wall synthesis.
Spectrum of activity and potential resistance:	Synergistic activity of this combination against Enterobacterales (including extended-spectrum beta-lactamase (ESBL) and *Klebsiella pneumoniae* carbapenemase (KPC) producers), but elevated MICs in MBL producers from in vitro data *(22–25)*. In vivo humanized exposure of the combination showed synergistic activity against CRAB and CRPA in a neutropenic murine lung infection model and neutropenic thigh infection model, despite elevated MICs *(25–29)*. Two recent case reports described activity in extensively drug-resistant New Delhi MBL (NDM)-expressing *P. aeruginosa* infection both in an intra-abdominal infection-induced sepsis patient and an acute T-cell leukaemia patient *(30,31)*. Note: *The enhanced in vivo bactericidal action of the combination, despite elevated MICs, is thought to be due to zidebactam-induced reduction of the percentage of time that the cefepime free drug concentration remains above the minimum inhibitory concentration (MIC) (% fT > MIC) required for in vivo killing of A. baumannii and P. aeruginosa. Human simulated regimens achieved eradication of CRAB and CRPA up to a MIC of 64 mg/L (2–3 log10 kill) in translational animal models (25,27,28)*. Resistance: Cefepime-zidebactam showed activity against aztreonam-avibactam-resistant NDM-like producing *E. coli (29)*.
Sought therapeutic indication:	cUTI and AP (currently in Phase 3 clinical development), and HABP/VABP (not yet in clinical development). A Phase 1 study (NCT03630094), to determine plasma and intrapulmonary concentrations in healthy individuals, was completed in 2017 *(32)*.
Pharmaceutical form, route of administration and proposed posology:	3 g (2 g cefepime + 1 g zidebactam) iv q8h.

Product name (INN or company code):	Cefepime + zidebactam (WCK 5222)
Phase of clinical development:	Phase 3.
Clinical trial(s):	• **Phase 3 (NCT04979806):** A randomized, double-blind, multicentre, non-inferiority study to evaluate the efficacy, safety and tolerability of cefepime-zidebactam (3 g (2 g cefepime + 1 g zidebactam) iv q8h) vs meropenem (1 g iv q8h) for treatment of hospitalized adults with cUTI or AP. – Study population: Approximately 528 hospitalized adult subjects (≥ 18 years of age) diagnosed with cUTI or AP, based on a combination of clinical symptoms and signs plus the presence of pyuria, will be randomized to receive either treatment for 7–10 days. – Time period: August 2022 to May 2024. – Sites: 46 sites located in nine countries (Bulgaria, China, Estonia, India, Lithuania, Mexico, Peru, Poland, United States). – Primary end-point: Percentage of subjects with overall success at TOC (day 17+2 days). Overall success is defined as complete resolution of cUTI or AP symptoms present at study entry (or return to premorbid state) and no new cUTI or AP symptoms, together with microbiologic eradication of the bacterial pathogen found at study entry (reduced to < 1000 CFU/mL).

Product name (INN or company code):	Xeruborbactam (QPX7728) + β-lactam (S-649228) (OMNIvance iv, OROvance per os)
Pharmacology: chemical class and MoA:	Xeruborbactam (QPX7728) + β-lactam (S-649228) is a bicyclic boronate BLI (new class) under development with a still undisclosed β-lactam. The preclinical development included testing in combination with several β-lactams. Phase 1 clinical studies are testing the combination with cefiderocol. QPX7831 is the oral prodrug of xeruborbactam (QPX7728) *(33–35)* undergoing clinical testing in phase 1 studies with ceftibuten.
Spectrum of activity: activity on pathogens (confirmed or potential) with details of activity on carbapenems for β-lactam/BLIs:	In vitro, xeruborbactam displays broad-spectrum β-lactamase inhibition, showing activity against numerous serine and MBLs, including carbapenemases such as Class A KPC, Class B NDM and VIM, and Class D OXA-48 in CREs and OXA-23 in *A. baumannii*, respectively *(35–37)*. It was tested in vitro, in combination with meropenem; compared with other BLI combinations (e.g. meropenem-vaborbactam, ceftazidime-avibactam and imipenem-relebactam), xeruborbactam-meropenem showed activity against CREs with multiple resistance mechanisms *(38)*. Limited data show in vitro activity against *P. aeruginosa (39,40)*. In in vivo experiments, xeruborbactam at 12.5, 25 or 50 mg/kg of body weight in combination with multiple β-lactams (including cephalosporins, carbapenems and monobactams) against carbapenem-resistant *K. pneumoniae* (CRKP) isolates, in a neutropenic mouse thigh infection model, showed bacterial killing utility at all doses *(41)*. This inhibitory activity of xeruborbactam was also seen in mouse thigh and lung infection models of infections, where in combination with meropenem showed efficacy against KPC-producing strains of Enterobacteriaceae (*K. pneumoniae*, *Enterobacter cloacae*), OXA-23-producing strains of *A. baumannii* and multidrug-resistant (MDR) strains of *P. aeruginosa* that did not respond to meropenem alone *(42)*.
Sought therapeutic indication:	Xeruborbactam (QPX7728) + β-lactam (S-649228) is being studied as treatment in carbapenem-resistant *Acinetobacter*, *Pseudomonas* and Enterobacterales infections. The oral formulation in combination with ceftibuten is intended as treatment of CRE.
Route of administration:	Intravenous and oral.
Phase of clinical development:	Phase 1.

Product name (INN or company code):	Xeruborbactam (QPX7728) + β-lactam (S-649228) (OMNIvance iv, OROvance per os)
Clinical trial(s):	• **Phase 1 complete (NCT04380207):** Randomized, double-blind, placebo-controlled, ascending single and multiple-dose study of the safety, tolerability and PK of iv QPX7728 alone and in combination with QPX2014 in 82 healthy adults (18–55 years old). • **Phase 1 complete (NCT05072444):** Randomized, double-blind, single-dose, drug–drug interaction study to determine the impact of co-administration of QPX7728 on the PK of QPX2014 in 12 healthy adult subjects (18–55 years old). • **Phase 1 complete (NCT03939429):** Randomized, double-blind, placebo-controlled, ascending single and multiple-dose study of the safety, tolerability, PK of oral QPX2015 in 40 healthy adult subjects (18–55 years old). • **Phase 1 (NCT06079775):** Open-label, drug–drug interaction, and randomized, double-blind, controlled, multiple-dose pharmacokinetics and safety study of xeruborbactam oral prodrug (QPX7831) in combination with ceftibuten in healthy adult participants. • **Phase 1 (NCT06547554, recruiting):** Randomized, double-blind, placebo-controlled, drug–drug interaction, pharmacokinetics and safety study of cefiderocol in combination with xeruborbactam in healthy adult participants. • **Phase 1 complete (NCT06157242):** Open-label, single-dose study to determine the safety and pharmacokinetics of ORAvance (ceftibuten/xeruborbactam oral prodrug [QPX7831]) in participants with renal impairment.
Clinical study results:	Phase 1 study results: IV formulation *(43)* xeruborbactam was safe and well-tolerated when administered alone and in combination with meropenem. After a loading dose, steady state plasma levels were reached within the first day of treatment. Xeruborbactam has a long elimination half-life. Oral formulation *(44)* xeruborbactam was safe and well tolerated at all doses tested. The formulation is 90–100% orally bioavailable and has linear plasma PK properties that support once-daily administration. Stasis was achieved with once-daily doses of 400 mg and >1-log of bacterial killing with 800 mg or higher.
Preclinical PK and safety/adverse events:	Plasma protein binding in the rat is 85% and it displays oral bioavailability in fasted rats, with values ranging between 43% and 53% at doses of 30–100 mg/kg, whereas it declined to 24–28% at higher doses *(35)*. QPX7728 was studied in a 7-day pilot toxicology study at daily doses of 30, 100 and 300 mg/kg in rats (five males and five females per dose level) administered by iv infusion. No changes were observed (tissue histology and clinical chemistry) *(35)*.

Product name (INN or company code):	Funobactam (XNW4107) + imipenem + cilastatin
Pharmacology: chemical class and MoA:	Funobactam (XNW4107) is a DBO-type BLI that confers protection against hydrolysis by Ambler Class A, C and D β-lactamases, including OXA-23 and -24 being developed in combination with imipenem and cilastatin. Imipenem is a carbapenem inhibitor of bacterial wall synthesis. Cilastatin is a renal dehydropeptidase inhibitor that is used to prevent degradation of imipenem. The XNW4107 combination is under development against both cUTI and HABP/VABP *(45)*.
Spectrum of activity:	In vitro and in vivo studies showed activity towards OXA-23, -27 and -51-producing CRAB, however the susceptibility rate is 57.5% *(46)*. No activity vs MBL *(45)*. Activity was also shown against KPC-producing CRKP, but not against carbapenem-resistant *E. coli* (CREC). Active against 3GCR *K. pneumoniae*, but insufficient data against 3GCR *E. coli*. Activity against CRPA appears poor: the susceptibility rate was 35.6% *(45,47)*.
Sought therapeutic indication:	cUTI and HABP/VABP. Pharmaceutical form, route of the administration and proposed posology: imipemen/cilastatin/funobactam 500/500/250 mg q6h, 0.5 h infusion.

Product name (INN or company code):	Funobactam (XNW4107) + imipenem + cilastatin
Route of administration and proposed posology:	Intravenous.
Phase of clinical development:	Phase 3.
Clinical trial(s):	Clinical trial(s): Two Phase 3 clinical trials in cUTI (NCT05204368) and HABP/VABP (NCT05204563) are listed. • **Phase 3 trial in cUTI (NCT05204368):** A multicentre, randomized, double-blind, double-dummy, comparative, Phase 3 study to evaluate the efficacy and safety of iv imipenem/cilastatin/XNW4107 (500/500/250 mg q6h) in comparison with meropenem (1 g, q8h) in hospitalized adults with cUTI infection, including AP. – Study population: Adult male or female patients (roughly 780), hospitalized or requiring hospitalization for cUTI or AP, showing at least one of the following: nausea or vomiting, chills or rigours or warmth associated with fever (temperature > 38°C), peripheral WBC count > 10 000/mm^3 or bandaemia , regardless of WBC count, with at least one complicating factor for cUTI (not required for AP). – Time period: March 2023 to December 2025. – Sites: Only one location listed at present: Baltimore (MD), United States. Not yet recruiting as accessed in March 2025. – Primary end-point: The proportion of patients who achieve overall success at the TOC day 21 (± 2 days) visit. Overall success requires symptomatic clinical success and microbiologic success at the TOC visit. – Primary efficacy evaluation will be performed in the micro-MITT population. • **Phase 3 trial in HABP/VABP (NCT05204563):** A multicentre, randomized, double-blind, comparative, Phase 3 study to evaluate the efficacy and safety of iv imipenem/cilastatin/XNW4107 (500/500/250 mg q6h) in comparison with imipenem/cilastatin/relebactam (1.25 g for injection) in adults with HABP or VABP (REITAB-2). – Study population: Adult patients (roughly 450) with HABP or VABP from a suspected Gram-negative infection with fever or hypothermia or leukocytosis/leukopenia or > 15% immature neutrophils on peripheral blood smear, fulfilling at least one of the following clinical criteria: new onset or worsening of pulmonary symptoms or signs, or requirement for mechanical ventilation; hypoxaemia; need for acute changes in the ventilator support system to enhance oxygenation; new onset of or increase in suctioned respiratory secretions, demonstrating evidence of inflammation and absence of contamination. All patients must have a chest radiograph showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia. – Time period: July 2022 to December 2025. – Sites: 35 sites in France, Israel, Spain and United States. – Primary end-point: Day 14 all-cause mortality rate. – Primary efficacy evaluation will be performed in the micro-MITT population.

Product name (INN or company code):	Ceftibuten + ledaborbactam (VNRX-7145)
Pharmacology: chemical class and MoA:	Ceftibuten + ledaborbactam (VNRX-7145) is a boronate-BLI + β-lactam (third-generation cephalosporin). Ledaborbactam (VNRX-7145) is an esterase-cleavable prodrug of the bicyclicboronate-type BLI (new class) of ledaborbactam etzadroxil (VNRX-5236) *(48)*, while ceftibuten is a third-generation cephalosporin that inhibits cell wall synthesis. It was first approved by the US-FDA for paediatric use in 1995.
Spectrum of activity:	Active against clinically derived Enterobacterales that express ESBLs and serine carbapenemases. In vitro, the combination has shown potent inhibitory activity against MDR Enterobacterales expressing Ambler Class A, C and D β-lactamases, including those that hydrolyse carbapenems, such as KPCs and OXA-48 *(49,50)*, but not in MBL-producing isolates *(49)*. VNRX-5236 alone does not demonstrate antibacterial activity. In vivo, ledaborbactam (VNRX-7145) restored ceftibuten activity in a mouse model of UTI due to ESBL- and KPC-producing strains of *E. coli* and *K. pneumoniae (51)*.
Sought therapeutic indication:	Under development as a carbapenem-sparing oral treatment in cUTI caused by Enterobacterales (ESBL, KPC and OXA-48 groups) *(49)*.
Route of administration and proposed posology:	Oral.
Phase of clinical development:	Currently being evaluated in a Phase 1 trial and previously completed three other Phase 1 trials.
Clinical trial(s):	• **Current Phase 1 trial (NCT05488678):** – An open-label study to evaluate the PK, safety and tolerability of ceftibuten/VNRX-7145 in 32 participants with varying degrees of renal function. • **Completed Phase 1 trials:** – **NCT04243863:** A randomized, double blind, placebo-controlled, sequential group, dose-escalation study to evaluate the safety and PK of single and repeat doses of VNRX-7145 in 83 healthy adult volunteers (January 2020 to April 2021). – **NCT04877379:** a randomized, drug–drug interaction study to assess the safety and PK of VNRX-7145 and VNRX-5024 (ceftibuten) in 53 healthy adult volunteers (June 2021 to November 2021); no published results. – **NCT05527834:** an open-label, crossover study to evaluate the effect of food on the PK, safety, and tolerability of ceftibuten/VNRX-7145 in 36 healthy participants (September 2022 to January 2023).
Clinical study results:	There are no published results as yet.
Preclinical PK and safety/adverse events:	In vivo, VNRX-5236 showed oral bioavailability in rats, dogs and monkeys *(45)*. It has been studied in patients with mild, moderate or severe renal impairment or end-stage renal disease undergoing standard intermittent dialysis, pending results.

Product name (INN or company code):	Ertapenem + zidebactam (WCK 5107) (combination WCK 6777)
Pharmacology: chemical class and MoA:	Ertapenem-zidebactam (WCK 5107) is a DBO-BLI/PBP2 binder and β-lactam (carbapenem) combination. The DBO-BLI/PBP2 binder acts as a β-lactamase inhibitor and antibacterial agent by means of PBP2 inactivation, and the β-lactam (carbapenem) inhibits cell wall synthesis by binding to PBPs.
Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactam/BLIs:	In vitro, WCK 6777 is active against *E. coli* with AmpC, ESBLs, KPC, metallo- or OXA-48 carbapenemases *(52)*. Zidebactam inhibits PBPs and several β-lactamases, while enhancing β-lactam *A. baumannii*, *P. aeruginosa* and CREs *(20,53)*. In vivo, human-simulated exposures of WCK 6777 demonstrated activity against carbapenemase-producing *K. pneumoniae* in a neutropenic murine pneumonia model, including those with WCK 6777 MICs up to 8 mg/L *(54)*.
Sought therapeutic indication:	Ertapenem-zidebactam is being developed as a potential once-daily outpatient therapeutic option to manage infections caused by carbapenem Gram-negative pathogens *(55)*. In October 2024, it was granted fast-track designation by the US-FDA for the treatment of cUTI, including pyelonephritis, and cIAI.
Route of administration and proposed posology:	Intravenous.
Phase of clinical development:	Phase 1.
Clinical trial(s):	A **Phase 1 (NCT05645757, completed)** randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, tolerability and PK of iv ertapenem in combination with zidebactam (WCK 6777) in 52 healthy adult subjects (18–45 years old). Beginning 19 April 2023, and completed in November 2023, the crucial primary end-points are the incidence of TEAEs and treatment-emergent serious adverse events.
Clinical study results:	Top-line results were released by the company *(56)*. Zidebactam (up to 3 g + 3 g daily) was well-tolerated, and no serious or unexpected adverse events were reported. None of the subjects withdrew or were discontinued from the study due to treatment-related adverse events. Pharmacokinetic analysis revealed consistent exposure levels of both ertapenem and zidebactam, with no significant interactions when co-administered daily for the duration of the study.

Product name (INN or company code):	Cefepime + nacubactam (OP0595); aztreonam + nacubactam (OP0595)
Pharmacology: chemical class and MoA:	Nacubactam is a DBO-type BLI with inhibiting activity against Class A and C β-lactamases and some class D (OXA) enzymes, and some intrinsic activity against serine β-lactamase producing Enterobacterales due to PBP2 inhibition *(57,58)*. Cefepime is a fourth-generation cephalosporin that inhibits cell wall synthesis.
Spectrum of activity:	Nacubactam has synergistic activity with various partners in serine β-lactamase-producing Enterobacterales. The combination with cefepime is active against CRE both in vitro and in vivo *(57,58)*. In vitro, the combination with aztreonam is active against MDR Enterobacterales and MBL-producing *P. aeruginosa (58)*. Among MBL-producing *P. aeruginosa* isolates, the susceptibility rates to aztreonam/nacubactam were 66.7% *(58)*. In vivo data support activity against KPC-producing *Klebsiella (59)*.
Sought therapeutic indication:	cUTI/AP; HABP/VABP and cIAI.
Route of administration and proposed posology:	2 g cefepime or 2 g aztreonam combined with 1 g nacubactam q8h (60 min iv infusion).
Phase of clinical development:	Phase 3.

Product name (INN or company code):	Cefepime + nacubactam (OP0595); aztreonam + nacubactam (OP0595)
Clinical trial(s):	Two Phase 3 studies are currently ongoing in cUTI/AP (NCT05887908), and in cUTI/AP, HABP/VABP and cIAI (NCT05905055). • **Phase 3 (NCT05887908):** Multicentre, randomized, double-blind study to assess the efficacy and safety of cefepime/nacubactam or aztreonam/nacubactam compared to imipenem/cilastatin in the treatment of cUTI or AP. – **Study population:** Male or female adult patients (roughly 600) expected to require treatment with at least 5 days of iv antibiotics for cUTI or AP, not due to a known imipenem- and/or meropenem-resistant Gram-negative uropathogen. Patients will be randomized to receive: 2 g cefepime and 1 g nacubactam q8h (60 min infusion), 2 g aztreonam and 1 g nacubactam q8h (60 min infusion) or combination of 1 g imipenem/1 g cilastatin q8h (60 min infusion). – **Time period:** May 2023 to August 2024. – **Sites:** Estonia; listed Bulgaria, Czechia, Latvia and Lithuania. – **Primary end-point:** The proportion of patients who achieve composite clinical and microbiological success at TOC (time frame: 7 (± 2) days after EOT (days 10–23)). Composite clinical and microbiological success is defined as the composite clinical outcome of cure and the microbiological outcome of eradication. – Primary efficacy evaluation will be performed in the micro-MITT population. • **Phase 3 (NCT05905055):** A multicentre, randomized, single-blind, parallel-group study to assess efficacy and safety when 1 g nacubactam is co-administered with 2 g cefepime or 2 g aztreonam (both q8h for 5–14 days, 60 min infusion), compared with best available therapy (dosage based per site's SOC), in the treatment of patients with cUTI, AP, HABP, VABP and cIAI, due to CRE. – **Study population:** Male or female adult patients (roughly 150) with known (evidence of positivity within 72 h or 96 h for cIAI, prior to the first dose of study drug) or suspected CRE infection. In case of known CRE infection, patients have either: (i) received no more than 24 h of an antimicrobial agent to which the known CRE is known to be susceptible; or (ii) documented clinical evidence of failure (i.e. clinical deterioration or failure to improve) after at least 48 h of treatment, within 72 h (or 96 h for cIAI) prior to the first dose of the study drug. In the case of suspected CRE infection, evidence may be determined within 90 days prior to the first dose of the study drug together with documented clinical evidence of failure after at least 48 h of treatment with empiric antimicrobial therapy for Gram-negative organisms within 72 h (or 96 h for cIAI) prior to the first dose of the study drug. Patients with known or suspected single or concurrent infection with *Acinetobacter* species or MBL-producing *P. aeruginosa* will be excluded Note: *CRE is defined as* Enterobacterales *by susceptibility data of MIC at least 2 mg/mL to imipenem or meropenem OR imipenem or meropenem disk diffusion (zone diameter < 22 mm).* – **Time period:** June 2023 to February 2025. – **Sites:** Greece, Japan, Spain. – **Primary end-point:** The proportion of patients with overall treatment success at TOC across all infection types (i.e. cUTI, AP, HABP, VABP cIAI), which is a composite end-point derived from the efficacy outcomes of each infection type (time frame: 7 (± 2) days after EOT (days 10–23)). For cUTI and AP, the composite clinical outcome of cure and the microbiological outcome of eradication are defined as the outcome of cure. For HABP and VABP, the clinical success is defined as the outcome of cure. For cIAI, the clinical success is defined as the outcome of cure.
Clinical study results:	No results as yet.

Product name (INN or company code):	Meropenem + ANT3310
Pharmacology: chemical class and MoA:	Meropenem-ANT3310 is a DBO-BLI + β-lactam (carbapenem). ANT3310 has a fluorine atom replacing the carboxamide, distinguishing it from other DBOs in restoring carbapenem activity against OXA-CRAB as well as serine β-lactamases (SBL)-carrying CRE pathogens *(60)*.
Spectrum of activity:	In vitro data showed activity of meropenem-ANT3310 against CRAB and OXA- and KPC-producing CREs. The combination of 8 µg/mL of both drugs prevented the growth of 97.5% of *A. baumannii* and 100% of OXA- and KPC-positive CREs *(60,61)*. Roughly 90% of 502 *P. aeruginosa* isolates (the resistance profile of which was not specified) also displayed meropenem MICs ≤8 µg/mL, although the addition of ANT3310 reduced only meropenem MIC50 without affecting the MIC90 value *(61)*. Furthermore, meropenem-ANT3310 was efficacious in both thigh and lung murine infection models with OXA-23 *A. baumannii (61)*.
Sought therapeutic indication:	US-FDA Qualified Infectious Disease Product status was granted to Meropenem-ANT3310 for treatment of cUTI, HABP, VABP and cIAI in 2019 *(62)*.
Route of administration and proposed posology:	Intravenous.
Phase of clinical development:	Phase 1.
Clinical trial(s):	A **Phase 1 (NCT05905913, completed):** Randomized, double-blind, placebo-controlled study to assess the safety, tolerability and pharmacokinetics of single- and multiple-ascending doses of iv ANT3310 alone (parts A and B) and in combination with meropenem (part C) in 72 healthy subjects (18–55 years old). The predicted period is between April 2023 and January 2024, with a primary end-point of number and severity of TEAEs. A **Phase 1 (NCT06527677):** Open-label, non-randomized, single-centre, single-dose study to assess the pharmacokinetics and safety of ANT3310 combined with meropenem administered as a single intravenous infusion to adult subjects with renal function impairment.
Clinical study results:	No results as yet.

Product name (INN or company code):	Meropenem + + KSP-1007 (MEROPEN)
Pharmacology: chemical class and MoA:	Meropenem-KSP-1007 is a novel BLI and β-lactam (carbapenem) combination.
Spectrum of activity:	In vitro and in vivo data support KSP-1007 broad-spectrum inhibition of SBL/MBL in combination with meropenem *(63)*. The combination was also active in NDM-producing *E. coli* with PBP3 mutations with decreased susceptibility to aztreonam/avibactam, cefepime/taniborbactam, and cefiderocol *(63)*.
Sought therapeutic indication:	Carbapenem-resistant bacterial infections: cUTI, cIAI, HABP and VABP *(64)*.
Route of administration and proposed posology:	Intravenous.
Phase of clinical development:	Phase 1.
Clinical trial(s):	• **Phase 1 (NCT05226923, completed October 2022):** A randomized, double-blind, placebo-controlled, dose-escalation study to assess the safety, tolerability and PK of single and repeat doses of KSP-1007 alone and co-administered with meropenem in approximately 123 healthy subjects.
Preclinical PK and safety:	After single and multiple doses, a dose-proportional increase in mean maximum concentration (Cmax) and area under the concentration–time curve (AUC) was observed, and KSP-1007 was predominately excreted in urine (> 90%) with T1/2 of 2–4 h. No serious adverse events were observed in the study. The most common adverse events at the highest dose (KSP-1007 1500 mg + 2 g merepenum) were nausea, vomiting and transient increases of serum creatinine (peak changes ranged from 0.31–0.74 mg/dl).

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Annex 3
Cell membrane disruptors

3.1 Polymyxins

Product name (INN or company code):	MRX-8
Pharmacology: chemical class and MoA:	MRX-8 is a polymyxin analogue of an undisclosed structure.
Spectrum of activity and potential resistance:	In an in vitro study *(1)* MRX-8, colistin and polymyxin exhibited nearly identical antimicrobial activities against Enterobacterales, *P. aeruginosa* and *A. baumannii* isolate sets. MRX-8 is not active against polymyxin/colistin-resistant *E. coli* and *K. pneumoniae* isolates (MIC90 was > 32 mg/L) *(1,2)*. In vivo, activity has been observed against clinically relevant Gram-negative species, including *P. aeruginosa*, *K. pneumoniae* and *A. baumannii* in neutropenic mouse thigh and lung infection models *(3)*.
Sought therapeutic indication:	In development for the treatment of infections caused by MDR Gram-negative pathogens, including *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii (4)*.
Route of administration:	Intravenous.
Phase of clinical development:	Completed two Phase 1 trials, one in the United States (NCT04649541) and one in China.
Clinical trial(s):	• The **Phase 1 trial in United States (NCT04649541)** was an adaptive, randomized, double-blind, placebo-controlled three-part study of the safety, tolerability and PK of MRX-8 administered iv to healthy volunteers in single and multiple ascending dose cohorts between November 2020 and 30 August 2021. The primary end-point was adverse events and other key laboratory and vitals parameters. No published results are available. • The **Phase 1 trial in China** was a randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability and pharmacokinetic characteristics of MRX-8 in healthy Chinese subjects. The trial included single ascending dose and multiple ascending dose components.
Clinical study results:	Topline data of the Chinese study have been released online *(5)*, showing that MRX-8 drug exposure in the human body increases proportionally with the dose. Throughout the study, no subjects withdrew or terminated the trial due to adverse events, and no grade 3 or higher adverse events occurred. The most common adverse events were mild (grade 1) sensory reduction and decreased glomerular filtration rate, which resolved without intervention. Only two subjects in the multiple dose group experienced grade 2 adverse events, both of which were injection site reactions.
Preclinical PK and safety:	In vivo using polymyxin B as a comparator, both MRX-8 and polymyxin B exhibited increased effects with increasing doses *(3)*. Compared to polymyxin B, MRX-8-induced nephrotoxicity was milder and reverted in 24 hours *(6)*.

Product name (INN or company code):	QPX9003 (F365, BRII-693)
Pharmacology: chemical class and MoA:	QPX9003 (previously F365) is a synthetic lipopolypeptide polymyxin derivative *(7)*.
Spectrum of activity and potential resistance:	QPX9003 has been reported to confer slightly better in vitro activity against *P. aeruginosa*, *A. baumannii* and *K. pneumoniae* isolates compared to polymyxin B *(7–9)*. QPX9003 is shown to be less prone to developing resistance than polymyxin B in serial passaging experiments *(7)*. QPX9003 was also tested in vivo in a neutropenic mouse lung infection model against polymyxin-susceptible MDR clinical isolates of *K. pneumoniae*, CRPA and CRAB *(7)*. In a neutropenic mouse thigh infection model, QPX9003 exhibited a reduction in CFU/thigh as compared to polymyxin B against polymyxin-susceptible CRAB clinical isolates.
Sought therapeutic indication:	The drug is being studied as treatment for MDR *Pseudomonas* or *Acinetobacter* infections.
Route of administration:	Intravenous.
Phase of clinical development:	Phase 1.
Clinical trial(s):	The **Phase 1 (NCT04808414)** trial was to assess the safety, tolerability and PK of single and multiple iv administered ascending doses of QPX9003 in 104 healthy adult subjects between 3 June 2021 and 14 July 2022.
Clinical study results:	Not yet publicly available.
Preclinical PK and safety:	Not yet publicly available.

Product name (INN or company code):	Upleganan (SPR-206)
Pharmacology: chemical class and MoA:	Upleganan (SPR-206) is a novel semi-synthetic polymyxin-B analogue.
Spectrum of activity and potential resistance:	SPR-206 has shown in vitro activity against MDR Gram-negative drug-resistant bacteria, Ambler Class A, B, C, and D β-lactamase-producing Enterobacterales strains *(8,9)*, and activity against OXA-23-expressing *A. baumannii*, KPC-expressing *K. pneumoniae* and NDM-expressing Enterobacterales *(10,11)*. In vivo studies (poster data) in thigh, lung and UTI models in mice suggest that SPR206 achieves efficacy end-points at similar or lower required doses than polymyxin B *(12,13)*. In a recent peer-reviewed publication *(14)*, in a thigh infection model, the translational bacteriostatic end-point was achieved in NDM-expressing *E. coli (2)* and *P. aeruginosa (1)*, and KPC-expressing *K. pneumoniae (2)*. The median static fAUC/MIC exposure was similar across the three pathogens (162.27, 129.78, and 95.15, respectively). Considering the translational end-point of 1-log10 kill, isolates of *E. coli* (1/2) and *P. aeruginosa* (1/1) achieved this end-point in vivo with median targets of 559.4 and 152.08, respectively. However, none of the two *K. pneumoniae* isolates tested reached the 1-log10 kill end-point.
Sought therapeutic indication:	Drug-resistant Gram-negative bacterial infection caused by CRAB, CRPA, CRE and ESBL-producing Enterobacterales (e.g. in cUTI, HABP, VABP and bloodstream infection (BSI)).
Route of administration:	Intravenous.
Phase of clinical development:	Phase 1.
Clinical trial(s):	SPR206 has completed **three phase 1 trials (NCT03792308, NCT04868292 and NCT04865393).** Spero Therapeutics announced that it has received US-FDA clearance for a phase 2, cross-indication resistant pathogen clinical trial designed to enrol patients. The most recently completed study (NCT04865393) was an open-label study to assess the safety and PK of SPR206 following a single iv dose of SPR206 in 38 adult participants with varying degrees of renal function. It occurred between June 2021 to December 2021, in New Zealand with primary end-points of time to the maximum plasma concentration (Tmax) and Cmax.

Product name (INN or company code):	Upleganan (SPR-206)
Clinical study results:	Not yet publicly available.
Preclinical PK and safety:	In vivo toxicology studies in mice, rats and primates show reduced nephrotoxicity compared to polymyxin *(15)*. It remains unclear whether lower MIC values in vitro will translate into useful activity in colistin-resistant strains, and what role nephrotoxicity will play in the clinical management of patients *(15)*. SPR206 was generally safe and generally well tolerated in Phase 1 trials *(16)*. While the incidence of adverse events increased with dose, most were of mild severity *(16)*. Urinary excretion of unchanged SPR206 was dose-dependent across single and multiple ascending dose cohorts, and approximately 50% of the dose was excreted as SPR206 *(16)*.

3.2 Host defence peptides

Product name (INN or company code):	OMN6
Pharmacology: chemical class and MoA:	OMN6 is a synthetic cyclic peptide composed of 40 amino acids that exerts a bactericidal effect by causing selective disruption of bacterial membrane integrity *(17)*.
Spectrum of activity and potential resistance:	OMN6 showed in vitro activity against laboratory strains and clinical isolates of multi-resistant *A. baumannii* and other Gram-negative pathogens (colistin-resistant *E. coli* and MDR *K. pneumoniae* at higher MICs) *(17,18)*. It was efficacious in two murine models of lethal bacteraemia and lung infection caused by CRAB *(17,18)*. Due to its MoA, OMN6 is expected to be efficacious against A. baumanni regardless of the bacterial genotype; the resistance phenotype exhibited a low propensity for resistance development in vitro as well as enhanced activity in the presence of lung surfactant *(18)*.
Sought therapeutic indication:	OMN6 is being developed as a novel therapy to treat HABP and VABP caused by *A. baumannii* infections *(18)*. In November 2023, OMN6 has received fast-track designation by US-FDA for the sought indication.
Route of administration:	Intravenous.
Phase of clinical development:	Phase 2.

Product name (INN or company code):	OMN6
Clinical trial(s):	• The **Phase 2a trial (NCT06087536)** is a prospective, multinational, multicentre, randomized, sequential, double-blind, placebo-controlled, clinical trial to assess the safety and pharmacokinetics of OMN6 in HABP or VABP caused by *A. baumannii* complex. **Study population:** Patients with HABP or VABP caused by *A. baumannii* based on a positive rapid testing of respiratory specimens. Patients will be randomized into four cohorts to receive OMN6 iv for 1 day + meropenem plus colistin for 7 to 14 days or meropenem plus colistin for 7 to 14 days. Cohort 1: 50 mg x 3/day OMN6, Cohort 2: 100 mg x 3/day OMN6, Cohort 3: 150 mg x 3/day OMN6. **Time period:** September 2024 to June 2026. **Sites:** Two sites in Israel. **Primary end-points:** Incidence of TEAE and serious adverse events (SAEs) by frequency, severity, relatedness, outcome, clinical laboratory findings change from baseline; vital signs and ECGs change from baseline; maximum observed plasma concentration; time to Cmax; AUC; and time to half-life. • The **Phase 1 trial** was a randomized, double-blind, placebo-controlled, single ascending dose study of 80 healthy volunteers, including a cohort of elderly patients in Groningen, Netherlands. The primary end-point was the safety and tolerability of single ascending iv doses of OMN6. There are no published results as yet. In a company topline data press release, the study met all end-points, and no severe or serious adverse events were observed at any dose level in the study. Clinically meaningful levels of OMN6 were reached in the blood, and the drug cleared completely, allowing multiple daily infusions *(19)*.
Clinical study results:	Not yet publicly available.
Preclinical PK and safety:	OMN6 has shown enhanced resistance to proteolysis, and no toxicity towards eukaryotic or mammalian cells in vivo *(18)*.

Product name (INN or company code):	murepavadin (POL7080, iMPV inhaled)
Pharmacology: chemical class and MoA:	Murepavadin (POL7080; iMPV) is a novel peptidomimetic antibiotic from the outer membrane protein targeting antibiotics class that inhibits LptD, an outer membrane protein involved in lipopolysaccharide biogenesis in Gram-negative bacteria *(20)*. By binding to LptD, murepavadin inhibits the lipopolysaccharide transport function of LptD and causes lipopolysaccharide alterations in the outer membrane of the bacterium and, ultimately, cell death *(21)*.
Spectrum of activity and potential resistance:	iMPV activity is restricted towards *P. aeruginosa*, including carbapenemase-producing and colistin-resistant *P. aeruginosa*. In vitro studies have demonstrated activity of murepavadin against a large collection of XDR *P. aeruginosa* from Europe and North America (MIC90 = 0.12 mg/L) and *P. aeruginosa* isolates recovered from people with cystic fibrosis (MIC90 = 2 mg/L) *(22–24)*. Intratracheal administration of murepavadin in a murine *P. aeruginosa* lung infection model resulted in > 2 log10 reduction in CFUs against *P. aeruginosa* strains at doses below 1 mg/kg with a > 1 log10 CFU reduction of *P. aeruginosa* at 1.25 mg/kg *(25)*. Aguilar et al. reported that murepavadin affinity for the cell surface may be reduced by mutations in genes related to lipopolysaccharide biosynthesis and transport, and that its resistance may also be caused by genes coding for multidrug efflux pumps (acrB) or genes that regulate colistin resistance *(23)*. Evidence of potential cross-resistance with colistin, involving lipopolysaccharide modifications that mitigate antibiotic cell membrane binding, has been shown by Romano et al. (2019) *(26)*.
Sought therapeutic indication:	Inhaled murepavadin (iMPV) is being investigated in *P. aeruginosa* infection; cystic fibrosis and non-cystic fibrosis bronchiectasis.

Product name (INN or company code):	murepavadin (POL7080, iMPV inhaled)
Route of administration:	Orally inhaled. Note: Two previous Phase 3 trials evaluating the efficacy and safety of the iv formulation of murapavadin in patients with HABP or VABP due to *P. aeruginosa* were terminated due to safety concerns. The new formulation for inhalation (iMPV), characterized by low systemic bioavailability, is currently under clinical development.
Phase of clinical development:	Phase 1b/2a.
Clinical trial(s):	The **Phase 1 trial** was a single-centre, double-blind, randomized, placebo-controlled trial to investigate the safety, tolerability and PK of single ascending doses of iMPV in 39 healthy volunteers.
Clinical study results:	From a Spexis press release *(27)*: "In Part A of the trial, three single-dose levels, 12.5mg, 25mg, and 50mg of the macrocycle compound were evaluated in four subjects per cohort. In Part B, single doses of 75mg, 150mg, and 300mg were evaluated in nine subjects per cohort. The PK of iMPV were assessed in blood samples and in epithelial lining fluid (ELF) obtained by bronchoalveolar lavage. At the highest single dose tested: • Systemic bioavailability of MPV was lower than 5 percent • Peak plasma concentrations were observed at 1–2 hours post start of inhalation • In the ELF, the concentration of MPV at the 24-hour timepoint was still above the concentration that would inhibit the growth of 90% of *P. aeruginosa* isolates (MIC90) obtained from people with CF."

3.3 Tethered macrocyclic peptides

Product name (INN or company code):	Zosurabalpin/RG6006 (also RO7223280, Abx MCP)
Pharmacology: chemical class and MoA:	Zosurabalpin (RG6006) is a macrocyclic peptide that disrupts Gram-negative bacterial cell membranes by inhibiting the transport of lipopolysaccharide *(28)*.
Spectrum of activity and potential resistance:	In vitro and in vivo data show that zosurabalpin is active against *Acinetobacter* spp., including carbapenem-resistant *A. baumannii*-calcoaceticus complex organisms *(28)*. Its activity was not affected by colistin or meropenem resistance in vitro. Zosurabalpin shows no activity against other Gram-negative or Gram-positive species *(28,29)*.
Sought therapeutic indication:	The drug is being studied for treatment of HABP, VABP and bacteraemia caused by CRAB.
Route of administration:	Intravenous.
Phase of clinical development:	Phase 1.
Clinical trial(s):	• A **Phase 1 trial (NCT04605718)** to investigate the safety, tolerability and PK of RO7223280 following iv administration in healthy participants is complete. It consisted of three parts: part 1 (a single iv dose of RO7223280 administered over 1 h, single ascending dose); part 2 (multiple ascending doses); and part 3 (safety, tolerability and PK of a single iv dose of RO7223280 in healthy elderly participants), starting with 124 healthy participants (18 years and older) between December 2020 and March 2023. The primary endpoint was the percentage of participants with adverse events. • A multicentre, phase 1, single-dose, uncontrolled, open-label, one group study to investigate the pharmacokinetics of RO7223280 in critically ill patients with bacterial infections **(NCT05614895)**.
Clinical study results:	Non-peer-reviewed comparison of data from part 1 of study NCT04605718 in healthy participants and study in patients from ICU have been presented by the developer in comparison to data in patients from intensive care unit (ICU) *(30)*. Results presented at the ESCMID 2024 showed that the PK of zosurabalpin was different and showed a larger variability in ICU patients than in healthy participants. On average, in ICU patients, mean Cmax was lower than in healthy participants, and the clearance of zosurabalpin was reduced and the AUCinf was increased in patients compared to healthy participants.
Preclinical PK and safety:	In single-dose and multiple-dose pharmacokinetic studies in mice, after sub-cutaneous (sc) administration, acceptable plasma exposures were reached; a low volume of distribution (0.7 l kg−1), a short terminal half-life (0.3 h) and moderate protein binding (fraction unbound, 37%) were also observed. No off-target activity or substantial interactions with the cytochrome P450 system were observed *(29)*.

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Annex 4
Protein synthesis inhibitors

4.1 Tetracyclines

Product name (INN or company code):	Zifanocycline (KBP-7072)
Pharmacology: chemical class and MoA:	Zifanocycline (KBP-7072) is a third-generation aminomethylcycline *(1)*.
Spectrum of activity and potential resistance:	In vitro, KBP-7072 has displayed activity against both Gram-positive and Gram-negative pathogens, including MRSA, geographically diverse *A. baumannii* (including activity against carbapenem-resistant ESBL- and MBL-producing isolates) and ESBL-producing Enterobacterales *(2–4)*. KBP-7072 was found to be minimally affected by the presence of acquired tetracycline genes *(3)*. It also showed similar or slightly higher MIC values for tetracycline-susceptible and -resistant *S. aureus* strains compared with tigecycline and omadacycline *(2)*. In vivo data show activity against an MRSA neutropenic murine pneumonia model *(2)* and against *A. baumannii* in a neutropenic murine thigh infection model *(6)*.
Sought therapeutic indication:	The drug is being studied for treatment of ABSSSI, CABP and cIAI *(2)*.
Route of administration:	Intravenous/oral.
Phase of clinical development:	Phase 1.
Clinical trial(s):	**Three Phase 1 clinical trials** have been reported, completed in 2015 **(NCT02454361)**, in 2016 **(NCT02654626)** and in October 2020 **(NCT04532957)**, respectively. No results have been published as yet. KBP-7072 is currently being evaluated in another Phase 1 trial: a double-blind, placebo-controlled, single and multiple iv dose, safety, tolerability and PK study in 56 healthy male and female subjects between August 2022 and 30 June 2023 (**NCT05507463**, completed June 2023). The study's primary end-point is adverse events and relevant laboratory and vital/physiological abnormalities.
Clinical study results:	Not yet publicly available.
Preclinical PK and safety:	Bactericidal activity was noted at ≥ 1 mg/kg/6 h for both methicillin-susceptible *S. aureus* (MSSA) and MRSA; a 3 log10 kill was achieved for all strains tested *(5)*. MICs of zifanocycline against *A. baumannii* ranged from 0.06 mg/L to 0.5 mg/L, with significant activity against all eight strains. Average daily doses of zifanocycline to achieve a static, 1 log10 kill and 2 log10 kill effect were projected to be 6.92, 9.63 and 13.22 mg/kg, and the mean free drug area under the concentration–time curve (fAUC)/MIC ratios were 6.91, 9.10 and 12.60, respectively *(6)*.

4.2 Aminoglycosides

Product name (INN or company code):	apramycin (EBL-1003)
Pharmacology: chemical class and MoA:	Apramycin (EBL-1003) is an aminoglycoside that was first licensed in 1980 for oral therapy in animals *(7)*.
Spectrum of activity and potential resistance:	In vitro studies of EBL-1003 show activity against 3GCRE, CRE, CRAB and CRPA *(8–11)*. Apramycin also shows broad-spectrum activity against MDR *N. gonorrhoea (12)*. Apramycin demonstrated in vitro activity against carbapenem-resistant hypervirulent *K. pneumoniae* isolates, including those resistant to amikacin and gentamicin *(11)*. Recent in vitro studies with genotypic analysis report that aminoglycoside-modifying enzymes and rRNA methyltransferases did not render cross-resistance to apramycin *(13)*. In vivo efficacy was measured in a neutropenic mouse pneumonia model for *K. pneumonia*; for two out of five strains studied, a delay in growth (approximately 5 h) was observed in vivo but not in vitro *(14)*. In recent in vitro studies in Mtb, Apramycin exhibited inhibitory activity against Mtb clinical isolates, with an MIC50 of 0.5 µg ml-1 and an MIC90 of 1 µg ml-1 *(15)*. Apramycin activity against methylated ribosomes was > 100-fold higher than that for other aminoglycosides *(16)*. Frequencies of resistance were < 10-9 at 8 × MIC. Tentative epidemiological cut-offs (TECOFFs) were determined as 8 µg/mL for *E. coli* and 4 µg/mL for *K. pneumoniae*. A single dose of 5 to 13 mg/kg resulted in a 1-log CFU reduction in the blood and peritoneum. Two doses of 80 mg/kg resulted in an exposure that resembles the AUC observed for a single 30 mg/kg dose in humans and led to complete eradication of carbapenem- and aminoglycoside-resistant bacteraemia *(16)*.
Sought therapeutic indication:	Under development for the treatment of BSI in humans and used to treat or prevent infections caused by Gram-negative bacteria such as *E. coli*, *Salmonella* spp. and *Shigella* spp. in animals.
Route of administration:	Intravenous 30 mg/kg (see preclinical PK).
Phase of clinical development:	Phase 1.
Clinical trial(s):	**Two Phase 1 trials:** An initial Phase 1 trial (NCT04105205) was completed in February 2021. • **Phase 1 trial (NCT05590728)** is a study of a single dose of 30 mg/kg of apramycin administered intravenously over 30 (± 5) min. The primary end-point is to assess the plasma PK profile of apramycin and lung penetration of apramycin in epithelial lining fluid and alveolar macrophages after a single 30 mg/kg iv apramycin dose (completed October 2022). • The completed **Phase 1 trial (NCT04105205)** was a first-in-human study to assess the safety, tolerability and PK of escalating single doses of apramycin in 40 healthy adults between September 2019 and October 2020.
Clinical study results:	Not yet publicly available.
Preclinical PK and safety:	Apramycin demonstrated good lung penetration and sustained exposure in healthy and lung-infected mice *(14)*. Pharmacometric PK/PD modelling showed that apramycin is expected to be efficacious at 30 mg/kg once daily against Gram-negative lung infections in humans. It is yet to be seen whether this will be effective in human trials *(14)*.

4.3 Macrolides and Ketolides

Product name (INN or company code):	Nafithromycin (WCK-4873)
Pharmacology: chemical class and MoA:	Nafithromycin is an oral lactone-ketolide derived from the macrolide erythromycin A, modified to overcome the problem of macrolide resistance. Nafithromycin is an inhibitor of protein synthesis. Ketolides bind to ribosomes with higher affinity than macrolides do. Note: *From available clinical data: Pharmacodynamically, ketolides display an element of concentration-dependent killing as opposed to macrolides, which are time-dependent killers.*
Spectrum of activity and potential resistance:	In vitro activity has been shown against Gram-positive aerobes and some Gram-negative aerobes *(17–20)*, as well as activity against drug-resistant *S. pneumoniae*, including efflux and some ribosomal protein mutation-mediated resistance *(21)*. In vivo data were recently published *(22)* showing superior activity of nafithromycin compared to telithromycin at the same dose range against some strains of macrolide-resistant *S. pneumoniae* and macrolide-resistant *S. pyogenes*; however, a certain degree of in vivo cross-resistance was observed for other Pneumococcal strains that exhibited in vitro nafithromycin MIC in the susceptible range *(22)*. The clinical relevance of this latter observation is at present not known. It should also be noted that results from a human lung penetration study *(23)* revealed sustained high lung nafithromycin concentration built-up over five days following just three days of dosing, and that the exposure of epithelial lining fluid and alveolar macrophages to the drug were higher than those reported for both telithromycin and solithromycin *(24)*. Note: *Macrolide resistance is mediated through two main mechanisms: drug-efflux pumps encoded by the mef gene and modification of the drug target site in the ribosome brought about by the action of Erm methyltransferases. Nafithromycin interacts at multiple positions on the ribosome and has been shown to maintain activity against both types of resistance in some bacteria strains (25).*
Sought therapeutic indication:	Being developed as a treatment for CABP in adults due to typical and atypical respiratory pathogens, including penicillin- and macrolide-resistant pneumococcal strains. The drug has the potential to provide all the clinical advantages of an oral, compliance-friendly, 3-day regimen in treatment of CABP while overcoming the macrolide resistance problem.
Pharmaceutical form, route of the administration and proposed posology:	In a Phase 3 RCT trial in India, the proposed dose for treatment of CABP in adults is 800 mg (two 400 mg tablets) orally q24h for 3 days.
Phase of clinical development:	NDA filed for the Drugs Controller General of India (DCGI) approval.
Clinical trial(s):	• A **Phase 3**, randomized, multicentre, double-blind, comparative study to determine the efficacy and safety of oral nafithromycin vs oral moxifloxacin in the treatment of CABP in adults. The study has been registered with the clinical trial registry of India (registration no. **CTRI/2019/11/021964)**. Study population: 488 male and female subjects ≥ 18–90 years of age with a diagnosis of CABP as defined by the study protocol (more details available via this link using keyword trial registration no. CTRI/2019/11/021964 , prospective, interventional, and date of registration: November 2019), were randomized and assigned in parallel to receive either nafithromycin 800 mg (two 400 mg tablets) administered orally every 24 h for 3 days, or moxifloxacin 400 g orally every 24 h for 7 days. Time period: 31 December 2019 to 14 June 2023. Sites: 40 sites in India. The primary end-point is defined as the successful outcome of clinical success (symptom resolution and no new symptoms) at the TOC visit (= day 4), in the modified intent-to-treat (MITT) analysis set. Information on the non-inferiority margin is not available at present.

Product name (INN or company code):	Nafithromycin (WCK-4873)
Clinical study results:	Topline results were released by the Company in December 2023 *(26)*, and in May 2024 the product has been filed for the Drugs Controller General of India (DCGI) approval which is expected in the Q3FY25 *(27)*. Nafithromycin administered as a 3-day treatment was non-inferior to a seven-day therapy with moxifloxacin, resulting in clinical cure for 96.7% of patients as against clinical cure rate of 94.5% in the moxifloxacin arm. A significant proportion of study patients were reported to be infected with pathogens showing resistance to azithromycin, amoxycillin-clavulanic acid and levofloxacin. All the reported adverse events were mild, and in line with those observed in the phase 2 study (NCT02903836). **Adverse events:** From a Phase 2 trial (NCT02903836) in CABP patients treated with 800 mg for either 3 or 5 days. The most frequent adverse events were gastrointestinal events (3 days/5 days: vomiting 4.5%/1.39%; nausea 4.05%/6.94%; diarrhoea 2.7%/2.78%) and hypertension (4.05%/1.39%). Ketolides hold the potential for liver toxicity. Potential nafithromycin liver toxicity is currently not characterized. Repeat-dose toxicity studies in rats and dogs revealed no adverse haematological, biochemical or histopathological changes suggestive of systemic or hepatobiliary safety concern at exposures 3–8-fold higher than targeted therapeutic exposures. In vitro studies showed that nafithromycin undergoes moderate CYP3A-mediated metabolism, is a weak inhibitor of CYP3A4/5 and does not inhibit other key CYP enzymes. In addition to hepatic clearance, nafithromycin is also eliminated unchanged by the kidneys in a significant amount, thereby minimizing accumulation in the liver *(28)*.

Product name (INN or company code):	Solithromycin (T-4288)
Pharmacology: chemical class and MoA:	Ketolide, inhibitor of protein synthesis.
Spectrum of activity: activity on pathogens (confirmed or potential (in vitro, in vivo, animal model, etc.)) with details of activity on carbapenems for β-lactams/BLIs:	Activity in vitro is similar to that of telithromycin *(29,30)*; however, solithromycin has three binding sites as opposed to two for telithromycin *(30,31)*. Efficacy against *S. pneumoniae* was demonstrated in a murine lung infection model *(32)*. Cross-resistance with telithromycin is not commonly found; no cross-resistance has been reported with macrolides in pneumococci or group A streptococci, but cross-resistance has been reported in *Staphylococci (33,34)*.
Sought therapeutic indication:	Treatment of ear, nose and throat infections; CABP.
Pharmaceutical form, route of the administration and proposed posology:	Intravenous and oral.
Phase of clinical development:	Phase 3.

Product name (INN or company code):	Solithromycin (T-4288)
Clinical trial(s) and study results:	• An NDA was filed but rejected by the US-FDA and withdrawn from EMA submission because the potential for liver toxicity had not been adequately characterized. To address this deficiency, the US-FDA recommended a comparative study to evaluate the safety of solithromycin in patients with CABP (study population of approximately 9000 patients exposed to solithromycin to enable exclusion of serious drug-induced liver injury events, occurring at a rate of approximately 1:3000, with 95% probability *(35)*. The company decided to discontinue the adult drug development programme both in the United States and the European Union (EU). The NDA was based on **two Phase 3 trials for CAP (NCT01756339, NCT01968733)** and **one Phase 3 trial for treatment of gonorrhoea (NCT02210325)**. In the NCT01756339 trial comparing 5 days of oral solithromycin versus 7 days of oral moxifloxacin for treatment of CABP in adults, solithromycin was non-inferior to moxifloxacin in both early clinical response and shorter follow-up *(36)*. Similarly, in the NCT01968733 trial, iv-to-oral solithromycin was non-inferior to iv-to-oral moxifloxacin in CABP among 863 adults *(37)*. In contrast, in the NCT02210325 trial solithromycin was not non-inferior to ceftriaxone-azithromycin for treatment of gonorrhoea *(38)*. A Phase 2/3 trial in children and adolescents with CABP, which was ongoing at the time of US-FDA rejection, was prematurely discontinued not due to any specific safety or effectiveness concerns in the enrolled paediatric population *(39)*. Before discontinuation, 97 participants were randomly assigned to solithromycin (n = 73) or comparator (n = 24). There were 24 participants (34%, 95% CI: 23%–47%) with a treatment-emergent AE in the solithromycin group and 7 (29%, 95% CI: 13%–51%) in the comparator group. The most common related AEs with solithromycin were infusion site pain and elevated liver enzymes. Three subjects (4.3%) discontinued the drug due to AEs in the solithromycin group and one (4.2%) in the comparator group. Forty participants (65%, 95% CI: 51%–76%) in the solithromycin group achieved clinical improvement on the last day of treatment versus 17 (81%, 95% CI: 58%–95%) in the comparator group. The proportion achieving clinical cure was 60% (95% CI: 47%–72%) and 68% (95% CI: 43%–87%) for the solithromycin and comparator groups, respectively *(39)*. • An NDA was submitted in Japan in April 2019 for treatment of ear, nose and throat infection, following the demonstration of non-inferiority to cefcapene-pivoxil in patients with sinusitis in a Phase 3 trial registered in Japan. No further information is available on the approval procedure. In November 2023, the results of the non-inferiority trial were published in a review paper by Kurono et al. *(40)*. 283 patients with acute rhinosinusitis or acute exacerbation of chronic rhinosinusitis were randomized into either the solithromycin group or cefcapene-pivoxil group. Solithromycin was administered 800 mg once daily on Day 1 and 400 mg once daily while on Days 2–7 in solithromycin group, and cefcapene-pivoxil was administered 150 mg three times a day while on Days 1–7 in cefcapene-pivoxil group. The primary end-point was the clinical response at TOC. The efficacy rate at the TOC was 87.7 % for solithromycin and 89.7 % for high-dose cefcapene-pivoxil. The difference in the efficacy rate (95 % confidence interval) was -2.0 % (-9.4 % to 5.4 %), verifying the non-inferiority of solithromycin to cefcapene-pivoxil. The most common adverse event in patients administered solithromycin was diarrhoea (20.7 %). Since solithromycin has a ketolide structure, it harbours the potential risk for liver injury, loss of consciousness and visual disturbance as previously reported for telithromycin. Hepatic function-related adverse events, including abnormal hepatic function tests, were reported in 7.8 % (15/193 patients) of patients administered solithromycin and in 5.5 % (8/145 patients) of patients receiving cefcapene-pivoxil. However, no serious liver-related adverse events or liver-related adverse events leading to discontinuation of the study drug were reported in patient with an otorhinolaryngological infection. All reported liver-related adverse events were assessed based on liver function test abnormalities and were not associated with symptoms observed at the onset of liver disorders, such as jaundice, right upper abdominal pain, and pruritus. No loss of consciousness was observed in patients administered solithromycin in the non-inferiority study. Visual disturbance was observed in 3.1 % (6/193 patients) of the 193 patients administered solithromycin (2 patients each for vision blurring and visual impairment, 1 patient each for allergic conjunctivitis and photopsia) and in 2.1 % (3/145 patients; 1 patient each for dry eye, eye pain, and asthenopia) of patients administered cefcapene-pivoxil; however, no significant differences were found between the two groups. All visual disturbances were reported as mild, and the only related event found in the cefcapene-pivoxil group was eye pain.

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Annex 5
Novel bacterial topoisomerase inhibitors (NBTIs)

Product name (INN or company code):	BWC0977
Pharmacology: chemical class and MoA:	BWC0977 is a novel bacterial topoisomerase inhibitor (NBTI), with similar activity against DNA gyrase GyrA and topoisomerase IV. BWC0977 triggers an SOS response in bacterial cells similar to ciprofloxacin through the induction of recA, recN, sulA and lexA promoters *(1–3)*.
Spectrum of activity and potential resistance:	BWC0977 has shown activity against CRAB, CRE, 3GCRE and CRPA in vitro and in vivo animal models, as well as in vitro activity against MRSA, vancomycin-resistant *E. faecium*, macrolide-resistant pneumococcus and *S. pyogenes (4)*. BWC0977 has shown lack of cross-resistance to current antibiotics *(4)*. In vitro, the resistance frequency of BWC0977 at 4× MIC was found to be < 10–9 in *E. coli* and *P. aeruginosa*, and < 10–9 in *A. baumannii (5,6)*.
Sought therapeutic indication:	BWC0977 is being developed as a treatment in critical care Gram-negative infections, including Enterobacterales (ESBL phenotype), and non-fermenter infections, including *A. baumannii* (oral step-down administration).
Route of administration:	Intravenous/oral.
Phase of clinical development:	Phase 1.
Clinical trial(s):	A **Phase 1 trial** to assess the safety, tolerability and PK of single ascending iv dose of BWC0977 when administered to healthy adult volunteers recently completed (28 May 2023, **NCT05088421**).
Clinical study results:	Trial results were summarized in the paper by Hameed et al., 2024 *(4)*. BWC0977 was generally well tolerated following single iv infusion dose of 120, 240, 480, 720 or 1050 mg. The plasma Cmax and AUC increased proportionally with dose. The average apparent terminal half-life increased gradually with dose. The amount of drug excreted in urine during the 48 h interval was less than dose-proportional to increasing dose, with fraction of dose excreted unchanged in urine gradually decreasing with increasing dosing. A second Phase 1 multiple-ascending dose study, NCT05942820, was terminated due to the evidence of thrombus at the infusion site. While further investigating the drug potential for clotting risk, the company is currently developing a new formulation to minimize injection-site reactions *(4)*.
Preclinical PK and safety:	BWC0977 was tolerated well, with no evidence of increased clotting risk in rats and dogs *(4)*.

Product name (INN or company code):	zoliflodacin (ETX0914)
Pharmacology: chemical class and MoA:	NBTI (spiropyrimidenetrione scaffold). Utilizes a distinct DNA gyrase binding site in GyrB compared with fluoroquinolones (GyrA).
Spectrum of activity and potential resistance:	Activity against *N. gonorrhoeae* and Gram-positive cocci (in vitro and in vivo data) *(7)*. Early findings indicated no cross-resistance with fluoroquinolones (or other topoisomerase inhibitors) *(8–10)*. However, recent observations showed that the GyrB D429N substitution reduces susceptibility to zoliflodacin. The GyrB D429N substitution can be acquired by *N. gonorrhoeae* in the presence of ciprofloxacin, resulting in increased ciprofloxacin MIC, at least in some backgrounds *(11)*. It was recently shown that *N. gonorrhoea* zoliflodacin resistance-conferring region located in gyrB can be horizontally transferred by transformation from commensal *Neisseria* species, highlighting the need for conducting surveillance of zoliflodacin susceptibility also in commensal *Neisseria (12)*.
Sought therapeutic indication:	Uncomplicated gonorrhoea. Potential to be effective against *N. gonorrhoeae* infections caused by fluoroquinolone-resistant strains *(13)*.
Pharmaceutical form, route of the administration and proposed posology:	Oral, 3 g single-dose formulation.
Phase of clinical development:	Phase 3.
Clinical trial(s):	• **Phase 3 (NCT03959527):** A multicentre, explanatory, open label, randomized, non-inferiority clinical trial comparing a single 3 g oral dose of zoliflodacin with a combination of ceftriaxone (500 mg, IM) and azithromycin (1 g, PO) in the treatment of 1092 adult patients with uncomplicated gonorrhoea. – Study population: Patients with urogenital infections caused by *N. gonorrhoeae*. – Time period: 27 September 2019 to 31 July 2023. Recruitment completed on 23 May 2023. Topline results have been published showing non-inferiority of microbiological respect to IM ceftriaxone and oral azithromycin *(14)*. – Sites: 17 sites located in Belgium, Netherlands, South Africa, Thailand, United States. – Primary end-point: Microbiological cure as determined by culture at urethral or cervical sites at the TOC visit. – Primary efficacy evaluation will be performed in micro-MITT patients with uncomplicated urogenital infection due to any *N. gonorrhoeae* strain that is non-resistant to the intervention. • **Phase 2:** Early results from a small **Phase 2 RCT** (141 patients in the micro-MITT population) indicated potential for comparable action in various infection sites with some variation *(15)*. Specifically, the study reported a cure rate of 96% in participants with urogenital infections (n = 113) and 100% cure for rectal infections (12 participants), while pharyngeal infections were cured in four of eight participants (50%) receiving 2 g of zoliflodacin and in nine of 11 participants (82%) who received 3 g of zoliflodacin *(15)*.
Clinical study results:	Phase 3 (NCT03959527) study: Topline results were released by the company in November 2023 *(16)*. The Phase 3 trial enrolled a total of 930 patients with uncomplicated gonorrhoea. Zoliflodacin met the pre-specified statistical test for non-inferiority when compared to ceftriaxone and oral azithromycin (5.31% (95%CI: 1.38%–8.65%)). Non-inferiority of zoliflodacin was demonstrated within the pre-specified margin of 12% and, furthermore, within the margin of 10% as specified in US-FDA guidance.
Adverse events:	A Phase 2 RCT study (NCT02257918) in approximately 180 adult male and female subjects, aged 18–55, reported a total of 84 adverse events in 59 participants, 21 of which were attributed to zoliflodacin and were generally mild, self-limiting GI tract-related events.

Product name (INN or company code):	Gepotidacin[4] (GSK2140944)
Pharmacology: chemical class and MoA:	Novel dual bacterial topoisomerase II inhibitor (triazaacenaphthylene). Selectively inhibits bacterial DNA replication by interacting at a unique site on the GyrA subunit of bacterial DNA gyrase and the Par C subunit of bacterial topoisomerase IV *(17)*.
Spectrum of activity and potential resistance:	Inhibitory activity against *N. gonorrhoeae (18)*. In vitro and in vivo data showed activity against ESBL and NDM-producing *E. coli* and MRSA *(19-22)*. Some cross-resistance with fluoroquinolones (potentially overlapping/close binding sites) has been reported *(23)*.
Sought therapeutic indication:	uUTI and uncomplicated urogenital gonorrhoea in adults and adolescents ≥ 12 years of age.
Route of administration:	– uUTI (tested in adult females only): oral, 1500 mg (two 750 mg tablets) of gepotidacin bid; every q12h for 5 days; – Uncomplicated urogenital gonorrhoea: 3000 mg oral dose (four 750 mg tablets) bid, q12h. Note: Oral dose is high due to poor absorption. Fifty-three per cent of the oral dose is eliminated through the faecal route due to poor absorption (59% of the iv dose is eliminated through urine). A higher dose, for urogenital gonorrhoea infection compared to uUTI, is needed to suppress resistance development to gepotidacin in *N. gonorrhoeae (24,25)*.
Phase of clinical development:	NDA for uUTI, Phase 3 for *N. gonorrhoeae* indication
Clinical trial(s):	• **EAGLE-1 trial in urogenital gonorrhoea (NCT04010539):** Interventional, randomized, multicentre, open-label study in adolescent and adult participants comparing the efficacy and safety of gepotidacin with ceftriaxone-azithromycin in the treatment of uncomplicated urogenital gonorrhoea caused by *N. gonorrhoeae*. Completed October 2023. – Study population: 600 adolescents and adults (≥ 12 years of age), with > 45 kg weight, presenting uncomplicated urogenital gonococcal infection with or without pharyngeal and/or rectal gonococcal infection and one of the following: prior *N. gonorrhoeae*-positive culture or presumptive for Gram-negative intracellular diplococci from up to 5 days before screening (without treatment) or a positive Gram stain (urogenital specimens only), or a positive nucleic acid amplification assay for *N. gonorrhoeae* from up to 7 days before screening (without treatment).The study population were randomized/assigned in parallel to receive either oral gepotidacin (single dose at baseline, i.e. day 1 site visit, followed by a self-administered second oral dose as an outpatient 6–12 h after the first dose) OR a single IM dose of ceftriaxone plus a single oral dose of azithromycin at the baseline, day 1 visit. – Note: the study started prior to the change in SOC recommended by the US Centers for Disease Control and Prevention, and as such uses ceftriaxone-azithromycin, rather than ceftriaxone alone *(26)*. – Time period: 21 October 2019 to 31 October 2023. – Sites: The study is being conducted at 47 locations in five countries (Australia, Germany, Spain, United Kingdom, United States). – Primary end-point: Number of participants with culture-confirmed bacterial eradication of *N. gonorrhoeae* from the urogenital site at the TOC (time frame: from day 4 to day 8). – Pre-treatment urogenital swab specimen will be obtained for bacteriological culture for *N. gonorrhoeae*. TOC is defined by urogenital site as culture-confirmed bacterial eradication of *N. gonorrhoeae* observed 4–8 days post-treatment.

[4] Post-review update: as of 25 March 2025, gepotidacin (Blujepa) has been approved by the US-FDA for treatment of uUTIs in female adults and paediatric patients 12 years of age and older *(16)*.

Product name (INN or company code):	Gepotidacin (GSK2140944)
Clinical trial(s):	• **EAGLE-2 and EAGLE-3** are near-identical **Phase 3**, randomized, multicentre, parallel-group, double-blind, double-dummy, comparator-controlled, non-inferiority studies in adolescent and adult female participants, comparing the efficacy and safety of gepotidacin (1500 mg bid for 5 days) with nitrofurantoin (100 mg bid for 5 days) for treatment of uUTI **(NCT04020341, NCT04187144)**. Both studies are completed. – Study population: 1533 + 1605 female patients (> 12 years) with acute symptomatic cystitis with onset < 96h prior to study entry, and with nitrite or pyuria from a pre-treatment clean-catch midstream urine sample based on local laboratory procedures, were randomized 1:1 to receive either treatment. For the long list of exclusion criteria see: NCT04020341. – Time period: October 2019 to November 2022. – Sites: EAGLE-2 was conducted across approximately 95 sites in Bulgaria, Czechia, Germany, Greece, Hungary, India, Mexico, Poland, Romania, Slovakia, Spain, the United Kingdom and the United States. EAGLE-3 was conducted across approximately 110 sites in Australia, Bulgaria, India, Poland, Republic of Korea and the United States. Participating sites in both studies were community-based outpatient clinics. – Primary end-points: ○ Number of participants with therapeutic response (combined per participant clinical and microbiological response) at the TOC visit (days 9–16). A therapeutic response was referred to participants who had been deemed both a "microbiological success" (reduction of all qualifying bacterial uropathogens (> 105 CFU/ mL recovered at baseline to < 103 CFU/mL as observed on quantitative urine culture without the participant receiving other systemic antimicrobials before the TOC visit) and a "clinical success" (resolution of signs and symptoms of acute cystitis present at baseline (and no new signs and symptoms) without the participant receiving other systemic antimicrobials before the TOC visit). Lack of clinical or microbiological success (including missing outcome assessments) was considered as therapeutic failure. ○ Number of participants who had been deemed both a microbiological success (reduction of all qualifying bacterial uropathogens recovered at baseline to < 103 CFU/mL without receiving other antimicrobials before the TOC visit) and a clinical success (resolution of symptoms of acute cystitis present at baseline and no new symptoms without receiving other antimicrobials before the TOC visit or antimicrobials for uUTI on day of TOC visit). Lack of clinical or microbiological success (including missing outcome assessments) was considered as therapeutic failure. – Primary efficacy evaluation was performed in two populations: The MITT NTF-S population, defined as all participants in the MITT population whose baseline qualifying uropathogens (105 CFU/mL) are all susceptible to nitrofurantoin (NCT04187144: 292 gepoptidacin/275 nitrofurantoin; NCT04020341: 336 gepoptidacin/298 nitrofurantoin. The MITT NTF-S (IA Set) population included participants in the MITT NTF-S group who per the interim analysis data had the opportunity to reach their TOC visit, or had not yet reached their TOC visit but were already known to be failures (NCT04187144: 277 gepotidacin/264 nitrofurantoin; NCT04020341: 320 gepotidacin/287 nitrofurantoin). The non-inferiority margin was set at –10%.

Product name (INN or company code):	Gepotidacin (GSK2140944)
Clinical study results:	• Topline data from the EAGLE-1 study have been released by the Company *(27)*. The study met its primary end-point, microbiological response at the TOC visit 3–7 days after treatment. Gepotidacin (oral, two doses of 3 g) was non-inferior with 92.6% success rates when compared to 91.2% success rates for intramuscular ceftriaxone (500mg) plus oral azithromycin (1 g) combined therapy, a leading combination treatment regimen for gonorrhoea. **Adverse events:** The most commonly reported adverse events of mild to moderate intensity were gastrointestinal. • EAGLE-2 and EAGLE-3 Phase 3 trials met the primary end-point of non-inferiority to nitrofurantoin; both trials were stopped for non-inferiority based on predefined non-inferiority success boundaries. In addition, EAGLE-3 demonstrated statistical superiority *(27)*. EAGLE-2 (IA Set): 162 (50.6%) patients assigned gepotidacin vs 135 (47%) patients assigned nitrofurantoin had therapeutic success, adjusted treatment difference was 4.3% (95% CI: -3.6%–12.1%). EAGLE-3: 277 (58·5%) patients assigned gepotidacin vs 264 (43·6%) patients assigned nitrofurantoin had therapeutic success, adjusted treatment difference was 14·6% (95% CI: 6·4–22·8). *E. coli* was the predominant pathogen (>90%). Unexpectedly, both trials had a relatively low response rate. The most common cause of failure in both studies was lack of clinical response despite microbiologic clearance.
Adverse events	The most commonly reported adverse events in gepotidacin subjects were gastrointestinal *(28)*: diarrhoea (16% of subjects), followed by nausea (9%). The maximum severity grades of most subjects were mild (69% grade 1) and moderate (28% grade 2). Grade 3 GI events were 3% of the total GI events and occurred in <1% of subjects. There was one drug-related serious adverse event in each treatment arm across the two trials. • The FDA accepted the NDA for gepotidacin in the uUTI indication on October 16, 2024 *(29)*.

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Annex 6
FabI inhibitors – pyrido-enamides

Product name (INN or company code):	Afabicin (Debio 1450) prodrug of Debio 1452 (previously AFN-1252)
Pharmacology: chemical class and MoA:	Afabicin (Debio 1450) is a pyridoenamide and a selective enoyl-ACP reductase (FabI) inhibitor, a key enzyme in bacterial fatty acid biosynthesis *(1)*.
Spectrum of activity and potential resistance:	Afabicin activity in vitro is comparable to that of rifampicin, active against extra- and intracellular *S. aureus* (MRSA S186) independent of resistance patterns *(2)*. The risk of emergence of high-level resistance may be offset by high affinity for its target *(3)*. AFN-1252 was efficacious in in vivo data of murine acute lethal septicaemia models *(4)*.
Sought therapeutic indication:	Afabicin is being studied in the treatment of ABSSSI and bone and joint infection due to drug-resistant *S. aureus (5)*.
Route of administration:	High-dose and low-dose iv formulation with oral switch given as described below.
Phase of clinical development:	Phase 2.
Clinical trial(s):	A **Phase 1 trial** to assess the safety, tolerability and PK of single ascending iv dose of BWC0977 when administered to healthy adult volunteers recently completed (28 May 2023, **NCT05088421**). **Two Phase 2 trials (NCT03723551, NCT02426918)**.

Product name (INN or company code):	Afabicin (Debio 1450) prodrug of Debio 1452 (previously AFN-1252)
Clinical study results:	Phase 2 (NCT03723551, currently recruiting). A randomized, active-controlled, open-label study to assess the safety, tolerability and efficacy of afabicin in the treatment of participants with bone or joint infection due to *S. aureus* (both MSSA and MRSA and/or coagulase-negative staphylococci (CoNS) and to compare it to SOC in two arms: • iv at a dose 160 mg bid for a minimum of 1 day (two doses) and up to a maximum of 14 days (2 weeks), followed by a switch to oral afabicin at a dose of 240 mg bid; and • iv at a dose of 55 mg bid for a minimum of 1 day (two doses) and up to a maximum of 14 days (2 weeks) followed by a switch to oral afabicin at a dose of 80 mg bid for the remaining treatment duration (with a conditional higher dose of 80 mg bid for a minimum of 1 day (two doses) and up to a maximum of 14 days (2 weeks) followed by a switch to oral afabicin at a dose of 120 mg bid for the remaining treatment duration. Patient population: 18 years and older with a diagnosis of bone or joint infection that fulfils the following conditions: (i) infection is due to *S. aureus* (MSSA or MRSA) and/or CoNS only; and (ii) participants had received no more than 7 days of empiric antibiotics prior to initiating treatment with the study drug unless the pathogen isolated was resistant to the administered empiric antibiotics; and (iii) biofilm is not considered to be yet established and/or has been mechanically eradicated; and (iv) infection is not associated with a diabetic foot; and (v) infection can involve periosteal or soft tissue. Primary end-point: Number of participants with adverse events and serious adverse events based on nature, incidence, severity, and outcome, and change from baseline in number of participants with incidence of laboratory abnormalities. Phase 2 ((NCT02426918, completed September 2016). The efficacy, safety and tolerability of afabicin were compared with that of vancomycin/linezolid in the treatment of ABSSSI due to staphylococci in this multicentre, parallel-group, double-blind, double-dummy Phase 2 study. 330 randomized patients (1:1:1 ratio) received either low-dose afabicin (iv 80 mg, followed by oral 120 mg bid), high-dose afabicin (iv 160 mg, followed by oral 240 mg bid), or vancomycin/linezolid (iv vancomycin 1 g or 15 mg/kg, followed by oral linezolid 600 mg bid). Patient population: 18–70 years old with clinically documented infection of the skin or skin structure suspected or documented to be caused by a staphylococcal pathogen. Primary end-point: Early clinical response rate: percentage of responders to treatment at 48–72 h from randomization as assessed by the investigator (time frame: at 48–72 h from randomization (day 4)). Primary efficacy evaluation: Performed in the micro-MITT population using a non-inferiority margin of 15%. Study results: Early clinical response at 48–72 h was comparable among treatment groups (94.6%, 90.1% and 91.1% for low-dose afabicin, high-dose afabicin and vancomycin/linezolid, respectively) in the MITT population *(5)*. Low- and high-dose afabicin were found to be non-inferior to vancomycin/linezolid (difference, −3.5% (95% CI: -10.8–3.9) for low-dose afabicin; difference, 1.0% (95% CI: -7.3–9.2) for high-dose afabicin)) *(5)*.
Adverse effects:	Most common TEAEs were mild; headache (9.1% and 16.8%) and nausea (6.4% and 8.4%) with low- and high-dose afabicin, respectively *(5)*.

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Annex 7
FtsZ inhibitors

Product name (INN or company code):	TXA709
Pharmacology: chemical class and MoA:	TXA709 is a filamenting temperature-sensitive mutant Z (FtsZ)-targeting benzamide prodrug. Inhibition of FtsZ assembly restrains the cell-division complex known as the divisome, which results in destruction of the cell *(1,2)*.
Spectrum of activity and potential resistance:	In vitro, *S. aureus* isolates, including MRSA, demonstrated a MIC of 1 mg/L, with β-lactam resistance showing no impact on TXA707 potency *(3)*. The same authors state that similar in vitro results were obtained in a population of over 60 clinical *S. aureus* isolates, including those with beta-lactam resistance, where the MIC range was 0.5–2 mg/L (unpublished data, 3). TXA709/707 was shown to exhibit dose-dependent in vivo activity against *S. aureus* isolates, including those with β-lactam resistance *(3)*. Kaul et al. (2022) demonstrated recently that oxacillin is efficacious in mouse models of both systemic and tissue infection with MRSA when co-administered with TXA709 at human-equivalent doses below recommended daily dosages *(4)*.
Sought therapeutic indication:	Anti-MRSA. TXA709 is developed as an anti-resistance drug for combination therapy with a beta-lactam antibiotic.
Route of administration and proposed posology:	Oral.
Phase of clinical development:	Phase 1.
Clinical trial(s):	**First-in-human Phase 1 trial** completed according to public information on developer website *(5)*. No serious adverse events were recorded (company's unpublished data, *(5)*). Registration and further details unavailable.
Preclinical PK and safety:	In mice, the half-life ranged from 3.2 to 4.4 h, and AUC and Cmax were relatively linear over the doses studied *(3)*.

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Annex 8
ATP disruptors

Product name (INN or company code):	RECCE 327 (R327)
Pharmacology: chemical class and MoA:	RECCE 327 (R327) is a fully synthetic (acrolein) polymer designed to disrupt bacterial energy (ATP) production, cell growth and division.
Spectrum of activity and potential resistance:	In vitro (poster) data suggest broad-spectrum antibacterial activity against MDR strains of Gram-positive and Gram-negative bacteria, including *Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and Enterobacter spp. (Recce Pharmaceuticals, unpublished data, 2021) *(1)*. In vivo (poster) activity in these 'ESKAPE' pathogens has also been described in mouse model studies for kidney and UTI bacterial infection *(1)*.
Sought therapeutic indication:	RECCE 327 is being studied as a broad-spectrum intervention in infected burn wound care and diabetic foot infection, and in cUTI/urosepsis caused by ESBL-producing *Enterobacteriaceae*.
Route of administration:	Intravenous and topical gel/spray.
Phase of clinical development:	Recent completion of a **Phase 1 single iv ascending dose safety and PK study** with no publications as yet. A **phase 2 trial in urinary tract infections** is ongoing, but not registered, in 2024. Commencement of a **Phase 1b/2a proof-of-concept trial** for topical application of RECCE 327 for mild diabetic foot infections is planned *(2)*.
Clinical trial(s):	Four trials are listed in the Australian New Zealand Clinical Trials Registry: • **ACTRN12621001313820:** a Phase 1 ascending-dose, randomized, placebo-controlled, parallel, double-blind, single-dose, first-in-human study to evaluate the safety and PK of RECCE 327 in 80 healthy male subjects 18–55 years of age (June 2021 to December 2022, completed). • **ACTRN12623000448640:** a Phase 1 open-label, adaptive design evaluation, crossover study of the safety and PK/PD of various RECCE 327 intravenous dose and infusion rates. • **ACTRN12623000056695:** a Phase 1/2 proof-of-concept study of RECCE 327 topical anti-infective therapy for mild skin and soft tissue diabetes foot infections. • **ACTRN12621000412831:** a Phase 1 proof-of-concept study of RECCE 327 topical antibiotic therapy for infected burn wounds in adults.
Clinical study results:	Not yet publicly available.
Preclinical PK and safety:	In vivo poster data describe no adverse clinical signs in rats treated with RECCE 327, and it achieved broad distribution with particular concentration in urine (Recce Pharmaceuticals, unpublished data, 2021). In tests comparing 50 mg/kg and 500 mg/kg of R327 to vehicle control, the antibacterial effect was dose-dependent ($P < 0.050$) *(1)*.

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Annex 9
Antibiotic hybrids

Product name (INN or company code):	TNP-2092
Pharmacology: chemical class and MoA:	TNP-2092 is a rifamycin-quinolizinone hybrid (lead ABT-719) designed to reduce resistance to rifamycin and analogues. TNP-2092 produces a bactericidal effect by inhibiting the multi-target synergy of RNA polymerase, DNA gyrase and topoisomerase IV, reducing the frequency of drug resistance and influencing biofilm infection *(1)*.
Spectrum of activity and potential resistance:	The in vitro activity of TNP-2092 against a panel of urease-producing bacteria was similar to that of rifaximin *(2)*. It has been shown to be active in vitro against planktonic MRSA among other Gram-positives *(3)*. In vivo, TNP-2092 demonstrated potent efficacy in a mouse *Clostridioides difficile* infection (CDI) model, with no relapse observed after treatment *(4)*. TNP-2092 is not a substrate of fluoroquinolone efflux pumps, likely because of steric interference from the rifamycin pharmacophore; this is believed to confer lower propensity for resistance development *(3)*.
Sought therapeutic indication:	TNP-2092 is being investigated in patients with PJI and in ABSSSI caused by Gram-positive pathogens.
Route of administration and proposed posology:	Intravenous. 300 mg iv every 12 h.
Phase of clinical development:	Phase 2.
Clinical trial(s):	• **Phase 2:** A double-blind, randomized, multicentre, parallel, controlled study in patients with ABSSSI to evaluate the safety, tolerability, PK and efficacy of TNP-2092, 300 mg iv every 12 hours, compared with vancomycin 1 g iv every 12 hours **(NCT03964493)**. – Study population: 120 adults 18 years and older with ABSSSI suspected or confirmed to be caused by Gram-positive pathogens, randomly assigned to TNP-2092 300 mg iv every 12 h or vancomycin 1 g iv every 12 h. – Primary end-points: Three primary end-points were selected: ○ early clinical response at the early assessment visit in the ITT population, all randomized participants; ○ early clinical response at the early assessment visit in the MITT population, all randomized participants in the ITT population excluding those who have Gram-negative pathogens only; and ○ early clinical response at the early assessment visit in the micro-ITT population (all randomized participants in the MITT population with culture evidence of a baseline Gram-positive ABSSSI pathogen (exclude sole Gram-negative and culture-negative participants). – Time frame: Screening 48–72 h after the first dose of study treatment. Early clinical response is defined as responder meeting two criteria: (i) the patient has at least a 20% reduction of ABSSSI primary lesion size compared to baseline measurements; and (ii) patient did not die of any cause within 72 h of the first dose of study treatment.

Product name (INN or company code):	TNP-2092
Clinical study results:	Topline results published online *(1)*: The early clinical response rates at early assessment point (within 48–72 h after initiation of treatment, primary end-point of US-FDA guidance) in the ITT population were 76.3% for TNP-2092 and 67.5% for vancomycin *(1)*. The post-treatment success rates in the clinical evaluable population were 96.4% for TNP2092 and 92.6% for vancomycin *(1)*. MRSA was the most common pathogen isolated, accounting for about 50% of all pathogens isolated. In a subpopulation analysis, TNP-2092 appeared to be equally efficacious against infections caused by MRSA and other pathogens. Incidence of TEAEs were similar between the two treatment groups *(1)*. Adverse events as per data released on clinicaltrials.gov *(5)*, the most common adverse events were: nausea (15.38% vs 5.13% vancomycin), vomiting (7.69% vs 5.13 vancomycin), wound infections (2.56% vs 5.13 vancomycin) and cellulitis (8.97% vs 12.82 vancomycin). MRSA bacteraemia and worsening cellulitis was observed in 1.28% of patients treated with TNP-2092 vs no case in the vancomycin group.

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Annex 10
Agents in development for treating drug-resistant TB

10.1 Respiratory chain inhibitors

Product name (INN or company code):	Sudapyridine (WX-081)
Pharmacology: chemical class and MoA:	Sudapyridine (WX-081) is respiratory chain inhibitor, a bedaquiline analog with improved non-clinical toxicology profile *(1,2)*.
Spectrum of activity and potential resistance:	It displayed exceptional anti-mycobacterial activity against *M. tuberculosis* H37Rv in vitro and in vivo *(1)*. WX-081 has a strong antimicrobial activity against different non-tuberculosis mycobacterium species with low cytotoxicity *(3)*. Yu et al (2024) *(4)* evaluated the efficacy of sudapyridine (S) with clofazimine(C) and the bacteriostatic candidate TB47 (SCT) in combination with linezolid (L) or pyrazinamide (Z) using a murine model of TB. Compared to the BPa (pretomanid) L regimen, SCT and SCTL demonstrated similar bactericidal and sterilizing activities.
Sought therapeutic indication:	Isoniazid- and Rifampicin-resistant (MDR) *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 3.

Product name (INN or company code):	Sudapyridine (WX-081)
Clinical trial(s):	**Phase 3:** A multicentre, randomized, double-blind, positive control study to evaluate the efficacy and safety of sudapyridine (WX-081) tablets in approximately 450 patients with rifampicin-resistant pulmonary TB (**NCT05824871**, enrolling by invite). **Study population:** Adult male or female, 18 to 65 year-old patients with clinically diagnosed TB whose drug sensitivity test has proved to be at least resistant to rifampicin, phenotypic or molecular drug sensitivity test results within three months before the subject signs informed consent can be accepted. **Primary outcome:** The percentage of participants with sputum culture conversion. **Phase 2:** A multi-centre, randomized, positive-controlled clinical trial to evaluate the early bactericidal activity, safety and tolerability of WX-081 in 99 participants with drug-naive and susceptible or drug-resistant pulmonary TB (**NCT04608955**, completed April 2022). **Study population:** Consented adults, 18 to 65 year-old male or female newly treated drug sensitive TB: clinically diagnosed as pulmonary TB, without treatment, sputum smear-positive for acid-fast bacilli (AFB at least 1+), and no resistance to rifampicin or isoniazid in the drug sensitivity test. Drug-resistant TB: re-treatment pulmonary TB patients, diagnosed as rifampicin resistance (RR-TB) or isoniazid and rifampicin resistance (MDR-TB) by molecular biology methods, and sputum smear-positive for acid-fast bacilli. Patients must be willing to discontinue all TB drugs to allow 7 days washout. **Two stages:** Core research stage (stage 1) and Extended research stage (stage 2): • During stage 1, a panel of 59 participants with drug-naive and susceptible TB will be randomized to receive either WX-081 (including three groups: 150mg qd, 300mg qd, 450mg qd, n=12 per group) or standard treatment (n=8) for 2 weeks, and then followed by a follow-up period of 2 weeks. • A panel of 40 participants with drug-resistant TB will be randomized to receive either WX-081 (400mg qd, n=20) or bedaquiline (400mg qd, n=20) for 2 weeks. During stage 2, the 40 participants with drug-resistant TB will receive WX-081(150mg qd) + MBT treatment (ie. multidrug background treatment) and bedaquiline (200mg tiw) +MBT treatment for 6 weeks respectively, and then followed by a follow-up period of 4 weeks. **Primary outcome:** Time to positive (TTP), early bactericidal activity (EBA) of WX-081. **Phase 1:** A single-centre, randomized, double-blind, placebo-controlled, dose-ascending trial to evaluate the safety, tolerability and pharmacokinetic characteristics of sudapyridine (WX-081) tablets in 82 healthy Chinese subjects (**NCT06117514**, completed July 2020).
Clinical study results:	No QTc prolongation was observed, and adverse events were not dose-dependent. The authors describe favourable exposure, tolerability, safety and an extended MRT0-t *(4)*.
Adverse effects/ preclinical PK and safety:	WX-081 improved pharmacokinetic parameters and, more importantly, had no adverse effects on blood pressure, heart rate, or qualitative ECG parameters from nonclinical toxicology studies *(3)*. WX-081 had excellent pharmcokinetic parameters in animals, better lung exposure and lower QTc prolongation potential compared to bedaquiline *(1)*.

Product name (INN or company code):	TBAJ-876
Pharmacology: chemical class and MoA:	TBAJ-876 is a diarylquinoline bedaquiline (BDQ) analogue with improved affinity for F-ATP synthase to inhibit mycobacterial respiratory chain *(5)*. Recent data suggest that TBAJ-876 action may be mainly mediated by its major active metabolite, TBAJ-876-M3 *(6)*.
Spectrum of activity and potential resistance:	TBAJ-876, displays improved in vitro activity and preclinical safety profile compared to BDQ *(7,8)*. In a murine model of TB, TBAJ-876 demonstrated lower MIC against an Rv0678 loss-of-function mutant with resistance to BDQ and clofazimine, and doses ≥6.25 mg/kg of TBAJ-876 had greater efficacy against both wild-type and mutant strains compared to BDQ at 25 mg/kg, with no selective amplification of BDQ-resistant bacteria observed *(8)*.

Product name (INN or company code):	TBAJ-876
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis*
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 2 (NC-009):** A partially-blinded, randomized trial assessing the safety and efficacy of TBAJ-876 or bedaquiline, in combination with pretomanid and linezolid in 309 adult participants with newly diagnosed, drug-sensitive, smear-positive pulmonary TB (**NCT06058299**, active, not recruiting) *(9)*. **Time period:** October 2023 to June 2026. **Study population:** Adults (18 to 65) with TB sensitive to rifampicin and isoniazid either newly diagnosed or with a history of being untreated for at least three years after cure from a previous episode of TB. Participants will be randomized in a 1:1:1:1:1 ratio using an interactive response technology that stratifies based on country and severity of disease (AFB 3+ and/or bilateral cavitation) to 1 of the 5 treatment arms. **Primary outcome measure:** Time to stable sputum culture conversion to negative status using data from weekly cultures through 8 weeks of treatment. **Phase 1:** A drug–drug interaction study to evaluate the safety, tolerability and the induction potential of TBAJ-876 on CYP3A4 and P-glycoprotein and the inhibition potential of TBAJ-876 on P-glycoprotein in 28 healthy adult subjects (**NCT05526911,** completed August 2022). **Phase 1:** A partially blind, placebo controlled, randomized, combined single ascending dose (SAD) with a food effect cohort and multiple ascending dose (MAD) study to evaluate the safety, tolerability, and pharmacokinetics of TBAJ-876 in 165 healthy adult subjects (N**CT04493671**, completed Nov 2022).
Clinical study results:	According to Lombardi et al. (2024) *(10)*, TBAJ-876 was well-tolerated at single doses up to 800 mg and multiple doses up to 200 mg for 14 days. No deaths or SAEs occurred. No episodes of clinically significant prolongation of the QTc interval were observed. TBAJ-876 exposures were dose proportional in the SAD and MAD studies. TBAJ-876 exhibited multicompartmental PK with a long terminal half-life yielding quantifiable concentrations up to the longest follow-up of 10 weeks after a single dose and resulting in accumulation with multiple dosing. In the fed state, TBAJ-876 exposures approximately doubled with the tablet formulation, whereas M3 metabolite exposures decreased by approximately 20%. The relative bioavailability of TBAJ-876 was similar between tablets and the oral suspension at 100 mg doses. With co-administration of TBAJ-876, the AUC0-inf of midazolam was unchanged and the Cmax was reduced by 14%; the AUC0-last of digoxin was increased by 51%, and the Cmax was increased by 18% *(10)*.
Adverse effects/ Preclinical PK and safety:	3,5-dialkoxypyridine analogues of BDQ are less lipophilic, have higher clearance, and display lower cardiotoxic potential *(11–14)*.

Product name (INN or company code):	Telacebec (Q203)
Pharmacology: chemical class and MoA:	Telacebec (Q203) is an imidazopyridine amide that targets the respiratory cytochrome bc1 complex to inhibit mycobacterial cellular energy production *(15)*.
Spectrum of activity and potential resistance:	Telacebec was found to be active in macrophages infected with both pan-susceptible and MDR-TB in in vitro studies *(15–19)*. In a mouse model of TB, the compound demonstrated efficacy at a dose of less than 1 mg per kg body weight *(15)*. Komm et al (2024) *(20)* describe that Telacebec was more effective in regimens against the clinical "hypervirulent" *M. tuberculosis* HN878 strain than the H37Rv strain, highlighting its unique potential *(20)*. A phase 2 study (TREAT-BU) commenced in 2024 to investigate Telacebec as a potential treatment in Buruli ulcer (NCT06481163).
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.
Clinical trial(s):	Phase 2: An open-label randomized study to evaluate the early bactericidal activity, safety, tolerability and PK of multiple oral doses of telacebec (Q203) in 60 treatment-naïve patients with newly diagnosed drug-sensitive, sputum smear-positive, pulmonary TB (**NCT03563599**, completed Sept 2019). **Study population:** Consented 18–65 year-old, male or female adults with newly positive pulmonary TB on effective contraceptive (or non-childbearing potential) *(18)*. **Primary outcome:** The early bactericidal activity (EBA) of Telacebec. **Phase 1b:** A randomized, placebo-controlled, double-blind, multiple ascending dose study to evaluate the safety, tolerability and PK of Q203 when administered orally to 47 healthy adult subjects (**NCT02858973,** Completed May 2018). **Phase 2:** An open-label, randomized controlled trial to evaluate the biomarker change, efficacy, PK, safety and tolerability of telacebec in participants with moderate COVID-19 disease (**NCT04847583,** Terminated).
Clinical study results:	In the Phase 2 trial (NCT03563599), increasing doses of telacebec were associated with greater reductions in viable mycobacterial sputum load. Daily increase in log10 time to positivity of 0.0036 (95% CI: 0.0013–0.0060), 0.0087 (95% CI: 0.0064 –0.0110), and 0.0135 (95% CI: 0.0112–0.0158) for telacebec at a dose of 100 mg, 200 mg and 300 mg, respectively *(19)*. Telacebec was associated with acceptable adverse event rates, and adverse events were equally distributed among all groups. There were no serious adverse drug reactions and no adverse drug reactions that resulted in early withdrawal from the study *(19)*. In the Phase 1b trial (NCT02858973), multiple oral doses of telacebec up to 320 mg daily for 14 days appeared to be safe and well tolerated by healthy adult subjects in this study *(21)*. There were no deaths, serious adverse events, or subject discontinuations due to adverse events. Three potential metabolites of telacebec have been identified, which may be relatively minimal compared to the parent drug *(21)*.

Product name (INN or company code):	TBAJ-587
Pharmacology: chemical class and MoA:	TBAJ-587 is a diarylquinoline bedaquiline (BDQ) analogue with a reduced cardiotoxicity profile compared to BDQ, beneficial in treating drug-resistant TB *(7,22)*.
Spectrum of activity and potential resistance:	TBAJ-587 has shown greater potency than BDQ in vitro, including against Rv0678 mutants with resistance to bedaquiline and clofazimine, and may offer a larger safety margin *(22)*. In a TB mouse model and different doses of BDQ and TBAJ-587, TBAJ-587 had greater efficacy against both strains than BDQ, whether alone or in combination with pretomanid and either linezolid or moxifloxacin and pyrazinamide *(22)*. TBAJ-587 also reduced the emergence of resistance to diarylquinolines and pretomanid *(22)*. In the TB mouse model, Li et al. *(23)* found that the combination of BDQ, GSK2556286, and TBA-7371 was more active than the first-line regimen and nearly as effective as BDQ, pretomanid and linezolid (BpaL) in bactericidal and sterilizing activity. GSK2556286 and TBA-7371 were also found to be as effective as pretomanid and the novel oxazolidinone TBI-223 when either drug pair was combined with TBAJ-587 and that the addition of GSK2556286 increased the bactericidal activity of the TBAJ-587, pretomanid and TBI-223 combination *(23)*. In a checkerboard assay, Fan et al *(24)* described that TBAJ-587 expressed bactericidal activity and was compatible with eight anti- nontuberculous mycobacteria (NTM) drugs commonly used in clinical practice; no antagonism was discovered.
Sought therapeutic indication:	Drug-resistant *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 1.
Clinical trial(s):	**Phase 1:** A partially blinded, placebo-controlled, randomized, combined single ascending dose with food effect cohort trial (part 1) and multiple ascending dose trial (part 2) to evaluate the safety, tolerability, and PK of TBAJ-587 in 106 healthy adults (**NCT04890535**, Completed Feb 2023)
Adverse effects/ Preclinical PK and safety:	BDQ analogues TBAJ-587 and TBAJ-876 had lower MICs than BDQ against clinical isolates of *M. tuberculosis*, efficacy demonstrated against murine TB at lower exposures than BDQ, lower potency against hERG, predicted higher human clearance, and an acceptable safety margin, based on the safe exposure in rats compared to the efficacious exposure in mice *(7)*.

Product name (INN or company code):	BTZ-043
Pharmacology: chemical class and MoA:	BTZ-043 is a benzothiazinone that inhibits DprE1, a crucial enzyme involved in *M. tuberculosis* cell wall synthesis *(25)*.
Spectrum of activity and potential resistance:	BTZ-043 is effective against various strains of *M. tuberculosis*, including those from MDR and XDR patients. In vitro, it shows a MIC range of approximately 0.1 – 80 ng/ml for fast growers and 1 – 30 ng/ml for *M. tuberculosis* complex members *(26)*. In mouse models, BTZ-043 exhibits enhanced activity compared to isoniazid, especially after 2 months and synergistic effects are observed when combined with rifampicin and bedaquiline *(26)*. Significant reductions in lung and spleen bacterial burdens were also observed following BTZ-043 monotherapy in the C3HeB/FeJ mouse that displays a human-like pathology *(27)*. BTZ-043-treated guinea pigs, subcutaneously infected with virulent *M. tuberculosis*, had reduced and less necrotic granulomas and a highly significant reduction of the bacterial burden compared with vehicle-treated controls *(28)*.
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.

Product name (INN or company code):	BTZ-043
Clinical trial(s):	**Phase 2A:** detailed in the product profile of Ganfeborole (GSK3036656) (**NCT05382312**, recruiting); sponsored by GlaxoSmithKline. **Phase 2B/C (PARADIGM4TB):** Randomized, open-label multicentre platform trial to evaluate multiple regimens and durations of treatment in pulmonary tuberculosis evaluating both BTZ-043 and Ganfeborole (GSK3036656) (**NCT06114628**, recruiting) **Study population:** 2500 consented adults (≥18 years old) male or female participants with clinical evidence of active TB disease meeting detailed eligibility criteria. • **Phase 2B:** Regimen selection; to identify novel regimens of 16 weeks' duration with acceptable safety profile and the greatest potential, based on assessment of quantitative sputum liquid culture and treatment failure/relapse, to progress to investigation of optimal treatment duration. Participants will be randomized (1:1:1:1) to following 12 arms initially with the potential of adding others. • **Phase 2C:** Duration randomization; for regimens selected for progression (following interim phase 2B evaluation). Participants will be randomized to treatment durations of either 8 weeks, 10 weeks, 12 weeks, 14 weeks, 16 weeks or to the 24-week SOC regimen (as described). Primary outcome measure: • **Phase 2B:** rate of change in log10 (TTP) over 0 to 12 weeks, where TTP is time to positivity measured in days from MGIT culture. • **Phase 2C:** Favourable/unfavourable status (binary) at week 48 from randomization. **Phase (PanACEA) 2B/C:** Randomized, open-label, multicentre controlled platform trial, will evaluate experimental arms including an increased dose of rifampicin, on optimized dose of pyrazinamide, moxifloxacin and BTZ-043, in adults with newly diagnosed, drug sensitive, smear-positive pulmonary tuberculosis (**NCT05807399**, recruiting). **Study population:** A total of up to 270 consented adult (≥ 18 years of age) male or female participants with newly diagnosed, previously treated, drug susceptible pulmonary TB will be enrolled. In stage 1, participants will be randomly allocated to the control or one of the 2 rifampicin-containing experimental regimens in the ratio 1:1:1. In stage 2, the experimental arm 4 containing Sutezolid will be added. Participants will be allocated to control or one of the three experimental regimens in the ratio 1:1:1:1. Towards the end of stage 2, when experimental arms 1 and 2 will be fully enrolled, participants will be randomized 1:1 to control and experimental arm 4 containing BTZ-043. **Primary outcome measure:** Time to stable culture conversion to negative in liquid media. **Phase 2b (DECISION):** Open-label, randomized controlled dose ranging multi-centre trial to evaluate the safety, tolerability, pharmacokinetics and exposure-response relationship of different doses of BTZ-043 in combination with bedaquiline and delamanid in 90 adult subjects with newly diagnosed, uncomplicated, drug-sensitive pulmonary tuberculosis (**NCT05926466**, recruiting) **Study population:** Consented adult male or female, 18 to 64 years-old, with newly diagnosed, previously untreated current episode of drug-susceptible pulmonary TB (presence of MTB complex with rapid molecular test result confirming susceptibility to rifampicin and isoniazid such as GeneXpert and/or HAIN MTBDR plus) able to provide sputum of adequate volume regularly and on effective contraceptive.

Product name (INN or company code):	BTZ-043
Clinical trial(s):	**There will be four study arms:** • An active comparator arm with moxifloxacin will be dosed at the licensed dose of 400 mg orally once daily for 16 weeks. Bedaquiline will be dosed at 400 mg orally once daily for the first 2 weeks, followed by 100 mg orally once daily for 14 weeks. Delamanid will be dosed at 300 mg orally once daily for 16 weeks. • Three experimental arms with bedaquiline and delamanid dosed as above stated + BTZ-043 at either 500 mg, 1000 mg or 1500 mg orally once daily for 16 weeks. **Primary outcome measure:** Time to positivity in BD MGIT liquid culture. Phase 1/2: A prospective Phase 1b/2a, active-controlled, randomized, open-label study to evaluate the safety, tolerability, extended early bactericidal activity and PK of multiple oral doses of BTZ-043 tablets in 77 subjects with newly diagnosed, uncomplicated, smear-positive, drug-susceptible pulmonary TB (**NCT04044001**, completed May 2022). **Phase 1:** A single-center, open label study to investigate the mass balance, excretion pathways and metabolites after a single oral dose of 500 mg, 3.7 MBq, [14C] BTZ-043 in 6 healthy male volunteers (**NCT04874948**, completed Oct 2021). **Phase 1:** A randomized, double blind, placebo-controlled, single ascending dose study to evaluate safety, tolerability and PK of single doses of BTZ043 in 30 healthy adult volunteers (**NCT03590600**, completed March 2019).
Clinical study results:	Study results for the Phase 1/2 trial (NCT04044001) were published as pre-prints without peer-review *(29)*. BTZ-043 was active and safe from 250 mg to 1750mg over 14 days. Among 24 participants in stage 1, dose escalation was conducted safely up to 1750 mg daily. In stage 2, 54 participants were randomized to 250 mg, 500 mg, 1000 mg BTZ-043, or control. Mild and moderate nausea were the most frequent AEs. Mild to moderate raises in transaminases were transient and declined despite continued dosing. All doses in stage 2 showed 14-day bactericidal activity, highest with 1000 mg at -0.115log10CFU/ml*d (95% CI: -0.162–0.069). BTZ-043 was active and safe from 250 mg to 1750 mg over 14 days *(29)*.
Adverse effects/ Preclinical PK and safety:	In preclinical toxicology (GLP) studies, BTZ-043 showed a low toxicologic potential, there was no observed adverse effect level (NOAEL) up to 170 mg/kg (NOAEL) in rats and 360 mg/kg in minipigs over 28 days *(26)*. In a safety panel (neurotoxicity, cardiotoxicity and respiratory toxicity) no negative effects were observed. Phototoxicity, genotoxicity and mutagenicity studies were negative *(26)*.

10.2 Mycobacterial cell wall synthesis disruptors

Product name (INN or company code):	Quabodepistat (OPC-167832)
Pharmacology: chemical class and MoA:	Quabodepistat (OPC-167832) is a 3,4 dihydrocarbostyril derivative that inhibits DprE1, an enzyme crucial to mycobacterium cell wall biosynthesis *(30–32)*.
Spectrum of activity and potential resistance:	OPC-167832 demonstrated potent bactericidal activity against *M. tuberculosis*, including MDR strains, with MICs ranging from 0.00024 to 0.002 µg/ml *(30,33)*. In a TB mouse model, OPC-167832 demonstrated potent bactericidal activity, particularly in combination with delamanid, bedaquiline, or levofloxacin moxifloxacin, or linezolid *(30,33)*.
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.

Product name (INN or company code):	Quabodepistat (OPC-167832)
Phase of clinical development:	Phase 2b/c.
Clinical trial(s):	**Phase 2b/c:** A multi-arm, 2-stage, duration randomized trial of the efficacy and safety of two to four months treatment with regimens containing bedaquiline, opc-167832 and sutezolid, plus either pretomanid or delamanid, in 514 adults with pulmonary TB (**NCT05971602**, active, not recruiting). **Study population:** Stage 1. Consented adults, 18–65 year-old, newly diagnosed within the past three weeks prior to informed consent, untreated (≤4 days of treatment), drug-susceptible pulmonary TB based on predetermined criteria, on appropriate contraception with further criteria for Stage 2 based on treatment for confirmed DS or RR-TB. **Primary outcome:** Stage 1: Percentage of participants with DS-TB reporting severe AEs (≥ Grade 3) and/or SAEs, by treatment group; percentage of participants with pulmonary DS-TB with unfavourable outcome, by treatment group. Stage 2: Percentage of participants with DS-TB reporting severe AEs (≥ Grade 3) and/or SAEs, by treatment group, percentage of participants with pulmonary DS-TB reporting unfavourable outcome, by treatment group **Phase 2b/c:** A multicentre, open-label, randomized, dose-finding trial to evaluate the safety and efficacy of a 4-month regimen of OPC-167832 in combination with delamanid and bedaquiline in 120 subjects with drug-susceptible pulmonary TB in comparison with standard treatment (**NCT05221502**, completed May 2024) *(34)*. **Study population:** Consented adults, 18–65 year old, male or female and newly diagnosed, rifampin- and isoniazid-susceptible (on the screening sample) pulmonary TB, and on effective contraception. **Primary outcomes:** • Incidence of TEAEs. • Incidence of potentially clinically significant changes of laboratory tests from baseline and abnormalities in the vital signs, physical examinations, ECGs at each visit were assessed and at end of study. • Number of participants with a grade 3 or higher AE. • Number of all cause treatment discontinuation. • Sputum culture conversion (SCC) in Mycobacteria Growth Indicator Tube® (MGIT). **Phase 1/2:** An active-controlled, randomized, open-label trial to evaluate the safety, tolerability, PK and efficacy of multiple oral doses of OPC-**167832** tablets in 122 subjects with uncomplicated, smear-positive, drug-susceptible pulmonary TB (**NCT03678688**, completed March 2022) . The study comprised two stages: In stage 1, multiple doses of OPC-**167832** (3, 10, 30 and 90 mg) once daily followed, from day 15 to day 20, by the combination of rifampicin, 75 mg isoniazid, 400 mg pyrazinamide, and 275 mg ethambutol (RHEZ) were tested against RHEZ from Day 1 to Day 20. **Study population:** Consented, adult (18–64 year-old), newly diagnosed, uncomplicated, drug-susceptible pulmonary TB able to provide an adequate volume of sputum regularly, and on effective contraception. **Stage 1 Primary outcomes:** • Safety. • PK parameters.
Adverse effects/ Preclinical PK and safety:	In the Phase 1/2, stage 1 study (**NCT03678688**), OPC 167832 was well tolerated at all single doses; nearly all treatment-related adverse events were mild and self-limiting, with headache and pruritus being the most common events *(35)*. Abnormal ECG results were rare and clinically insignificant. OPC-167832 plasma exposure increased in a less than dose-proportional manner, with mean accumulation ratios ranging from 1.26 to 1.56 for Cmax and 1.55 to 2.01 for AUC time curve from 0 to 24 h (AUC0–24h). Mean terminal half-lives ranged from 15.1 to 23.6 h *(35)*.

Product name (INN or company code):	TBA-7371 (AZ 7371)
Pharmacology: chemical class and MoA:	TBA-7371 is a substituted 1,4-azaindole that inhibits DprE1, a crucial enzyme involved in *M. tuberculosis* cell wall synthesis *(36)*.
Spectrum of activity and potential resistance:	In vitro, TBA-7371 showed an MIC value of 1 µg/mL in a broth microdilution assay, with a 2-fold shift in the presence of 4% human serum albumin in the same study *(37)*. In a comparative analysis of DprE1 inhibitors, TBA-7371, PBTZ169 and OPC-167832 were effective in treating TB in the C3HeB/FeJ mouse model after two months of treatment *(37)*. In the TB mouse model, Li et al. *(23)* found that the combination of bedaquiline, GSK2556286 and TBA-7371 was more active than the first-line regimen, and nearly as effective as bedaquiline, pretomanid and linezolid (BpaL) in bactericidal and sterilizing activity. GSK2556286 and TBA-7371 were also found to be as effective as pretomanid and the novel oxazolidinone TBI-223 when either drug pair was combined with TBAJ-587 and that the addition of GSK2556286 increased the bactericidal activity of the TBAJ-587, pretomanid, and TBI-223 combination *(23)*.
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 2a:** A dose escalation, controlled, randomized study to evaluate safety, early bactericidal activity (EBA) and pharmacokinetics of TBA-7371 in 93 adult patients with rifampicin-sensitive pulmonary tuberculosis (**NCT04176250**, completed Oct 2022). **Study population:** Consented adults, 18-60 year-olds, male or female with untreated, rifampicin-sensitive pulmonary TB, on effective birth control. **Primary outcome:** Slope of average change per Day, from Day 0 to Day 14 [BAcfu (0-14)] of the Log CFU counts, number of participants who experienced one or more severe (≥ grade 3) and/or serious adverse events (SAEs). **Phase 1:** A partially blind, placebo controlled, randomized, combined SAD with food effect cohort and MAD and DDI Study to evaluate safety, tolerability, PK and PK interaction between TBA-7371 with midazolam and bupropion in 74 healthy subjects. (**NCT03199339**, completed July 2018)
Adverse effects/ Preclinical PK and safety:	TBA-7371 demonstrated safety in vitro without cytotoxicity up to 100 µM and efficacy in both acute and chronic BALB/c mouse models, with a more than 2-log10 CFU reduction in lungs in the acute model and a 1.5-log10 CFU reduction in the chronic model at 100 mg/kg QD dosing *(37)*.

Product name (INN or company code):	Macozinone (MCZ, PBTZ-169)
Pharmacology: chemical class and MoA:	Macozinone (PBTZ-169) is a piperazine-benzothiazinone that inhibits the enzyme DprE1, which is necessary for the growth and viability of mycobacteria *(31,32,38)*. It is a second-generation analogue of BTZ043 with physicochemical and pharmacokinetic optimization efforts underway *(39)*.
Spectrum of activity and potential resistance:	In vitro, piperazine-benzothiazinones (PBTZ) have been shown to reach MICs between 0.19–0.75 ng/ml for *M. tuberculosis*, and PBTZ169 was shown to be highly active against a panel of nine MDR- and XDR-clinical isolates of *M. tuberculosis (25)*. Cross-resistance between BTZ043 and PBTZ169 was confirmed for BTZ-resistant strains of *M. tuberculosis*, *M. bovis* BCG and *M. smegmatis*, indicating the common MoA *(25)*. The in vivo efficacy of BTZ043 was assessed four weeks after a low-dose aerosol infection of BALB/c mice in the chronic (lung and spleen) model of TB. Treatment with BTZ043 reduced the bacterial burden in the lungs and spleens by 1 and 2 logs, respectively which was time- (rather than dose-) dependent *(40)*. The in vitro and in vivo synergistic effect of PBT169 and TBI-166 showed a reduction of MIC by 6.25–25.00% and a lower amount of viable *M. tuberculosis* mouse lung tissues with respect to TBI-166 monotherapy *(38,41)*.

Product name (INN or company code):	Macozinone (MCZ, PBTZ-169)
Sought therapeutic indication:	MDR-, XDR- *M. tuberculosis*.
Pharmaceutical form, route of administration:	PO tablet, capsule or suspension (extended- and immediate-release).
Phase of clinical development:	Phase 1.
Clinical trial(s):	**A Phase 2a** study in the Russian Federation was terminated due to very slow enrolment (**NCT03334734**, last update 2020). **Phase 1:** A randomized, double-blind, placebo-controlled, multiple ascending dose study conducted at a study centre in Switzerland (**NCT03776500**, completed March 2020). **Phase 1:** An open-label, prospective, non-comparative, ascending dose randomized cohort study of single and multiple oral administration of PBTZ169 (capsules 80 mg) in healthy volunteers (**NCT04150224**, completed February 2019). Phase 1: An open-label, prospective, non-comparative safety, tolerability and PK ascending dose, randomized cohort study of PBTZ169 (capsules 40 mg) in fasted healthy volunteers after single and multiple oral administration (**NCT03036163**, completed November 2016). **Phase 1a:** A safety, tolerability, pharmacokinetic profile and ex-vivo antitubercular activity study of PBTZ169 formulated as spray- dried dispersion versus native crystal powder: single ascending doses, randomized, placebo- controlled, cross-over phase trial in healthy volunteers (**NCT03423030**, completed March 2018).
Clinical results:	In the Phase 2a study (NCT03334734, now terminated) the developer reported an acceptable safety profile in drug-sensitiveTB patients and a statistically significant EBA after 14 days monotherapy in the group of seven patients treated with 640 mg of PBTZ169 *(42)*.
Adverse effects/ Preclinical PK and safety:	Acute (5 g/kg) and chronic (25 and 250 mg/kg) toxicology studies in uninfected mice showed that, even at the highest dose tested, there were no adverse anatomical, behavioural, or physiological effects after one month *(40)*.

Product name (INN or company code):	Sutezolid (PF-2341272, PNU-100480
Pharmacology: chemical class and MoA:	Sutezolid (PF-2341272, PNU-100480) is an oxazolidinone that targets an early step in protein synthesis involving the binding of N-formylmethionyl-tRNA to the ribosome *(43)*.
Spectrum of activity and potential resistance:	Sutezolid demonstrated MIC90 values of 0.50 micrograms/mL or less against drug-sensitive and five multidrug-resistant strains of *M. tuberculosis (44)*. In vivo, oral sutezolid showed efficacy against *M. tuberculosis* and *M. avium* like that of clinical comparators isoniazid and azithromycin, respectively *(44)*. Both in vitro and in vivo studies showed its improved antimycobacterial action and safety profile compared to linezolid. Sutezolid (PNU-100480), TMC207 and SQ109, were predicted to have cumulative activity comparable to standard TB therapy based on concentration-activity relationship and pharmacokinetic data in a rapid evaluation in whole blood culture *(45)*. The addition of sutezolid to current first-line anti-TB drugs and moxifloxacin improved bactericidal activities, resulting in a significant reduction in lung CFU counts (2.0-log(10)-unit) during the first two months of treatment *(46)*. The combination of PNU-100480, moxifloxacin and pyrazinamide was also more active than rifampin, isoniazid and pyrazinamide *(46)*. In a *M. tuberculosis* murine model, a dose-response study showed that sutezolid was more active than linezolid (at 25, 50 and 100 mg/kg of body weight) and its efficacy increased with an escalation of the dose *(47)*. Of note these are preclinical data described.
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis* and NTM.
Pharmaceutical form, route of administration:	Oral.

Product name (INN or company code):	Sutezolid (PF-2341272, PNU-100480
Phase of clinical development:	Phase 2/3.
Clinical trial(s):	See quabodepistat (OPC-167832) for **Phase 2 study** (NCT05971602), a multicentre, two-stage, open-label, randomized trial will aim to assess the efficacy, safety, optimal duration and PK of delamanid, bedaquiline, OPC-167832, and sutezolid (DBOS) and pretomanid, bedaquiline, OPC-167832, and sutezolid (PBOS) in adult participants with DS-TB and rifampicin or multidrug-resistant TB (RR/MDR-TB) (Active, not recruiting). **A Phase 2/3:** A novel 4-month, pan-TB regimen targeting both host and microbe (panTB-HM) (**NCT05686356**, currently recruiting). **Study population:** 352 participants randomized, parallel assignment. **Primary outcome measures:** The proportion of patients achieving durable (non-relapsing) cure. **Phase 2 (A5409/RAD-TB):** An adaptive, randomized, controlled, open-label, dose-ranging, platform protocol to evaluate the safety and efficacy of multidrug regimens for the treatment of adults with DS-TB (**NCT06192160**, not yet recruiting). The study includes novel agents sutezolid and TBI-223 and hypothesizes that novel regimens for the treatment of pulmonary TB will result in superior early efficacy. **Study population:** Adult patients (18 years or older) with pulmonary TB identified within 7 days prior to study entry by at least one sputum specimen by Xpert. **Primary outcome measure:** • Difference in mean log10 (time to positivity (TTP)) slope from longitudinal mycobacteria growth indicator tube (MGIT) liquid culture measurements over the first 6 weeks of treatment. • Difference in the cumulative proportion of participants having at least one new Grade 3 or higher adverse event (AE) by week 8 of treatment. **Phase 2a:** Open-label, randomized study in 59 treatment-naive, sputum smear-positive subjects with drug-sensitive pulmonary TB, to assess EBA and whole blood activity (WBA) of PNU-100480 (PF-02341272) (**NCT01225640**, completed December 2011). **Study population:** Consented adults, male or female, and reasonably healthy newly diagnosed sputum smear-positive pulmonary TB confirmed with AFB smear and chest x-ray. Patients with TB more than five years ago who completed treatment, were healthy, and met other inclusion criteria, were considered for inclusion. Parallel assignment. **Primary End-point:** Rate of change in sputum log CFU/mL count (EBA) from Days 0–2. **A Phase 2B (SUDOCU):** Open-label, randomized controlled dose ranging multicentre trial to evaluate the safety, tolerability, PK and exposure-response relationship of different doses of sutezolid in combination with bedaquiline, delamanid and moxifloxacin in adult subjects with newly diagnosed, uncomplicated, smear-positive, drug-sensitive pulmonary tuberculosis (**NCT03959566**, completed Sept 2022). **Study population:** A total of 75 male/female subjects, aged between 18 and 65 years, with newly diagnosed, drug-sensitive, uncomplicated, smear-positive, pulmonary TB will be included and randomized to one of five arms containing bedaquiline, delamanid and moxifloxacin with different doses of sutezolid : (0mg, 600mg once daily (OD), 1200mg OD, 600 mg twice daily (BD), 800 mg BD). **Primary efficacy end-point:** Change in sputum mycobacterial load over time. **Primary safety end-point:** Proportion of patients experiencing adverse events.

Product name (INN or company code):	Sutezolid (PF-2341272, PNU-100480
Clinical trial(s):	**Phase 2b/c (PanACEA):** A multiple arm, multiple stage (MAMS), open label, randomized, controlled platform trial to evaluate experimental arms including an increased dose of rifampicin, an optimized dose of pyrazinamide, moxifloxacin and sutezolid, in 360 adult subjects (**NCT05807399**, recruiting). **Study population:** Newly diagnosed, smear-positive pulmonary TB: In stage 1, participants will be randomly allocated to the control or one of the 2 rifampicin-containing experimental regimens in the ratio 1:1:1. In stage 2, the experimental arm 4 containing sutezolid will be added. Participants will be allocated to control or one of the three experimental regimens in the ratio 1:1:1:1. Towards the end of stage 2, when experimental arms 1 and 2 will be fully enrolled, participants will be randomized 1:1 to control and experimental arm 4. **Primary outcome measure:** Time to stable culture conversion to negative in liquid media. **Phase 1 study:** Safety, tolerability, pharmacokinetics and measurement of WBA of PNU-100480 after multiple oral doses in healthy adult volunteers: (**NCT00990990**, completed May 2010).
Clinical results:	In the Phase 1 study (NCT00990990, completed May 2010), all doses were safe and well tolerated *(48)*. There were no haematologic or other safety signals during 28 days of dosing at 600 mg twice daily *(48)*. Cumulative whole-blood bactericidal activity of PNU-100480 at this dose (−0.316 ± 0.04 log) was superior to the activities of all other doses tested ($P < 0.001$) and was significantly augmented by pyrazinamide (−0.420 ± 0.06 log) ($P = 0.002$) *(48)*. In the Phase 2a study (NCT01225640, completed December 2011), all patients completed treatments per protocol. The study showed positive bactericidal activity in sputum over 14 days across all treatments. No SAEs occurred, and QT intervals remained unchanged. Seven sutezolid patients (14%) experienced temporary, asymptomatic alanine aminotransaminase (ALT) elevations that normalized quickly, with no cases meeting Hy's criteria for serious liver injury *(48)*.

Product name (INN or company code):	Delpazolid (RMW2001, LCB01-0371)
Pharmacology: chemical class and MoA:	Delpazolid is an oxazolidinone with a cyclic amidrazone *(49)* that targets an early step in protein synthesis involving the binding of N-formylmethionyl-tRNA to the ribosome *(43)*.
Spectrum of activity and potential resistance:	LCB01-0371 was evaluated for in vitro and in vivo activity against clinical isolates and showed good activity against Gram-positive pathogens, with MIC90 of 2 µg/ml for MSSA and MRSA, and 2-fold more activity than linezolid against vancomycin-resistant enterococci (VRE) *(49)*. In another study, linezolid and delpazolid MIC90 values for *M. tuberculosis* isolates were 0.25 mg/L and 0.5 mg/L, respectively *(50)*. In vivo LCB01-0371 was also more active than linezolid against systemic infections in mice and showed bacteriostatic activity against MRSA *(49)*. While no significant difference in resistance rates was observed between linezolid and delpazolid among XDR-TB isolates, a significantly greater proportion of linezolid-resistant isolates than delpazolid-resistant isolates was found within the MDR-TB group *(50)*.
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis*, *M. abscessus*, MRSA bacteraemia.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.

Product name (INN or company code):	Delpazolid (RMW2001, LCB01-0371)
Clinical trial(s):	**Phase 2b (DECODE):** An open-label, randomized controlled dose ranging multi-centre trial to evaluate the safety, tolerability, PK and exposure-response relationship of different doses of delpazolid in combination with bedaquiline delamanid moxifloxacin in 76 adult subjects with newly diagnosed, uncomplicated, smear-positive, drug-sensitive pulmonary TB (**NCT04550832**, completed). Study protocol is available online *(51)*. **Study population:** Consented adults (18–65 year-olds), newly diagnosed, previously untreated, drug-susceptible pulmonary TB: presence of MTB complex and rapid molecular tests result confirming susceptibility to RIF and INH such as GeneXpert and/or HAIN MTBDR plus. **Primary efficacy endpoint:** The change in sputum mycobacterial load. **Primary safety end-point:** Proportion of patients experiencing adverse event/s. **Phase 2a:** Multicentre, double-blinded, randomized, parallel design, clinical trial to evaluate the efficacy, safety and PK of lcb01-0371 with vancomycin versus vancomycin monotherapy in 100 patients with MRSA bacteraemia (**NCT05225558**, Terminated due to difficulties enrolling subjects: decrease in patients with MRSA bacteraemia – update as of May 2024). **Study population:** Consented male or female adults (19 years old or older), confirmed positive MRSA at least one set of blood cultures within 72 hours prior to randomization or subjects who confirmed positive MRSA by at least one set of blood culture within 96 hours prior to randomization and treated with vancomycin at least 72 hours prior to randomization or with clinical signs of MRSA bacteraemia by investigator judgement. **Primary end-point:** Overall cure rate by Day 14 (composite response rate: clinical improvement plus clearance of bacteraemia). **Phase 2:** Prospective, randomized, open, active-controlled, interventional, exploratory, study to evaluate the EBA, safety and PK of orally administered LCB01-0371 in 79 adult patients with smear-positive pulmonary TB (**NCT02836483**, completed July 2019). **Study population:** Consented Korean patients, male or female, 19 to 75 year-old , with first diagnosis of TB and have not received TB treatment. **Primary end-point:** The extended early bactericidal activity (extended EBA) expressed as the change of log CFU of sputum from baseline at Day 15 (EBA0-14). **Others: Phase 2 study** (NCT06004037): Open-label, single-arm, multi-center study to evaluate the efficacy and safety of lcb01-0371 (delpazolid) as add-on therapy in patients with refractory *Mycobacterium abscessus* complex pulmonary disease is currently recruiting.
Adverse effects/ Preclinical PK and safety:	Lee et al (2009) *(52)* describe that LCB01-0371 exhibited favourable ADMET and PK profiles, including high aqueous solubility and good absorption, distribution, metabolism, excretion and toxicity.

Product name (INN or company code):	TBI-223
Pharmacology: chemical class and MoA:	TBI-223 is a novel oxazolidinone *(53,54)* which targets an early step in protein synthesis involving the binding of N-formylmethionyl-tRNA to the ribosome *(43)*.
Spectrum of activity and potential resistance:	TBI-223 has shown activity against: DS- and DR-TB strains including clinical strains from all global lineages; activity against MRSA; and efficacy in mouse TB infections *(53,55)*. Gordon et al (2022) *(53)* describe additive activity in combination with bedaquiline and pretomanid. In mouse models of MRSA bacteraemia, skin wound infection, and orthopaedic-implant-associated infection, TBI-223 and linezolid had comparable dose-dependent efficacies in reducing bacterial burden and disease severity, compared with sham-treated control mice *(53)*.
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral capsule.

Product name (INN or company code):	TBI-223
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 2 (A5409/RAD-TB):** An adaptive, randomized, controlled, open-label, dose-ranging, platform protocol to evaluate the safety and efficacy of multidrug regimens for the treatment of adults with DS-TB (**NCT06192160**, not yet recruiting). The study includes novel agents sutezolid and TBI-223, and hypothesizes that novel regimens for the treatment of pulmonary TB will result in superior early efficacy. **Study population:** Consented adult patients (18 years or older) with pulmonary TB identified within 7 days prior to study entry by at least one sputum specimen by Xpert. **Primary outcome measure:** Difference in mean log10 TTP slope from longitudinal mycobacteria growth indicator tube (MGIT) liquid culture measurements over the first 6 weeks of treatment. Difference in the cumulative proportion of participants having at least one new grade 3 or higher AE by week 8 of treatment. **Phase 1:** A partially-blinded, placebo-controlled, randomized, multiple ascending dose study to include a single dose food-effect study to evaluate the safety, tolerability, and the PK profile of TBI-223 in 28 healthy subjects (**NCT04865536**, completed March 2022. **Phase 1:** A partially blinded, placebo-controlled, randomized, single ascending dose with a food effect cohort study to evaluate the safety, tolerability, and PK of TBI-223 in 91 healthy adult participants. (**NCT03758612**, completed March 2020).
Adverse effects/ Preclinical PK and safety:	TBI-223 has high oral bioavailability in dogs with moderate clearance (6.6 mL/min/kg) and a reasonable volume of distribution in mice (half-life 3 hr) and rats (half-life 8 hr; poster data) *(55)*. It has shown reduced myelosuppression and toxicity compared to linezolid and has a projected human efficacious dose of 800 mg QD *(55)*. In a translational platform study for dose optimization, Strydom et al *(56)* suggest that TBI-223 be administered in combination with bedaquiline and pretomanid at a daily dose of 1200–2400 mg, could potentially achieve efficacy comparable to the linezolid-containing BPaL regimen, with >90% of patients predicted to reach culture conversion by two months.

Product name (INN or company code):	TBD09 (MK7762)
Pharmacology: chemical class and MoA:	TBD09 (MK7762) is an oxazolidinone that targets an early step in protein synthesis involving the binding of N-formylmethionyl-tRNA to the ribosome *(43)*.
Spectrum of activity and potential resistance:	In vitro and in vivo evaluation of MK-7762 and MK-3854 have shown that both candidates have antibacterial activity against *M. tuberculosis*, including some resistant strains *(57)*.
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 1.
Clinical trial(s):	Phase 1: A randomized, double-blind, placebo-controlled, single ascending dose and multiple ascending dose trial in 119 healthy adults to evaluate the safety, tolerability, and PK of MK-7762 (NCT05824091, completed March 2024).
Adverse effects/ Preclinical PK and safety:	Planning is underway for Phase 2a trial evaluating TBD09 in TB patients *(58)*.

Product name (INN or company code):	Ganfeborole, GSK3036656 (GSK070)
Pharmacology: chemical class and MoA:	Ganfeborole, GSK3036656 (GSK070) belongs to a novel class (oxaborole) with a new MoA that inhibits leucyl-tRNA synthetase (Leu-Rs) thereby blocking protein synthesis *(59)*.
Spectrum of activity and potential resistance:	GSK3036656 has shown in vitro antitubercular activity (*M. tuberculosis* H37Rv MIC = 0.08 µM) with high selectivity for *M. tuberculosis* LeuRS enzyme, good PK profiles, and efficacy against *M. tuberculosis* in mouse TB infection models *(59)*.
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 1:** Open-label, fixed sequence, one-way drug–drug interaction study to investigate the PK of GSK3036656 and an oral contraceptive containing ethinyl oestradiol and levonorgestrel when the oral contraceptive is administered alone and in combination with GSK3036656 in healthy female participants of non-childbearing potential, aged 18 to 65 years of age (**NCT06354257**, recruiting). **Phase 2a:** A parallel group, randomized, open label, four treatment arm study to assess the early bactericidal activity, safety and tolerability of oral GSK3036656 in combination with either oral delamanid or oral bedaquiline, oral delamanid in combination with oral bedaquiline, or SOC (**NCT05382312**, recruiting). **Study population:** 55 males and females (aged 18 to 65 years inclusive), with drug-sensitive (rifampicin-susceptible) pulmonary TB at 1:1 parallel assignment. **Primary end-point:** Change from baseline in log10 CFU of *M. tuberculosis* (per mL of respiratory sputum samples). **Phase 2a:** an open-label trial to investigate the early bactericidal activity, safety and tolerability of GSK3036656 in 76 participants with drug-sensitive pulmonary TB (**NCT03557281**, completed December 2021). **Study population:** Consented, 18 to 65 year-old participants with normal cardiac profile with a new episode of untreated, rifampicin-susceptible pulmonary TB and at least one positive sputum sample on direct microscopy for AFB, willing to be on contraceptive (if child-bearing age) who are relatively well at screening. The study had four cohorts, with 12 to 20 participants in each cohort. The participants were randomized in a 3:1 ratio to receive either GSK3036656 at doses 1 mg, 5 mg, 15 mg, and 30 mg or SoC regimen for drug-sensitive TB. **Primary outcome measure:** Rate of change in log10 CFU/mL direct respiratory sputum samples from baseline to Day 14.
Clinical results:	In the Phase 2a study (NCT05382312), Diacon et al. (2024) *(60)* reported that 75 male participants received either ganfeborole (1/5/15/30 mg) or SOC (Rifafour e-275 or generic alternative) once daily for 14 days *(60)*. Numerical reductions were observed in daily sputum-derived CFU from baseline in participants receiving 5, 15 and 30 mg once daily but not those receiving 1 mg ganfeborole. Adverse event rates were comparable across groups; all events were grade 1 or 2. In a participant subset, post hoc exploratory computational analysis of 18F-fuorodeoxyglucose positron emission tomography/computed tomography findings showed measurable treatment responses across several lesion types in those receiving ganfeborole 30 mg at day 14 *(60)*. Analysis of whole-blood transcriptional treatment response to ganfeborole 30 mg at day 14 indicated an association with neutrophil-dominated transcriptional modules *(60)*.
Adverse effects/ Preclinical PK and safety:	From the Phase 2a Study (NCT03557281, completed December 2021): GSK3036656 doses of 5 mg to 30 mg showed bactericidal activity as evidenced by both endpoints after 14 days *(61)*. GSK3036656 30 mg had the highest bactericidal activity *(61,62)*.

10.3 Mycolic acid disruptors

Product name (INN or company code):	SQ109
Pharmacology: chemical class and MoA:	SQ109 is a 1,2-ethylenediamine that specifically targets MmpL3 in *M. tuberculosis* *(63,64)*. It is currently the only inhibitor of the MmpL3 mycolic acid transporter, which is essential for the incorporation of mycolic acid into the *M. tuberculosis* cell wall, in clinical development *(65,66)*.
Spectrum of activity and potential resistance:	SQ109 has shown activity against microM H37Rv, Erdman and drug-resistant strains of *M. tuberculosis* with an MIC of 0.7–1.56, a selective index (SI) of 16.7 and 99% inhibition activity against intracellular bacteria *(67)*. In further in vitro studies by Jing et al (2024) *(68)*, the MIC90, MIC95 and MIC99 values of SQ109 for 225 clinical isolates of *M. tuberculosis* were 0.25 mg/L, 0.5 mg/L and 1.0 mg/L, respectively. It has also demonstrated potency in vivo and limited toxicity in vitro and in vivo *(67)*. Recently, SQ109 is being investigated as a potential novel antiplasmodial in multidrug-resistant strains *(69)*. Ongoing research is focused on optimizing SQ109 as a novel MmpL3 inhibitor and exploring its effectiveness against multidrug-resistant strains *(70,71)*.
Sought therapeutic indication:	Drug-sensitive and drug-resistant *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 2 (PanACEA MAMS-TB):** Multiple arm, multiple stage, open label, randomized, controlled trial to evaluate four treatment regimens of SQ109, increased doses of rifampicin, and moxifloxacin in 365 adults with newly diagnosed, smear-positive pulmonary TB (**NCT01785186**, April 2013 to March 2025). **Study population:** Consented adults, male or female (18 years or older) with diagnosis of pulmonary TB from a health clinic established by sputum smear and/or GeneXpert MTB/RIF® and/or chest X-ray and a valid rapid test result (GeneXpert MTB/RIF®) from sputum positive for MTB complex and indicating susceptibility to rifampicin. Participants were randomly allocated to control or one of the four experimental intensive phase regimens in the ratio 2:1:1:1:1. The control and four experimental regimens were: • Control: HRZE isoniazid, rifampicin standard, pyrazinamide, ethambutol. • Arm 1: HRZQlow isoniazid, rifampicin standard, pyrazinamide, SQ109 150 mg. • Arm 2: HRZQhigh isoniazid, rifampicin standard, pyrazinamide, SQ109 300 mg. • Arm 3: HR20ZQhigh isoniazid, rifampicin 20 mg/kg, pyrazinamide, SQ109 300 mg. • Arm 4: HR20ZM isoniazid, rifampicin 20 mg/kg, pyrazinamide, moxifloxacin 400mg. **Primary outcome:** Sputum culture conversion (two negative cultures) using liquid media. **Phase 2a:** To evaluate the extended early bactericidal activity, safety, tolerability and PK of **SQ109** in 90 adult subjects with newly diagnosed, uncomplicated, smear-positive, pulmonary TB (**NCT01218217,** completed May 2012). **Primary outcome measure:** The extended EBA of daily 75 mg, 150 mg and 300 mg **SQ109**, and of daily 150 mg or 300 mg **SQ109** with daily RIF standard dose in adults with newly diagnosed, uncomplicated, smear positive, pulmonary TB. **Phase Ia:** A randomized, placebo-controlled, single-dose, double-blind, dose-escalation study to evaluate safety, tolerability and pharmacokinetics of SQ109 in 62 normal, healthy male and female volunteers (**NCT01585636**, Completed February 2007) **Phase 1b:** A randomized, placebo-controlled, double-blinded, dose-escalation study to evaluate safety, tolerability and PK of single-daily doses of SQ109 in 10 healthy, male and female volunteers (**NCT00866190**, completed November 2009). **Phase 1c:** A randomized, placebo-controlled, double-blinded study to evaluate the safety, tolerability and PK of 300 mg of SQ109 given once daily for 14 days in 10 healthy male and female volunteers (**NCT01358162**, Completed April 2011).

Product name (INN or company code):	SQ109
Clinical results:	In the Phase 2 trial (PanACEA MAMS-TB, NCT01785186), time to stable culture conversion in liquid media was faster in the 35 mg/kg rifampicin group than in the control group (median 48 days vs 62 days, adjusted hazard ratio 1·78; 95% CI: 1·22–2·58, p=0·003), but not in other experimental arms *(72)*. 45 (12%) of 365 patients reported grades 3 to 5 adverse events, with similar proportions in each arm *(72,73)*. SQ109 did not seem to contribute significant improvement to the effectiveness of the anti-TB regimen or its impact on the microbiome. Among all the regimens, HRZQlow led to the smallest decrease in alpha diversity *(74)*.

10.4 Miscellaneous agents

Product name (INN or company code):	Pyrifazimine (TBI-166)
Pharmacology: chemical class and MoA:	Pyrifazimine (TBI-166) is a novel riminophenazine (clofazimine (CFZ) analogue) that inhibits mycobacterial growth and binds preferentially to mycobacterial DNA with improved side effect profile *(75)*.
Spectrum of activity and potential resistance:	The in vitro activity of TBI-166 against both drug-sensitive and drug-resistant *M. tuberculosis* was found to be more potent than that of CFZ *(76)*. The combination of TBI-166 with bedaquiline and pyrazinamide is highly effective, demonstrating sterilizing activity similar to the BPaL regimen in a mouse model *(77)*. In another study, TBI-166+BDQ group showed negative lung tissue culture and significantly lower live bacteria count compared to BDQ monotherapy 1.49 log10CFU (P<0.01) in low-dose aerosol infection models of acute and chronic murine TB. Spontaneous resistance to TBI-166 was reported in *M. tuberculosis* wild-type strains *(76)*. The in vitro fm value indicated that the CYP3A4 pathway contributed more than 75% to BDQ metabolism to N-desmethyl-bedaquiline (M2), and TBI-166 was a moderate (IC50 2.65 µM) potential CYP3A4 inhibitor. Coadministration of BDQ and TBI-166 greatly reduced exposure to metabolite M2 (AUC0-t 76310 vs 115704 h ng/mL, 66% of BDQ alone), whereas the exposure to BDQ and TBI-166 did not change *(78)*. The same trend was observed both in healthy and TB model mice. The plasma concentration of M2 decreased significantly after coadministration of BDQ and TBI-166 and decreased further during treatment in the TB mode *(78)*.
Sought therapeutic indication:	MDR *M. tuberculosis*
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 1a:** A clinical trial in China in 2018 (ChiCTR 1800018780). **Phase 2 EBA:** Evaluation of early bactericidal activity and safety in pulmonary tuberculosis with pyrifazimine (TBI-166) (**NCT04670120**, status unknown). **Study population:** 56 consented adults, male or female, 18 to 65 years old, diagnosed with (initial treatment) TB, and the untreated sputum smear is 2+ or 2 times 1+ or more in relative stable condition on effective contraceptive. **Primary Outcome:** Early bactericidal activity, counted by daily log (CFU) change.
Adverse effects/ Preclinical PK and safety:	TBI-166 causes less skin discolouration than CFZ and various studies have described its improved PK/PD profile *(76,77)*.

Product name (INN or company code):	Sanfetrinem cilexetil (GV118819)
Pharmacology: chemical class and MoA:	Sanfetrinem cilexetil is a first-in-class tricyclic carbapenem (beta-lactam) and oral prodrug of sanfetrinem (developed in the 1990s, GSK) *(79)*.
Spectrum of activity and potential resistance:	In vitro studies against methicillin-resistant *S. aureus*, demonstrated the MIC range of sanfetrinem was from 0.125 to 128 *(80)*. Nevertheless, when compared with parenterally administered compounds, oral carbapenem have been shown lose some in vitro antibacterial activity *(81)*. In 2019, sanfetrinem was tested against a panel of *M. tuberculosis* strains, including DS and MDR/XDR clinical isolates from different geographical origins: it was more active and with a narrow spectrum of activity (MIC90 = 1-4 µg/mL) than the clinically active meropenem (MIC90 = 2-64 µg/mL), with these activities enhanced in the presence of clavulanate, although to a lesser extent *(82)*. Mouse studies demonstrated the oral prodrug's effectiveness compared to a combination of meropenem and amoxicillin/clavulanate *(82)*. Ramon-Garcia et al (2024) further described in preclinical in vitro and in vivo studies *(83)*: • media composition impacts the activity of sanfetrinem against *M. tuberculosis*, being more potent in the presence of physiologically relevant cholesterol as the only carbon source, compared to the standard broth media; • sanfetrinem shows broad spectrum activity against *M. tuberculosis* clinical isolates, including MDR/XDR strains; • sanfetrinem is rapidly bactericidal in vitro against *M. tuberculosis* despite being poorly stable in the assay media; • there are strong in vitro synergistic interactions with amoxicillin, ethambutol, rifampicin and rifapentine; and, • sanfetrinem cilexetil is active in an in vivo model of infection.
Sought therapeutic indication:	Repurposed for the treatment of drug-susceptible and drug-resistant *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 2:** To evaluate the early bactericidal activity, safety and tolerability of sanfetrinem cilexetil administered orally to 105 adults with newly diagnosed, smear-positive, rifampicin-susceptible pulmonary TB (**NCT05388448**, unknown status as of last update May 2022). **Study population:** Consented male or female adults, 18 to 65 years old, newly diagnosed, previously untreated, rifampicin-susceptible pulmonary TB, with investigator-confirmed with chest x-ray, able to produce adequate volume of sputum regularly, and on effective contraceptive. Stage 1 will recruit 20 participants followed by a recruitment pause and an interim analysis to determine if sanfetrinem cilexetil has early bactericidal activity (EBA). Should EBA be demonstrated, stage 2 will focus on optimizing sanfetrinem cilexetil. **Primary outcome:** Rate of change in *M. tuberculosis* load in sputum from pre-treatment to day 14 on-treatment, based on colony forming unit (CFU) count on solid culture media (7H11 agar plates).

Product name (INN or company code):	GSK2556286 (GSK286)
Pharmacology: chemical class and MoA:	GSK2556286 is a novel small-molecule adenylyl cyclase Rv1625c agonist *(85)* that interferes with cholesterol regulation to reduce bacterial growth intracellularly (within macrophages) and extracellularly (in cholesterol-rich caseum) *(86)*.
Spectrum of activity and potential resistance:	GSK2556286 was discovered by screening against *M. tuberculosis* that resides within human (THP-1) macrophage-like differentiated monocytes and had a 50% inhibitory concentration [IC50] of 0.07 µM *(86)*. GSK2556286 required cholesterol to show activity in an axenic culture and resistance mutations were mapped to *M. tuberculosis* adenylyl cyclase (cya) Rv1625c *(85–88)*, which has been implicated in cholesterol utilization *(85)*. In the TB mouse model, Li et al. *(23)* found that the combination of bedaquiline, GSK2556286, and TBA-7371 was more active than the first-line regimen and nearly as effective as bedaquiline, pretomanid, and linezolid (BpaL) in bactericidal and sterilizing activity. GSK2556286 and TBA-7371 were also found to be as effective as pretomanid and the novel oxazolidinone TBI-223 when either drug pair was combined with TBAJ-587 and that the addition of GSK2556286 increased the bactericidal activity of the TBAJ-587, pretomanid, and TBI-223 combination *(23)*.
Sought therapeutic indication:	Drug-sensitive, MDR and XDR *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 1.
Clinical trial(s):	The **Phase 1** FTIH study is to evaluate the safety, tolerability and PK of single and repeated ascending doses to GSK2556286 in healthy adults. Food effect cohorts will investigate the influence of food on the PK (**NCT04472897**, recruiting).
Adverse effects/ Preclinical PK and safety:	Evaluated in single-dose oral toxicity studies in rats, dogs and cynomolgus monkeys and in repeated-dose oral toxicity studies (4 weeks) in Wistar Han rats and cynomolgus monkeys with no adverse respiratory, cardiovascular or neurobehavioral effects *(86)*.

Product name (INN or company code):	TBD11 (CLB073)
Pharmacology: chemical class and MoA:	TBD11 is a novel small-molecule adenylyl cyclase Rv1625c agonist *(85)* which interferes with cholesterol regulation to reduce bacterial growth by eliminating its carbon source *(89)* intracellularly (within macrophages) and extracellularly (in cholesterol-rich caseum) *(86)*.
Spectrum of activity and potential resistance:	When administered as monotherapy in in vivo TB mouse models, Rv1625c/Cya agonists have been shown to lower the Mtb CFU burden in lungs of mice ~0.2–0.5 log10 and reduce the extent of lung inflammation *(86–88,90)*. Furthermore, TBD11 was shown to enhance the efficacy of Nix-TB drug regimen, (B, bedaquiline; Pa, pretomanid; L, linezolid) *(90,91)*.
Sought therapeutic indication:	Drug-sensitive, MDR and XDR *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 1.

Product name (INN or company code):	TBD11 (CLB073)
Clinical trial(s):	**Phase 1:** A randomized, double-blind, placebo-controlled, single ascending dose and multiple ascending dose trial in healthy adult participants to evaluate the safety, tolerability and PK of TBD11 with an open label (single dose) food effect panel (**NCT0670714**, recruiting). The trial will be conducted in two parts: Part 1 will consist of single ascending dose (SAD) and food effect (FE) cohorts; and Part 2 will consist of multiple ascending dose (MAD) cohorts.
Adverse effects/ Preclinical PK and safety:	Not yet publicly available.

10.4 Non-traditional agents

Product name (INN or company code):	Alpibectir (BVL-GSK098) + ethionamide (Eto)/prothionamide (Pto)
Pharmacology: chemical class and MoA:	Alpibectir (BVL-GSK098) inactivates a *M. tuberculosis* TetR-like repressor, EthR2, to reverse ethionamide-acquired resistance and increase Eto efficacy *(92,93)*.
Spectrum of activity and potential resistance:	BVL-GSK098 has shown rapid bactericidal effects against Eto-resistant strains in both laboratory and animal studies. It is expected to reduce the required dose of Eto by at least 3-fold, potentially minimizing side-effects and improving patient compliance *(92)*. The combination of BVL-GSK098 and low-dose Eto/Pto could be a safer and better-tolerated treatment for drug-resistant TB, including MDR, XDR, and isoniazid mono-resistant strains *(92,94,95)*.
Sought therapeutic indication:	Pulmonary *M. tuberculosis*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 1:** A double-blind, randomized, placebo-controlled study to investigate the safety, tolerability and pharmacokinetics and food effect of BVL-GSK098 administered as single and multiple oral doses to 80 healthy volunteers (**NCT04654143**, completed January 2023) **Study population and treatment:** Eighty participants were randomized. In single ascending dose (SAD), a total of six dose levels of alpibectir (0.5 to 40 mg) were tested under fasted and fed (10 mg) conditions as single daily doses in sequential cohorts. In multiple ascending dose (MAD), repeat doses (5 to 30 mg) were administered once daily for 7 days in three sequential cohorts. **Phase 2:** To evaluate the EBA, safety and tolerability of ethionamide alone and in combination with BVL-GSK098 administered orally to 105 adults with newly diagnosed, rifampicin- and isoniazid-susceptible pulmonary TB (**NCT05473195**, completed October 2024). No results publicly available as of 31 December 2024. **Study population:** Participants randomized 5:1, consented adults, male or female, 18 to 65 years old, newly diagnosed and untreated pulmonary TB, rifampicin- and isoniazid-susceptible pulmonary TB as determined by molecular testing able to produce adequate volume of sputum regularly, and on effective contraceptive. **Primary outcome:** Early bactericidal activity (EBA) as confirmed by CFU measurement. **Phase 2:** A multicentre, randomized, open-label clinical trial of the early effects, safety, and acceptability of oral alpibectir in combination with ethionamide over a 14-day period (ENABLE) (**NCT06748937**, not yet recruiting).

Product name (INN or company code):	Alpibectir (BVL-GSK098) + ethionamide (Eto)/prothionamide (Pto)
Clinical trial(s):	The overarching objective is to optimize the dose of both alpibectir and ethionamide, and to confirm the safety of the A45mg+E25mg regimen, in combination with rifampicin, pyrazinamide and ethambutol, for future evaluation as an alternative regimen for INH mono-resistant TB. The data from the TASK-010 phase 2A and the ENABLE study will support evaluation of the optimal dose combination of AlpE to move forward into later phase studies. EBAs have historically been conducted between 2 and 14 days. This study will be a standard 14-day EBA design with multiple parallel and sequential treatment arms. **Time period:** 13 January 2025 to 30 March 2026. **Study population and treatment:** 15 participants, aged between 18 and 65 years, with rifampicin- and isoniazid-susceptible pulmonary TB as determined by molecular testing, will be recruited into each treatment arm in two sequential cohorts. Each cohort will have participants enrolled onto the experimental regimen(s) or the SOC (HRZE) control arm. • Cohort 1 aims to generate safety data for a higher dose of alpibectir plus ethionamide 125 mg and 250 mg (arm 1: A45E125 and arm2: A45E250). Once five participants have enrolled into arms 1 and 2 each, and completed 14 days of treatment, an interim safety review will be conducted to determine whether the study can advance to cohort 2. • Cohort 2 will investigate safety of alpibectir and ethionamide (A45E250) in combination with rifampicin, pyrazinamide and ethambutol (A45E250RZE). Participants on HRZE will serve as control for the EBA quantitative mycobacteriology in each cohort, and additionally as a safety benchmark for the A45E250RZE arm. The study is not statistically powered to make between-arm comparisons of activity or safety. The treatment will not be blinded but the mycobacteriology laboratory staff performing the end-point assays will remain blinded until analysis of the EBA results. **Primary outcome:** The EBA time-to-positivity (TTP; 0–14) as determined by the rate of change in log10TTP in sputum over the period day 0 (baseline sample) to Day 14 will be described using linear, bi-linear, or non-linear functions using nonlinear mixed effects modelling of log10TTP over time.
Adverse effects/ Preclinical PK and safety:	Phase 1 (NCT04654143): No serious adverse event was reported. Alpibectir was generally well tolerated, and no clinically relevant safety findings were identified in the participants treated during SAD or MAD. The PK is dose-proportional and affected by food *(95)*.

Product name (INN or company code):	Dovramilast (CC-11050, AMG-634)
Pharmacology: chemical class and MoA:	Dovramilast (CC-11050, AMG-634) is an isoindole phosphodiesterase type 4 inhibitor (PDE4i) which acts by blocking the breakdown of cyclic adenosine monophosphate (cAMP) decreasing host inflammatory response *(96)*.
Spectrum of activity and potential resistance:	Dovramilast shows activity in various models of inflammatory disease *(96–98)*. In an in vivo rabbit model with experimental *M. tuberculosis* infection, CC-11050 plus isoniazid therapy reduces bacillary load and lung pathology *(96,98)*. Additionally, the expression of host genes associated with tissue remodelling, tumour necrosis factor alpha (TNF-α) regulation, macrophage activation and lung inflammation networks was dampened in CC-11050-treated, compared to the untreated rabbits *(97)*. Combined treatment with CC-11050 and isoniazid improves bacterial clearance and reduces lung pathology in rabbits with *M. tuberculosis* infection *(96)*. Dovramilast is also being investigated as a potential treatment in erythema nodosum leprosum (Phase 2, NCT03807362).
Sought therapeutic indication:	Under development as host-directed therapy (HDT) in drug-sensitive and drug-resistant *M. tuberculosis* and leprosy.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.

Product name (INN or company code):	Dovramilast (CC-11050, AMG-634)
Clinical trial(s):	**Phase 2:** A randomized trial to evaluate the safety preliminary efficacy and biomarker response of host-directed therapies added to rifabutin-modified standard therapy in 200 adults with drug-sensitive smear-positive pulmonary TB (**NCT02968927**, completed). **Study population:** Consented adults, 18 to 65 year-olds, male or female with first episode of pulmonary TB diagnosed by positive sputum AFB smear with subsequent culture confirmation OR positive Xpert TB/RIF with Ct <20, RIF susceptibility diagnosed by Xpert TB/RIF OR Hain test, chest radiograph meeting criteria for moderate or far advanced pulmonary tuberculosis, HIV-1 seronegative, and HBsAg negative. Eligible patients were randomly assigned (1:1:1:1:1) to receive one of the four oral host-directed treatments plus standard TB treatment or standard treatment alone (the control group). Host-directed treatments were: • CC-11050 (200 mg twice daily, taken with food; day 1-112); • everolimus (0·5 mg/day; day 1-112); • auranofin (3 mg/day for seven doses, then 6 mg/day; day 1-112); and • ergocalciferol (5 mg on day 1, then 2·5 mg on day 28 and day 56). **Primary outcome:** For auranofin, everolimus and vitamin D: the proportions of patients experiencing suspected, unexpected serious adverse reactions (SUSARs). For CC-11050: the proportion of patients experiencing treatment emergent serious adverse events (SAEs). Observation period: up to day 210. **Secondary preliminary efficacy end-points** were treatment effects on sputum microbiology (culture status at day 56 and the hazard ratio for stable culture conversion up to day 180) and lung function (FEV_1 and forced vital capacity (FVC)) measured by spirometry at day 56, day 180, and day 54. Safety was analysed in the ITT population and preliminary efficacy primarily in the per-protocol population. **Phase 2:** A single centre, open label, pilot study to evaluate the safety and efficacy of CC-11050 in Nepalese patients with erythema nodosum leprosum (**NCT03807362**, recruiting, estimated completion December 2024). **Phase 1:** A study to evaluate the safety, tolerability, PK and PD of a new spray dried dispersion (SDD) formulation of CC-11050 after single dose of CC-11050, and to evaluate the PK of CC-11050 under fasted and fed conditions and after coadministration with omeprazole (**NCT04139226**, completed February 2020). **Phase 2:** A pilot, multicentre, sequential, ascending dose study to evaluate the preliminary safety, tolerability, PK, PD and efficacy of CC-11050 in 48 subjects with discoid lupus erythematosus and sub-acute cutaneous lupus erythematosus (**NCT01300208**, completed March 2013). **Phase 1:** CC-11050 in 38 human immunodeficiency virus-1-infected adults with suppressed plasma viraemia on antiretroviral therapy (**NCT0265254**6, completed November 2018).
Adverse effects/ Preclinical PK and safety:	In the Phase 2 (NCT02968927) study, no treatment-emergent, treatment-attributable serious adverse events occurred in patients receiving CC-11050 or everolimus *(99)*. Adverse events reported in the CC-11050 group were mostly mild (37.5%) and moderate (47.5%) *(100)*. CC-11050 and everolimus were safe and reasonably well tolerated as adjunctive therapies for TB *(99)*. **Secondary study findings:** Mean FEV_1 in the control group was 61·7% of predicted (95% CI: 56·3–67·1) at baseline and 69·1% (95% CI: 62·3–75·8) at day 180. Patients treated with CC-11050 and everolimus had increased recovery of FEV1 at day 180 relative to the control group (mean difference from control group 6·30%, 95% CI: 0·06–12·54; p=0·048; and 6·56%, 95% CI: 0·18–12·95; p=0·044, respectively), whereas auranofin and ergocalciferol recipients did not. None of the treatments had an effect on FVC during 180 days of follow-up or on measures of sputum culture status over the course of the study *(100)*. Early biomarkers did not predict HDT effects on inflammation or infection consistently, suggesting specific responses related to HDT mechanisms of action *(100)*.

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Annex 11
Non-traditionals – antibodies

Product name (INN or company code):	Salvecin (Tosatoxumab, AR-301)
Pharmacology: chemical class and MoA:	Anti-*S. aureus* immunoglobulin G1 (IgG1) antibody
Spectrum of activity:	IgG1 fully human monoclonal antibody targeting *S. aureus* α-toxin, an important virulence factor that is secreted by both MRSA and MSSA *(1–3)*. The AR-301 mode of action is independent of the antibiotic resistance profile of *S. aureus*, and it is active against infections caused by both MRSA and MSSA.
Sought therapeutic indication:	Adjunctive treatment of severe *S. aureus* pneumonia, including HABP, VABP or CABP, treated in the ICU. In July 2023 AR-301 was granted a US-FDA Qualified Infectious Disease Product (QIDP) designation as an adjunctive therapy for pneumonia caused by Gram-positive *S. aureus* in critically ill hospitalized patients *(4)*.
Pharmaceutical form, route of administration and proposed posology:	20 mg/kg daily intravenously.
Phase of clinical development:	Phase 3.

Product name (INN or company code):	Salvecin (Tosatoxumab, AR-301)
Clinical trial(s):	Two superiority studies evaluating the efficacy and safety of Salvecin (tosatoxumab) for adjunctive therapy of pneumonia caused by *S. aureus* in patients with VABP have been performed. **Phase 1/2 (NCT01589185)**: a randomized, double-blind, placebo-controlled, single ascending dose study to assess the safety, pharmacokinetics, efficacy and pharmacodynamics of KBSA301 in severe pneumonia caused by *S. aureus*. **Phase 3 (NCT03816956)**: an international, multicentre, prospective, randomized, double-blind, placebo-controlled, parallel design protocol in patients with VABP caused by *S. aureus*. **Study population:** 174 adult patients with pneumonia treated in an ICU for a documented infection with *S. aureus*, mechanically ventilated for at least 48 hours, and with at least one of the following signs: fever, hypothermia, total peripheral white blood cell (WBC) count >10 000 cells/µL, and leukopenia with total WBC < 4500 cells/µL (mm3) vs greater than 15% immature neutrophils (bands) noted on peripheral blood smear. Patients were randomized 1:1 to be treated with placebo plus SOC or AR-301 (20 mg/kg, single iv infusion) plus SOC. The selection of SOC antibiotics is made in accordance with local best practices at the discretion of the investigator. **Time period:** May 2019 – October 2022; completed. **Sites:** 45 locations in Brazil, China, Europe, Georgia, Israel, Mexico, the Russian Federation, South Africa, Türkiye, Ukraine and the United States. **Primary end-point:** Clinical cure rates of SOC alone and SOC with AR-301 at Day 21 as measured by all-cause mortality, need for mechanical ventilation and signs and symptoms of pneumonia. **Confirmative Phase 3 study:** The study is not yet registered; however, the following information is available online: Based on US-FDA and EMA inputs, a larger patient population is planned to be enrolled, including *S. aureus* VABP, HABP and ventilated CAP patients *(4)*. • Primary end-point: Clinical cure rates of SOC alone and SOC with AR-301 in patients > 65 years old, at day 21 as measured by all-cause mortality, need for mechanical ventilation and signs and symptoms of pneumonia *(4)*.
Clinical results:	In the Phase 1/2 study (NCT01589185), the primary efficacy endpoint of the study, all-cause mortality by day 28, was not met. Based on data from the company website, in the Phase 3 trial (NCT03816956), the study did not meet its primary endpoint *(5)*. An improvement trend in absolute efficacy in the clinical cure rate at day 21 of 11.3% (P = 0.23) was observed in the microbiologically confirmed modified full analysis set 'mFAS' population (n = 120) as compared to placebo. In the prespecified older adult population of 65+ years, the absolute efficacy on day 21 was increased to 33.6% (P = 0.056), and to 37.9% (P = 0.025) on day 28 vs +11% improvement (P = 0.24) in the overall mFAS population. According to the company, the increase in absolute efficacy was driven by the lower efficacy of SOC antibiotics in > 65 year-old adults compared to ≤ 65 year-old adults (30% vs 75%, respectively). In the patients with MRSA, the day 21 absolute efficacy trend was 28% higher than SOC alone (P = 0.831) *(5)*. The increase in absolute efficacy was also driven primarily by the lower efficacy of SOC antibiotics in MRSA patients compared with MSSA patients (38% vs 63%, respectively) *(5)*. In agreement with both US-FDA and EMA, results from the Phase 3 study (NCT03816956) will be used to design a second confirmative trial (still not registered) in a restricted patient population (> 65 years old).

Product name (INN or company code):	Suvratoxumab (AR-320)
Pharmacology: chemical class and MoA:	Anti-*S. aureus* IgG1 antibody
Spectrum of activity:	Human monoclonal IgG1 antibody targeting the pore-forming α toxin of *S. aureus*, an important virulence factor that is secreted by both MRSA and MSSA *(1–3)*. AR-320 has a long half-life and is able to sustain effective toxin neutralizing activities for approximately three months post-dose and above baseline level at one-year post-dose.
Sought therapeutic indication:	Pre-emptive treatment in *S. aureus* colonized, mechanically ventilated patients in the ICU.
Pharmaceutical form, route of administration and proposed posology:	Single dose iv.
Phase of clinical development:	Phase 3.
Clinical trial(s):	1. **Phase 2 (NCT02296320)**: a randomized, double-blind, placebo-controlled, single-dose, dose-ranging superiority study of the efficacy and safety of MEDI4893 in mechanically ventilated adult subjects **Study population:** 213 adult patients with confirmed *S. aureus* colonization of the lower respiratory tract were randomly assigned (1:1:1) to receive either a single intravenous infusion of suvratoxumab 2000 mg, suvratoxumab 5000 mg, or placebo. At an interim analysis, the suvratoxumab 2000 mg group was discontinued on the basis of predefined pharmacokinetic criteria. The study design was modified and approximately 206 patients were randomly assigned (1:1) to either the suvratoxumab 5000 mg group or the placebo group. The power of the study was reduced to 70%, for this exploratory proof-of-concept study to provide data for a future confirmatory efficacy trial. **Time period:** October 2014 – October 2018 **Sites:** 49 locations in United States and the European Region **Primary endpoint:** the incidence of *S. aureus* pneumonia at 30 days after treatment. **The primary efficacy evaluation** was performed in the mITT population included all participants, who received any dose of study drug and analysed according to their randomized treatment group. 2. **Phase 3 (NCT05331885)**: a randomized, double-blind, placebo-controlled study evaluating the efficacy of a single iv dose of suvratoxumab in mechanically ventilated subjects in the ICU who are at high risk for *S. aureus* infections, and who are currently free of active *S. aureus*-related disease but are colonized with *S. aureus* in the lower respiratory tract. **Study population:** 564 mechanically ventilated adult patients in the ICU colonized with *S. aureus* randomly assigned 1:1 to either a single iv dose of suvratoxumab or placebo. **Time period:** September 2022 – June 2024. No further information available. **Sites:** France, Netherlands. **Primary end-point:** Incidence of nosocomial all-cause pneumonia through 30 days post dose [time frame of 30 days]. All-cause pneumonia based on clinical, radiographic, and microbiologic criteria.
Clinical results:	In the Phase 2 trial (NCT02296320), the study did not meet its primary end-point *(6,7)*. At 30 days after treatment, 17 (18%) of 96 patients in the suvratoxumab 5000 mg group and 26 (26%) of 100 patients in the placebo group had developed *S. aureus* pneumonia (relative risk reduction 31·9% (90% CI -7·5–56·8; p=0·17). The study was underpowered to identify a significant difference between the suvratoxumab 5000 mg group and the placebo group. No inferences regarding the potential benefits of suvratoxumab in patients colonized with MRSA could be made, due to the insufficient sample size (only 12 [6%] of 196 patients, were MRSA colonized) *(6,7)*.

Product name (INN or company code):	9MW1411
Pharmacology: chemical class and MoA:	9MW1411 is an anti-*S. aureus* α-toxin IgG1 antibody. It binds to the pore-forming α-toxin (α-hemolysin) protein monomer, which inhibits its binding to the ADAM10 receptor on the cell membrane *(8)*.
Spectrum of activity:	ADAM10 receptor binding reduces the toxicity of α-toxin and its detrimental effect in *S. aureus* infections by modulating the functional activities of pro-inflammatory macrophages *(9)*.
Sought therapeutic indication:	Under investigation as therapy in ABSSSI caused by *S. aureus*.
Pharmaceutical form, route of administration:	Intravenous.
Phase of clinical development:	Phase 2.
Clinical trial(s):	9MW1411 has been evaluated in two trials: 1. **Phase 1a:** Clinical study to evaluate the safety, tolerability, pharmacokinetic characteristics and immunogenicity of a single dose of 9MW1411 injection in healthy subjects (**NCT04784312**, completed 08/2021). Forty-two Chinese subjects received a single ascending dose of 9MW1411 or a placebo. The subjects were randomized to five dose cohorts: 200, 600, 1500, 3000 and 5000 mg. There were two male subjects in the 200 mg dose cohort, and 10 subjects (male or female, 9MW1411: placebo = 4:1) in the other four dose cohorts, respectively. 2. **Phase 2:** A multicentre, randomized, double-blind, placebo-controlled trial design used to evaluate the efficacy and safety of two doses of 9MW1411given as a single injection in adjunction to linezolid, 600mg, given iv or orally every 12 hours, for no more than 14 days, in patients with ABSSSI caused by *S. aureus* (**NCT05339802**). The Phase 2 dose of 9MW1411 injection for this placebo-controlled study will be selected based on the results of Phase 1 clinical trials and preclinical PK/PD analysis. • **Study population:** 90 consenting male/female participants between 18 and 75 years old with ABSSSI + systemic response and positive *S. aureus* laboratory finding. • **Time period:** February 2022, planned to complete in December 2023. As per 30 December 2024 no information on the study status is available. • **Primary end-point:** ○ Efficacy: Clinical cure in the MITT population at the TOC visit (Timeframe: TOC 14 days after the last day of therapy). ○ Safety: Incidence and severity of adverse events (AEs) and/or serious adverse event (SAEs) (Timeframe: From day 1 to day 57 ±7 after administration). ○ Incidence of abnormal clinical laboratory findings in 12-lead ECG parameters, vital signs, physical examination (Timeframe: Screening (within 48 hours prior to the first dose of test article) to follow-up (Day 57±7)). ○ Pharmacokinetics profile: maximum observed concentration (Cmax) (Timeframe from day 1 to day 57 ±7 days after administration). ○ Immunogenicity: Incidence of anti-drug antibodies (Timeframe from day 1 to day 57 ±7 days after administration). • **Trial results**: Not yet publicly available.
Clinical results:	In the Phase 1a trial (NCT04784312), the mean Cmax increased from 85.40 (± 5.43) to 2082.11 (± 343.10) μg/mL and AUC from 29 511.68 (± 5550.91) to 729 985.49 (± 124,932.18) h·μg/mL *(10)*. The elimination half-life was 19–23 days. 9MW1411 ADA was positive in three subjects. Monte Carlo simulations (MCS) were performed to predict the probability of target attainment (PTA) after single dose iv administration of 9MW1411. MCS indicated that a single dose of 3 g or 5 g 9MW1411 could achieve PTA > 90% for *S. aureus (10)*.
Adverse effects:	In the Phase 1a trial (NCT04784312), five cases of AEs (two cases of ALT increased and one case each of AST increased, conjunctivitis and enteritis) were assessed as potentially related to 9MW1411 *(10)*. All the AEs were mild or moderate in severity. No deaths, SAEs, major AEs, or AEs leading to withdrawal from this study were reported *(10)*.

Product name (INN or company code):	Calpurbatug (TRL1068)
Pharmacology: chemical class and MoA:	TRL1068 is a monoclonal antibody (mAb) that targets a highly conserved epitope on the DNABII family of bacterial DNA binding proteins produced by Gram-positive and Gram-negative bacterial pathogens, disrupting biofilm formation *(11,12)*. The DNABII epitope bound by TRL1068 has no homologs in the human proteome.
Spectrum of activity and potential resistance:	In vitro, TRL1068 has been shown to disrupt biofilm thereby releasing bacteria that revert to the antibiotic sensitive planktonic state *(12,13)*. In vivo activity is described in three animal model experiments: ○ In the murine infectious implant model, TRL1068 in combination with daptomycin (DAP) reduced both planktonic and residual adherent MRSA bacteria *(11)*. ○ In the infective endocarditis rat model, TRL1068 in combination with vancomycin (VAN) reduced MRSA densities in biofilm vegetation relative to controls, as well as reducing propensity for septic metastases and mortality *(14)*. ○ In the murine soft tissue infection model the increased exposure to imipenem in combination with TRL1068 showed a significant improvement in efficacy as compared to untreated and imipenem plus isotype control mAb (-1.8 and -1.6 log10 CFU/catheter, respectively; p<0.001) *(15)*. TRL1068, has been granted fast track and QIDP designations by US-FDA as of March 2024 *(16)*.
Sought therapeutic indication:	Being investigated as adjunctive therapy in bacterial biofilm pathogens such as MRSA, Enterobacter, *Enterococcus*, *Streptococcus* and *Pseudomonas* *(17)*.
Pharmaceutical form, route of administration:	Intravenous.
Phase of clinical development:	Phase 2.
Clinical trial(s):	Three clinical trials are currently registered: an on-going Phase 2 trial in PJI, a Phase 1 trial in patients with acute exacerbation of chronic rhinosinusitis (not yet recruiting), and a Phase 1 trial in PJI, that is now completed: 1. **Phase 1** (NCT05355207): To evaluate the safety, pharmacokinetics and pharmacodynamics of TRL1068 in subjects with acute exacerbation of chronic rhinosinusitis with nasal polyps due to start in January 2024 (as of December 2024, not yet recruiting). 2. **Phase 1** (**NCT04763759**): A double-blind, randomized controlled study designed to assess overall safety and PK of TRL1068 was completed March 2024. **Study population:** 15 patients with chronic PJI of the knee or hip between 18–85 years old (male and female) planned/scheduled for primary two-stage exchange arthroplasty, with identified pathogen(s) including both monomicrobial and polymicrobial infections, that are highly resistant to antibiotics due to biofilm formation. TRL1068 was administered via a single pre-surgical intravenous infusion in three sequentially ascending dose groups (6, 15 and 30 mg/kg) *(18)*. 3. **Phase 2** (NCT06621251): A study to assess efficacy and safety of TRL1068 in combination with a DAIR (debridement, antibiotics, and implant retention) procedure for chronic PJIs of the knee and hip, specifically, eliminating the need for the SOC two-stage exchange surgery, so that the original prosthesis can be retained. **Study population:** patients with chronic prosthetic joint infections of the knee and hip randomized to TRL1068 (15 mg/kg iv on Day 1 and subsequently at 7.5 mg/kg on days 15, 29, and 43) or two-stage surgery as is SoC for PJI. The DAIR procedure will be completed between Day 15 – 22. **Time period:** January 2025 – March 2027. **Study primary endpoint:** Incidence of resolved PJI (i.e. completion of planned surgical interventions for PJI (DAIR or two-stage exchange arthroplasty), and not receiving systemic antibiotics for PJI or antibiotic suppression therapy for PJI or any other planned interventions to treat PJI by end of study).

Product name (INN or company code):	Calpurbatug (TRL1068)
Adverse effects/ Preclinical PK and safety:	In the Phase 1 study (NCT04763759), no adverse events attributable to TRL1068 were reported *(18)*. TRL1068 serum half-life was 15–18 days. By day 8, the concentration in synovial fluid was about 60% of the blood level. Elimination of the implant bacteria was observed in three of the 11 patients who received TRL1068. None of the patients who received TRL1068 experienced a relapse of the initial infection by the conclusion of the study on day 169 *(18)*.

Product name (INN or company code):	CMTX-101
Pharmacology: chemical class and MoA:	CMTX-101 is a humanized biofilm-disrupting anti-DNABII monoclonal antibody. Biofilm collapse combats pathogens through three methods: making bacteria sensitive to antibiotics, boosting the immune system, and reducing inflammation in targeted areas *(19)*.
Spectrum of activity:	Because the target is universally present across bacteria, CMTX-101 can be employed to treat a range of bacterial infections in combination with antibiotics against both Gram-positive as well as Gram-negative bacteria. In unpublished data, CMTX-101 has shown activity against biofilms formed by MRSA and other non-BPPL drug-resistant pathogens *(19)*.
Sought therapeutic indication:	It is being investigated as an adjunctive therapy to SOC antibiotics in CF patients with chronic *P. aeruginosa* infection *(20)*.
Pharmaceutical form, route of administration:	Intravenous.
Phase of clinical development:	Phase 2a.
Clinical trial(s):	1. **Phase 1b/2 (NCT05629741)**: A two-part first-in-human study aimed at assessing the safety, tolerability, pharmacokinetics, and immunogenicity of CMTX-101, was officially terminated in August 2024. The decision to halt the study was due to slow enrolment rates, with no safety concerns reported. Part 1, involving healthy volunteers, reached full enrolment, while Part 2, focused on CABP patients, completed enrolment for the first two cohorts. The data is currently under review, and results are pending *(20)*. **Study population:** In 28 consented, adults >18 years old; healthy (Part 1) and hospitalized participants with suspected or confirmed CABP of moderate severity (Part 2). 2. **Phase 1b/2a** (NCT06159725): A study to evaluate the safety of CMTX-101 in combination with inhaled tobramycin in people with CF chronically infected with *Pseudomonas aeruginosa***.** The Phase 1b was successfully completed *(21)*. The Phase 2a study portion (currently recruiting) is a randomized, parallel-group, placebo-controlled, double-blind study aimed to enrol up to 41 adults diagnosed with CF to evaluate the safety and tolerability of CMTX-101 in combination with inhaled tobramycin. The company expects to report initial findings from the study in 2025 *(22)*.
Adverse effects/ Preclinical PK and safety:	Preliminary (webpage) results of the Phase 1 trials describe no drug-related safety events observed, no anti-drug antibodies were detected, and preliminary pharmacokinetic results aligned with animal modelling for CMTX-101 *(18)*.

Product name (INN or company code):	RESP-X (INFEX702)
Pharmacology: chemical class and MoA:	RESP-X (INFEX702) is a novel humanized monoclonal antibody with antivirulence activity against *P. aeruginosa (23)*.
Spectrum of activity and potential resistance:	MDR *P. aeruginosa*.
Sought therapeutic indication:	It is being investigated as therapy in chronic *P. aeruginosa* infection in non-cystic fibrosis bronchiectasis patients.
Pharmaceutical form, route of administration:	Intravenous.
Phase of clinical development:	Phase 2a.
Clinical trial(s):	1. **Phase 1:** Was a double-blind, placebo-controlled, ascending single intravenous dose, safety, tolerability, pharmacokinetic and pharmacodynamic study in healthy participants and non-cystic fibrosis bronchiectasis patients colonized with *P. aeruginosa* (**ISRCTN17978477**, completed). Four cohorts of eight healthy volunteers (six active, two placebos in each group) received single doses of RESP-X intravenously at 1mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg. Primary outcomes were safety and pharmacokinetics, with exploratory end-points looking for anti-drug antibodies and assessing anti-cytotoxicity effect of serum samples following iv dosing. 2. **Phase 2a** (on-going): Is a 12 patient, single centre, double-blind, placebo-controlled, dose-ranging study to evaluate the safety, initial efficacy and determine the optimal dosing of RESP-X ahead of a planned Phase IIb efficacy study. Dosing of RESP-X at 6mg/kg and 10mg/kg will be assessed *(24)*.
Adverse effects/ Preclinical PK and safety:	In the Phase 1 study (ISRCTN17978477), there were no significant drug-related adverse effects at any of the dose levels *(25)*. Half-life was >30 days *(27)*. No significant anti-drug antibodies were detected. RESP-X maintains inhibition of *P. aeruginosa*-mediated cytotoxicity ex vivo. Long half-life supports Phase 2 patient dosing at 3-month intervals *(26)*.

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Annex 12 Non-traditionals – anti-virulence agents

Product name (INN or company code):	GSK3882347
Pharmacology: chemical class and MoA:	GSK3882347 is a type 1 fimbrin D-mannose-specific adhesin (FimH) inhibitor, present in *E. coli*, which stops it from attaching and infecting the bladder wall (antivirulence) *(1)*. Its structure is undisclosed.
Spectrum of activity:	No publicly available non-clinical data accessed.
Sought therapeutic indication:	Being developed in the treatment of MDR uropathogenic *E. coli*.
Pharmaceutical form, route of administration and proposed posology:	Oral.
Phase of clinical development:	Completed a Phase 1 trial, currently in a Phase 1b trial.
Clinical trial(s):	• **Phase 1b:** A double-blind, double dummy, randomized, Phase 1b, nitrofurantoin controlled, repeat oral dose study to investigate the safety, tolerability, PK and microbiological response of GSK3882347 in 80 female participants with acute uUTI (NCT05138822, completed December 2024). • **Phase 1:** To determine the magnitude and clinical relevance of a potential drug–drug interaction of GSK3882347 with midazolam (MDZ) in healthy participants. It is an open-label study in 30 healthy participants aged 18 to 65 years (NCT05760261, completed August 2024). • **Phase 1:** A double-blind, randomized, placebo-controlled, single and repeated oral dose escalation study to investigate the safety, tolerability, PK (including food effect) of GSK3882347 in 61 healthy participants (NCT04488770, completed May 2021).
Clinical results:	Not yet publicly available.
Adverse effects/ Preclinical PK and safety:	Not yet publicly available.

Product name (INN or company code):	ALS-4
Pharmacology: chemical class and MoA:	ALS-4 is a small molecule antivirulence agent that inhibits a key enzyme in the biosynthesis of the carotenoid pigment staphyloxanthin *(2)*.
Spectrum of activity:	Studies have indicated that inhibiting pigment synthesis may reduce pathogenicity both in vitro and in vivo *(3–5)*. Unpublished in vitro data have shown that in the absence of staphyloxanthin, antibacterial activity of antibiotics such as vancomycin may be enhanced *(6)*. In the same data ALS-4 was shown to inhibit staphyloxanthin in MRSA and vancomycin-resistant *S. aureus* strains, reducing virulence with no activity on bacterial growth *(6)*.
Sought therapeutic indication:	ALS-4 is being studied in the treatment of MRSA-related bacterial infection *(3,4)*.
Pharmaceutical form, route of administration and proposed posology:	Oral.
Phase of clinical development:	Phase 1.
Clinical trial(s):	1. **Phase 1**: To evaluate the safety, tolerability and PK of ALS-4 (IM032) in a single ascending dose and multiple ascending dose in healthy adult subjects (NCT05274802, completed January 2022 *(2)*). Phase 2 under planning *(4)*. **Study population:** 72 healthy volunteers 18–60 years old. **Primary end-point:** Number of participants with adverse events. **Primary efficacy:** Not yet publicly available.
Clinical results:	Not yet publicly available.
Adverse effects/ Preclinical PK and safety:	Not yet publicly available.

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Annex 13
Non-traditionals – bacteriophages and phage-derived enzymes

Product name (INN or company code):	TP-122A
Pharmacology: chemical class and MoA:	TP-122 is a bacteriophage cocktail divided into two different components: TP-122A and TP-122B *(1)*.
Spectrum of activity:	TP-122A comprises three bacteriophages against infections caused by *Pseudomonas aeruginosa* and TP-122B includes three bacteriophages against *K. pneumoniae (1)*.
Sought therapeutic indication:	TP-122A is being investigated as add-on therapy to standard-of-care antibiotics (SOC) in VABP caused by *P. aeruginosa*.
Pharmaceutical form, route of administration:	Inhalation.
Phase of clinical development:	Phase 1/2a.
Clinical trial(s):	**Phase 1/2a:** A randomized, parallel, open label, study to assess the safety and tolerability of multiple doses of TP-122A administered by nebulization every eight hours for seven days in addition to SOC, compared to SOC alone, in adult subjects with VABP. SOC being defined as the treatment dispensed in ICU by the medical team in their usual manner, which will include antibiotic treatment according to current guidelines (**NCT06370598**, not yet recruiting). **Time period:** September 2024 to June 2025. **Study population:** 15 subjects who will be randomly allocated into two arms in a 3:2 ratio, with 9 subjects receiving TP-122A in addition to SOC, and 6 subjects receiving the SOC alone.
Adverse effects/ Preclinical PK and safety:	Not yet available.

Product name (INN or company code):	AP-PA02
Pharmacology: chemical class and MoA:	AP-PA02 is a therapeutic phage cocktail that targets *P. aeruginosa (2)*.
Spectrum of activity:	AP-PA02 contains five phages against *P. aeruginosa*. Antibacterial and antibiofilm activity have been demonstrated in vitro against MDR isolates originating from CF and non-CF patients *(3)*. In other preclinical reports, therapy shows limited organ distribution, stability in biological fluids, compatibility with standard antibiotics, and efficacy with other CF therapies *(2)*. In an acute murine lung infection model with *P. aeruginosa*, phages significantly reduced infective burden, and 86% phage-treated mice cleared *P. aeruginosa* infection at 24 h (median, 0 CFU/ml (range, 0 - 160 CFU/ml)); whereas infection persisted in all control mice (median, 1,305 CFU/ml (range, 190 to 4,700 CFU/ml), $P < 0.01$) *(4)*.
Sought therapeutic indication:	AP-PA02 is being investigated in the treatment of respiratory *P. aeruginosa* infection in patients with CF and in non-CF bronchiectasis (NCFB).
Pharmaceutical form, route of administration:	Inhalation.
Phase of clinical development:	Phase 2.
Clinical trial(s):	Investigated in a Phase 2 trial (Tailwind) and a Phase 1b/2 trial (SWARM-Pa): **Phase 2 (Tailwind):** A multicentre, double-blind, randomized, placebo-controlled study to evaluate the safety, phage kinetics, and efficacy of inhaled AP-PA02 multi-phage therapeutic twice daily for 10 days in subjects with non-cystic fibrosis bronchiectasis and chronic pulmonary *Pseudomonas aeruginosa* infection (**NCT05616221**, completed August 2024). **Study population:** 1:1 Parallel assignment, 48 male or female participants 18 years or older, with evidence of chronic pulmonary *P. aeruginosa* infection and bronchiectasis per CT. Patients were separated into cohorts based on their exposure to chronic inhaled antipseudomonal antibiotics. **Time period:** Completed August 2024. **Primary end-point:** *P. aeruginosa* recovery in sputum following multiple doses of AP-PA02 administered by inhalation. **Phase 1b/2a (SWARM-Pa):** A multicentre, double-blind, randomized, placebo-controlled, single and multiple ascending dose study to evaluate the safety and tolerability of AP-PA02 multi-phage therapeutic candidate for inhalation in subjects with cystic fibrosis and chronic pulmonary *P. aeruginosa* infection **(**NCT04596319**,** completed 12/2022).

Product name (INN or company code):	AP-PA02
Clinical results and adverse effects:	**Phase 2** (Tailwind, NCT05616221): Topline results were released on the company website *(5)*. The study did not meet its primary end-point (change in sputum bacterial counts compared to baseline). The company argues that trial failure was due to small numbers of subjects in each cohort (a total of 48 enrolled over 23 sites). A post-hoc intent-to-treat analysis (n=33 active and n=15 placebo; all subjects from both cohorts) demonstrated a statistically significant reduction of *P. aeruginosa* CFUs in the lung at day 17 (AP-PA02 vs. placebo; P=0.05). The reduction in *P. aeruginosa* CFUs persisted two weeks following completion of dosing with AP-PA02 when compared with placebo at day 24 (AP-PA02 vs. placebo; P=0.015). Additionally, paired analysis of *P. aeruginosa* CFU density at baseline compared to day 10 (P=0.03), day 11 (P=0.01), day 17 (P=0.003) and day 24 (P=0.018) was significant in the AP-PA02-treated cohort. Approximately one-third of subjects treated with phage monotherapy exhibited at least a 2-log CFU reduction in *P. aeruginosa* compared to no reduction in placebo treated subjects. AP-PA02 was well-tolerated with mild and self-limiting TEAEs. One possibly related serious adverse event was an acute pulmonary event requiring hospitalization that was responsive to antibiotics *(5)*. **Phase 1b/2a** (SWARM-Pa, NCT04596319): No serious adverse events noted in phage candidate groups *(6)*. AP-PA02 was well-tolerated with a treatment emergent adverse event profile similar to placebo. PK findings confirm that AP-PA02 can be effectively delivered to the lungs through nebulization with minimal systemic exposure, with single ascending doses and multiple ascending doses resulting in a proportional increase in exposure. Additionally, bacterial levels of *P. aeruginosa* in the sputum measured at several timepoints suggest improvement in bacterial load reduction for subjects treated with AP-PA02 at the end of treatment as compared to placebo after ten days of dosing *(6)*.
Preclinical PK and safety:	Not yet publicly available.

Product name (INN or company code):	YPT-01
Pharmacology: chemical class and MoA:	Yale phage therapy 01 (YPT-01) is a bacteriophage therapy that targets MDR *P. aeruginosa (8)*. YPT-01 consists of three anti-*Pseudomonas* phages.
Spectrum of activity:	An in vitro study showed that phage selection causes a trade-off in MDR *P. aeruginosa*, leading to increased sensitivity to drugs from multiple antibiotic classes *(9)*.
Sought therapeutic indication:	Being investigated as a potential treatment for chronic (MDR) *P. aeruginosa* in CF patients.
Pharmaceutical form, route of administration:	Inhalation.
Phase of clinical development:	Phase ½.
Clinical trial(s):	Phase1/2: A prospective, randomized, placebo-controlled, double-blinded, single-site study aimed to determine the safety and efficacy of daily YPT-01 over seven days in CF subjects with chronic *P. aeruginosa* airway infections. The study had two parallel arms of phage therapy and placebo (CYPHY, **NCT04684641**, completed). **Study population**: Clinically stable subjects with confirmed diagnosis of CF with *P. aeruginosa* in sputum cultures on at least two occasions within the past year, and in sputum at screening visit. **Primary end-point:** reduction in sputum bacterial culture (14 days).
Clinical results:	The study did not reach its target enrolment of 36 subjects. Although phage therapy in the study was safe, no differences in sputum in bacterial load or outcome were observed between the treated and placebo groups *(10)*.
Adverse effects:	One possibly related serious adverse event was a CF-related pulmonary exacerbation requiring hospitalization *(10)*.

Product name (INN or company code):	LBP-EC01
Pharmacology: chemical class and MoA:	LBP-EC01 is a bacteriophage cocktail composed of six bacteriophages, three of which are engineered with clustered, regularly interspaced short palindromic repeats (CRISPR) technology targeting the *E. coli* genome. The cocktail combines lytic phage activity with the DNA-targeting activity of Cas3 *(11)*.
Spectrum of activity:	Unpublished in vitro and in vivo UTI animal models show increased LBP-EC01 activity against *E. coli* compared to corresponding natural bacteriophages (website data) *(11)*.
Sought therapeutic indication:	It is under development for the treatment of uncomplicated UTI (uUTI) in combination with antibiotics and other infections caused by MDR *E. coli*.
Pharmaceutical form, route of administration:	Intraurethral and iv.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 2 (ELIMINATE, NCT05488340, recruiting):** A double-blind, randomized, active-controlled evaluation of the safety, tolerability, PK and efficacy of LBP-EC01 in the treatment of acute uUTI caused by MDR *E. coli*. The trial is structured in two parts: the first part will be an open label to determine the optimal dosage for uUTIs, whereas the second part will be conducted as a randomized, controlled, double-blind study. • Part 1:Each arm receives the same IU dose of LBP-EC01 (2x10^12 PFU) on D1 and D2 along with twice daily antibiotics (oral trimethoprim 160 mg/sulfamethoxazole 800mmg) on D1 through D3 and will vary in the dose and delivery of daily LBP-EC01 iv over D1-D3: a bolus of 1x10^11 PFUor1x10^10 PFU or an infusion of 1x10^12 PFU in 100 mL over two hours. • Part 2: LBP-EC01 given by dose regimen selected from Part 1 and oral TMP/SMX. **Study population:** With an initial three-arm PK lead-in portion of 30 patients to evaluate the optimal dosing regimen to be used in the subsequent 288 patient portion of the study which will be randomized 1:1 comparing LBP-EC01 plus antibiotic versus placebo plus antibiotic in patients with a history of prior UTI caused by *E. coli*. All patients will be required to have an active acute uncomplicated UTI at baseline. **Time period:** Start July 2022, recruiting. **Primary end-point:** Part 1: Levels of LBP-EC01 in urine and blood measured by quantitative plaquing assay across the treatment period and over 48 h after the last dose. Proportion of patients with resolution of clinical symptoms of an uUTI and microbiologic response of uUTI caused by MDR *E. coli* as defined at Day 10. **Primary efficacy evaluation:** The efficacy of LBP-EC01 when used concomitantly with TMP/SMX compared to placebo when used concomitantly with TMP/SMX on resolution of acute uUTI symptoms and demonstration of microbiologic response of acute uUTI caused by MDR *E. coli* will be assessed. **Phase 1:** To evaluate the safety, tolerability and PK/PD of LBP-EC01 in patients with lower-tract *E. coli* colonization (NCT04191148, completed 11/2020).
Clinical results:	**Phase 2** (ELIMINATE, NCT05488340): A regimen consisting of 2 days of intraurethral LBP-EC01 and 3 days of concurrent intravenous LBP-EC01 (1×10^10 PFU) and oral TMP–SMX twice a day was well tolerated, with consistent pharmacokinetic profiles in urine and blood *(12)*. LBP-EC01 and TMP–SMX dosing resulted in a rapid and durable reduction of *E. coli*, with corresponding elimination of clinical symptoms in evaluable patients *(12)*. **Phase 1b** (NCT04191148): LBP-EC01 was found to be safe and well-tolerated in the 36 patients enrolled in the Phase 1b study. It showed proof of mechanism by amplifying phage in patients with sensitive *E. coli* isolates. There was an apparent difference in PD effect between LBP-EC01 and placebo regardless of MDR status *(13)*. The placebo arm showed increased levels of *E. coli* and higher variability over the treatment period. An average difference of 2-3 log (100x to 1,000x) existed in urine *E. coli* concentration (CFU/mL) between the LBP-EC01 and placebo arms across the duration of the treatment period.

Product name (INN or company code):	LBP-EC01
Adverse effects:	The study protocol of the initial Part 1 of the ELIMINATE study was amended after three of the first eight participants experienced TEAEs (tachycardia and afebrile chills), which involved modifying the original intended dosing of iv and intraurethral (IU) administration. Only one participant experienced an episode of tachycardia (n=1/31) under the modified dosing regimens that were used for subsequent dose selection for Part 2 of the study *(12)*.

Product name (INN or company code):	SNIPR-001
Pharmacology: chemical class and MoA:	SNIPR001 is a cocktail of four CRISPR-armed phages that selectively target fluoroquinolone-resistant E coli *(14)*.
Spectrum of activity:	SNIPR-001 has been shown to target bacteria in biofilms such as carbapenem-resistant, ESBL-producing or MDR, and fluoroquinolone-resistant *E. coli* in vitro. As a complementary bacteriophage cocktail, it is more effective in reducing *E. coli* load in mice and minipigs compared to its constituents *(15)*.
Sought therapeutic indication:	It is being developed to prevent infections caused by antibiotic-resistant *E. coli* through gut decolonization in patients with haematological cancer.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 1.
Clinical trial(s):	**Phase 1:** A randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study in healthy participants investigating the safety, tolerability, recovery, and PD of multiple oral administrations of SNIPR001 (**NCT05277350**, completed and planning for Phase 2). **Study population:** 36 healthy participants, 18 to 65 years old with *E. coli* present in faeces sample.
Clinical results and adverse effects:	Based on company webpage data *(16)*, in the 36-participant Phase 1 trial, 24 participants received three different dose levels of SNIPR001 and 12 received a placebo. Oral dosing over seven days was well tolerated with only mild to moderate side-effects and no withdrawals. Furthermore, SNIPR001 could be recovered in faeces from treated individuals in a dose dependent manner, and treatment with SNIPR001 numerically lowered gut *E. coli* levels *(16)*. SNIPR Biome has received funding from CARB-X in 2024 to support a Phase 1b/2a clinical trial under development in haematological cancer patients *(17)*.
Preclinical PK and safety:	SNIPR001 has been studied in mouse and minipig models, and there were no adverse effects on health or immune cells compared to the vehicle treatment *(15,18)*.

Product name (INN or company code):	BiomX Phagebank (BX004-A, BX211 and WRAIR-PAM-CF1)
Pharmacology: chemical class and MoA:	BiomX Phagebank consists of numerous phages against clinically relevant bacteria *(19)*. Note: *BiomiX acquired Adaptive Phage Therapeutics in March 2024.*
Spectrum of activity:	Both empiric phage cocktails and personalized treatments are under development. The empiric phage cocktails are pre-defined cocktails developed based on epidemiologic data in a number of clinical indications and directed against clinical syndromes caused by difficult-to-treat pathogens (the one in clinical development is against *P. aeruginosa*) *(19)*. The personalized therapies consist of a library of phages that are matched in vitro to the pathogen that has infected an individual patient (the one in clinical development are against MRSA).
Sought therapeutic indication:	Three products are currently in clinical trials: BX004-a, a three-phage cocktail for inhalation treatment in CF patients with chronic *P. aeruginosa* infection; BX211, a personalized phage treatment, for patients with diabetic foot osteomyelitis (DFO) associated with *S. aureus*; and WRAIR-PAM-CF1, a four-phage cocktail (to be IV administered) originally developed by the Walter Reed Army Institute of Research, for the treatment of CF patients with chronic *P. aeruginosa* infection. The third trial is funded by the United States National Institutes of Health and is a joint effort with the Antibacterial Resistance Leadership Group.
Pharmaceutical form, route of administration:	Inhalation and iv.
Phase of clinical development:	Phase 2.

Product name (INN or company code):	BiomX Phagebank (BX004-A, BX211 and WRAIR-PAM-CF1)
Clinical trial(s):	**Phase 1b/2 (***WRAIR-PAM-CF1*, **NCT05453578**) *(20)*: A multicentre, randomized, placebo-controlled, double-blind study in subject diagnosed with CF to evaluate the safety and microbiological activity of a single dose of IV bacteriophage. **Study population:** 72 subjects with confirmed CF diagnosis based on a compatible clinical syndrome confirmed by either an abnormal sweat chloride testing or CFTR gene variations. Stage 1: 2 subjects in each of the three dose arms: 4x10^7 PFU, 4x10^8 PFU, and 4x10^9 PFU to determine safety of the selected doses. Stage 2a: 4 arms (placebo IV, 4x10^7 PFU, 4x10^8 PFU, and 4x10^9 PFU) in a 1:1:1:1 allocation. Stage 2b: bacteriophage at the dose determined by Stage 2a or placebo. **Time period:** October 2022 to December 2024. **Primary end-points:** 1. Describe the safety of a single dose of IV bacteriophage therapy in clinically stable CF subjects with *P. aeruginosa* in expectorated sputum. 2. Describe the microbiological activity of a single dose of IV bacteriophage therapy in clinically stable CF subjects with *P. aeruginosa* in expectorated sputum. 3. Describe the benefit-to-risk profile of a single dose of IV bacteriophage therapy in clinically stable CF subjects with *P. aeruginosa* in expectorated sputum. *BX211*: **Phase 2b** (DANCE, **NCT05177107**): A randomized, parallel, double-blind, placebo-controlled, repeat dose, multi-site study for safety, tolerability, and efficacy of personalized phage treatment and SOC for subjects with DFO due to *S. aureus*. **Time period:** November 2021 to December 2024. **Study population:** 2:1 (phage:placebo) parallel assignment of 126 consented adults, male or female, 18 to 85 years old, with diabetes meeting clinical criteria for intervention in DFO. **Primary outcome measure:** Percent area reduction of study ulcer through Week 13. **Trial results.** Study topline results are expected in Q1/2025. *BX004-A*: **Phase 1b/2a** (**NCT05010577**): A randomized, double-blind, placebo-controlled, multicentre study to evaluate the safety and tolerability of BX004-A in CF subjects with chronic *P. aeruginosa* pulmonary infection. The study was divided into two parts, a single-ascending and multiple-dose phase (Part 1) and a multiple dose phase (Part 2). Subjects in both parts included in a 6-month safety follow-up. **Time period:** June 2022 to March 2024. As per December 2024, the study is active, not recruiting. **Study population:** 32 participants were randomized to receive the standard dose of nebulized bacteriophage vs nebulized placebo (parallel assignment). CF patients with chronic *P. aeruginosa* pulmonary infection receiving standard-of-care CF medications, ≥ 18 years or age, with clinically stable lung disease. **Primary outcome measure:** Incidence of TEAEs following single and multiple doses of BX004-A administered by inhalation.

Product name (INN or company code):	BiomX Phagebank (BX004-A, BX211 and WRAIR-PAM-CF1)
Clinical results:	Non-peer-reviewed data reported *(21,22)* that there were no safety issues in the Phase 1b/2a study of BX004 in relation to the treatment received with BX004. Mean *P. aeruginosa* CFU at day 15 (compared to baseline): -1.42 log10 CFU/g (BX004) vs. -0.28 log10 CFU/g (placebo). There was no emerging resistance to BX004 during or after treatment with BX004 and there was no detectable effect on % predicted FEV1 *(21,22)*. Unpublished webpage data *(23)* reported that in Part 2, 14% of subjects receiving BX004-A had a negative *P. aeruginosa* sputum culture on day 10 (end of treatment), compared to placebo (0%). In addition, lung function, as measured by forced expiratory volume in 1 second (FEV1), increased in subjects receiving the cocktail (+5.66%) from baseline compared to placebo (-3.23%), in the subgroup on continuous inhaled antibiotics (same antibiotic with no cycling or alternating regimen; n=4), on elexacaftor/tezacaftor/ivacaftor (ETI) and with lower lung function (FEV1 <70%). All study subjects completed the six-month follow up *(23)*. In view of the positive data from trial NCT05010577, BiomX announced a future randomized, double blind, placebo-controlled, multicentre Phase 2b trial in CF patients with chronic *P. aeruginosa* pulmonary infections *(23)*. The trial is designed to enrol approximately 60 patients randomized at a 2:1 ratio to BX004 or placebo. Treatment is expected to be administered via inhalation twice daily for a duration of 8 weeks. End-point of the trial will be the safety and tolerability of BX004 and the demonstration of improvement in microbiological reduction of *P. aeruginosa* burden and evaluation of effects on clinical parameters such FEV1 and patient reported outcomes *(23)*. The US-FDA has granted BX004 Fast Track designation and Orphan Drug Designation *(23)*.

Product name (INN or company code):	Phages: PP1493 and PP1815
Pharmacology: chemical class and MoA:	Two phage products.
Spectrum of activity:	Designed to target *S. aureus (24)*.
Sought therapeutic indication:	Being investigated in the treatment of *S. aureus*-related prosthetic joint infection (PJI).
Pharmaceutical form, route of administration:	Intra-articular.
Phase of clinical development:	Phase 2.

Product name (INN or company code):	Phages: PP1493 and PP1815
Clinical trial(s):	The phage products are being investigated in a pilot Phase 2 trial (DAIR-I) with a larger-scale planned Phase 2 trial (GLORIA) for next year. **Phase 2:** A non-comparative pilot study assessing the clinical control of infection of debridement antibiotics and implant retention (DAIR) + suppressive antibiotics therapy (SAT) +NaCl and DAIR + SAT + Phages anti-*S. aureus* in patients with *S. aureus* PJI with an indication of DAIR + SAT (**NCT05369104**) *(25)*. **Study population:** Consented, male/female participants, over 18 years of age (non-pregnant, on contraceptives) with life expectancy over two years and no concomitant super infection with known: • *S. aureus* monomicrobial knee or hip PJI >3 months after prosthesis implantation with clinical signs of infection and with indication of DAIR with direct closure and SAT; • *S. aureus* only in joint fluid within 6 months before randomization or in case of relapse of infection under antibiotics therapy after a DAIR performed within 6 months before the pre-inclusion visit. **Primary outcome measures:** Clinical control of infection at week 12 visit. **Phase 2 trial (GLORIA):** A proof of concept multicentre, randomized, double-blind study to assess the safety and efficacy of phage therapy in patients with hip or knee PJI due to *S. aureus* treated by DAIR (**NCT06605651**, not yet recruiting). **Time period:** January 2025 to January 2026. **Study population:** The study plans to include 100 patients with PJI (hip or knee replacement) irrespective of infection onset with open surgical debridement (DAIR), who will be treated with PHAXIAM's anti-*S. aureus* phages or placebo, in combination with antibiotics. **Primary outcome measure:** Incidence of SAEs and percentage of patients with clinical cure at 12 weeks without SAT.
Clinical results and adverse effects:	In a company briefing, it was reported that the study enrolled 29 of the anticipated 64 patients, 26 of which were evaluated for clinical activity; an imbalanced number of patients were allocated to the non-phage arm *(25)*. The study demonstrated high phage safety profile for the phage products and a 74% infection control rate in the phage-treated arm (n=14/19) for patients who received a single intra-articular injection compared to 71% for the placebo-treated patients (n=5/7). An additional two of seven patients who relapsed benefited from additional phage administrations (weekly intra-articular injections for three weeks) *(25)*.
Preclinical PK and safety:	Not yet publicly available.

Product name (INN or company code):	EcoActive™
Pharmacology: chemical class and MoA:	EcoActive™ is a seven-phage bacteriophage cocktail *(26)*.
Spectrum of activity:	In vitro, EcoActive™ showed activity against clinical adherent invasive *E. coli* (AIEC) strains *(26)*. In the murine model of induced colitis, twice daily administration of oral EcoActive prevented clinical and microscopical manifestations of inflammation in animals infected with AIEC strain LF82 compared to placebo *(26)*. Note: *in 2024, the company received safe-quality-food (SQF) hazard analysis and critical control points (HACCP) certification (27).*
Sought therapeutic indication:	It is being investigated as therapy targeting adherent invasive AIEC in Crohn's disease patients.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 1/2a.
Clinical trial(s):	**Phase 1/2a:** is a double-blind, randomized, placebo-controlled study evaluating the safety of oral administration of EcoActive to patients with inactive Crohn's disease and how it affects the levels of AIEC in stool (**NCT03808103**, currently recruiting). **Study population:** 30 consented participants (male and non-pregnant females on contraception) ≥ 18 years old with inactive Crohn's Disease history and adherent-invasive *E. coli* (AIEC) detected in stool, by parallel assignment. The experimental intervention dosed at 1mL of bacteriophage preparation given orally twice a day for 15 days compared to oral placebo (saline). **Primary end-point:** Incidence and severity of TEAEs and inflammatory parameters related to Crohn's disease.
Clinical results and adverse effects:	Not yet publicly available.
Preclinical PK and safety:	Not yet publicly available.

Product name (INN or company code):	ShigActive™
Pharmacology: chemical class and MoA:	ShigActive™ is a phage cocktail composed of five lytic bacteriophages *(28)*.
Spectrum of activity:	In vitro ShigActive showed activity against resistant *S. flexneri* strains *(29)*. In a mouse model, treatment regimen elicited a 10- to 100-fold reduction in the CFUs of the challenge strain in faecal and cecum specimens compared to untreated control mice ($P < 0.05$) *(29)*.
Sought therapeutic indication:	It is being investigated in the treatment of Shigellosis.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 1/2a.
Clinical trial(s):	**Phase 1/2a:** A first-in-human Phase 1/2a randomized, double-blind, placebo-controlled trial to assess the clinical safety and efficacy of ShigActive in healthy adults with experimental *Shigella* challenge (**NCT05182749**, active; not recruiting). **Study population:** Healthy consented participants (male and non-pregnant females on contraception), 18 to 50 years old, parallel assignment in a 4:1 ratio of ShigActive to placebo. The experimental intervention dosed at 1mL of bacteriophage preparation given orally three times a day for 7 days (Phase 1) or 6 days (Phase 2a). **Primary end-point:** Solicited or unsolicited adverse reactions and onset of shigellosis post-challenge (Phase 2a only).

Product name (INN or company code):	ShigActive™
Clinical results and adverse effects:	Ten patients were enrolled in the study. Fifty percent of the subjects receiving ShigActive™ reported mild GI-related symptoms, while one participant experienced moderate fatigue *(30)*. No serious or medically attended AEs occurred through day 90. No significant differences in GI-associated inflammatory mediators or faecal microbiome changes were observed between placebo- and ShigActive™-treated subjects, or from a participants' baseline value *(30)*. Phage titres persisted in stool for prolonged periods of time after the final dose for some patients *(30)*.
Preclinical PK and safety:	In the mouse model, no toxic side-effects of phage administration were observed during the studies, and the phage cocktail showed less impact on the normal gut microbiota than treatment with a commonly prescribed antibiotic *(29)*. Long-term safety studies did not identify any side-effects or distortions in overall gut microbiota associated with bacteriophage administration *(29)*.

Product name (INN or company code):	VRELysin™
Pharmacology: chemical class and MoA:	VRELysin™ comprises bacteriophages designed to combat vancomycin-resistant enterococci (VRE).
Spectrum of activity:	VRELysin™ is designed to decrease VRE quantities in the human GI tract and prevent infection *(31,32)*.
Sought therapeutic indication:	It is being studied as a decolonizing agent for VRE-colonized patients to prevent associated bacteraemia.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 1/2a.
Clinical trial(s):	**Phase 1/2a:** is a double-blind, randomized, placebo-controlled trial to assess the safety and efficacy of oral VRELysin™, in 80 healthy (Phase 1) and VRE-colonized (Phase 2a) subjects. VRELysin will be orally administered three times per day for 7 days (Phase 1) or 14 days (Phase 2a) with sodium bicarbonate solution (**NCT05715619**, currently recruiting). **Time period:** October 2023 to 31 March 2025. **Primary end-point:** Number and severity of solicited and unsolicited adverse reactions in each phase.
Clinical results and adverse effects:	Not yet publicly available.
Preclinical PK and safety:	Not yet publicly available.

Product name (INN or company code):	AP-SA02
Pharmacology: chemical class and MoA:	AP-SA02 is a bacteriophage cocktail.
Spectrum of activity:	Targets methicillin-resistant *S. aureus* and vancomycin-resistant *S. aureus* in non-clinical studies (website data) *(33)*.
Sought therapeutic indication:	It is being developed for the treatment of *S. aureus* bacteraemia *(33)*.
Pharmaceutical form, route of administration:	Intravenous.
Phase of clinical development:	Phase 1b/2a.
Clinical trial(s):	**Phase 1b/2a** diSArm Trial (**NCT05184764**): A multicentre study to determine the safety, tolerability and efficacy of IV AP-SA02 as an adjunct to best available antibiotic therapy (BAT) compared to BAT alone for the treatment of adults with bacteraemia due to *S. aureus*. **Time period:** April 2022 to March 2025. **Study population:** 50 hospitalized patients (male and female), ≥ 18 years old with a positive blood culture for *S. aureus*: • Phase 1b evaluated the safety and tolerability of multiple ascending intravenous doses of AP-SA02 or placebo as an adjunct to BAT compared to BAT alone in subjects with *S. aureus* bacteraemia. • Phase 2a evaluated the efficacy, safety and tolerability of multiple doses of AP-SA02 or placebo as an adjunct to BAT compared to BAT alone in subjects with *S. aureus* bacteraemia. **Primary end-point:** Incidence of TEAEs with multiple doses of intravenous AP-SA02.
Clinical results and adverse effects:	The study demonstrated a lack of clinically significant adverse events in patients receiving high doses of 5E10 PFU every six hours (2E11 PFU every 24 hours) for five days. Additional data is expected to be released by mid-2025 *(34)*.
Preclinical PK and safety:	Not yet publicly available.

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Annex 14 Non-traditionals – immunomodulating agents

Product name (INN or company code):	Rhu-pGSN (rhu-plasma gelsolin)
Pharmacology: chemical class and MoA:	Rhu-pGSN (recombinantly produced human plasma protein gelsolin) regulates inflammatory homeostasis by binding to extracellular actin and preventing its inhibition of deoxyribonuclease I *(1)*. Concurrently, pGSN enhances bacterial uptake and killing by macrophages *(2)*.
Spectrum of activity:	In vivo, researchers found that treating mice with Gram-negative sepsis caused by *P. aeruginosa* with Rhu-pGSN resulted in decreased inflammation and bacterial growth *(3)*. In a mouse model of pneumococcal pneumonia, rhu-pGSN without antibiotics increased survival and reduced morbidity and weight loss after infection with either penicillin-susceptible or penicillin-resistant *S. pneumoniae (4)*.
Sought therapeutic indication:	Researchers are currently studying the potential of Rhu-pGSN as an adjunctive treatment in acute CABP, sepsis and acute respiratory distress syndrome (ARDS).
Pharmaceutical form, route of administration:	Intravenous.
Phase of clinical development:	Phase 2 ARDS; Phase 1b/2a CABP.

Product name (INN or company code):	Rhu-pGSN (rhu-plasma gelsolin)
Clinical trial(s):	ARDS: 1. **Phase 2** (**NCT05947955**, recruiting as of October 2024): A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of adjunctive Rhu-pGSN with standard care for moderate-to-severe ARDS (P/F ratio ≤150) due to pneumonia or other infections. Subjects will receive rhu-pGSN 24 mg/kg once, followed by five daily doses of 12 mg/kg based on actual body weight in addition to standard care. **Study population:** 600 consented male/female patients ≥18 years old diagnosed with ARDS. Potential subjects hospitalized with pneumonia or other infections are to be screened within 24 hours of diagnosis of ARDS. **Time frame:** October 2024–March 2027. **Primary end-point:** All-cause mortality rate at study day 28. All-cause mortality will also be assessed on Days 7 and 14. Survival at Day 60 will be confirmed by telephonic contact or after three failed attempts, review of hospital and public records that document survival or death. CABP: 2. **Phase 1b/2a:** A double-blind, placebo-controlled, dose-escalation study to evaluate the safety, pharmacokinetics, and pharmacodynamics of recombinant human plasma gelsolin (rhu-pgsn) added to SOC in subjects hospitalized for acute non severe CABP (**NCT03466073**). **Timeframe:** August 2018–April 2019. **Primary end-point:** Incidence, causality and severity of AEs and SAEs. Exploratory outcome measures were baseline and sequential pGSN levels during the study, 28-day survival, ICU days, days on a ventilator or vasopressors, and duration of hospitalization.
Clinical results:	In the Phase 1b/2a trial (NCT03466073), the proportion of rhu-pGSN recipients with AEs was highest in the lowest-dose group (four subjects, 66.7% rhu-pGSN at 6 mg/kg) compared with the middle-dose group (three subjects, 50.0% rhu-pGSN at 12 mg/kg) and the highest-dose group (two subjects, 33.3% rhu-pGSN at 24 mg/kg) *(5)*. Two patients reported nausea and increased blood pressure. None of the AEs in the rhu-pGSN arms were considered related to drug treatment *(5)*.

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Annex 15
Non-traditionals – microbiome-modulating agents

Product name (INN or company code):	SER-155
Pharmacology: chemical class and MoA:	SER-155 is a fermented microbiome therapeutic composed of cultivated spores and vegetative bacterial strains *(1)*.
Spectrum of activity:	Preclinical in vitro and in vivo data indicate potential to reduce infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) and vancomycin-resistant Enterococci (VRE) *(1)*. In vivo studies suggest SER-155 may decolonize VRE and CRE, and further modulate epithelial barrier integrity and T cell biology with relevance to graft vs. host disease (GvHD) *(1,2)*.
Sought therapeutic indication:	SER-155 is being developed to reduce the risk of bacteraemia and GvHD in allo-haematopoietic stem cell transplant (HSCT) recipients by decolonizing potential pathogens and restoring GI colonization resistance *(3)*. The developer is pursuing SER-155 strategic partnership to accelerate further study in allo-HSCT and expand to multiple target populations.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 1b.

Product name (INN or company code):	SER-155
Clinical trial(s):	Phase 1b: A multiple-dose study to evaluate the safety, tolerability, PK and efficacy of SER-155 in 75 adults undergoing HSCT to reduce the risk of infection and GvHD (**NCT04995653**, completed). The study included two cohorts: • **Cohort 1** was designed to assess safety and drug pharmacology, specifically the drug strain engraftment in the gastrointestinal tract. Cohort 1 included 13 subjects who received any dosing of the SER-155 regimen, with 11 subjects subsequently receiving an allo-HSCT. • **Cohort 2** utilized a randomized, double-blinded, 1:1 placebo-controlled design to further evaluate safety and drug strain engraftment, as well as key secondary and exploratory endpoints such as the incidence of bacterial bloodstream infections and related medical consequences such as febrile neutropenia and antibiotic use. **Cohort 2 patient population:** 45 patients in the intention-to-treat (ITT) population. Of the ITT population, 20 received SER-155 and 14 received placebo, each of whom subsequently received an allo-HSCT, with data available for clinical evaluation through day 100, the study's prespecified primary observation point. The median age in Cohort 2 was 63, and most subjects had acute myeloid leukaemia, acute lymphocytic leukaemia, myelodysplastic syndrome or myeloproliferative neoplasia as their primary disease and received reduced intensity conditioning pre-transplant. Most patients received peripheral blood stem cells from a matched unrelated donor. A majority received post-transplant cyclophosphamide as part of GvHD prophylaxis. **Statistical evaluation:** Exploratory hypothesis testing was conducted at the two-sided α=0.05 level. Ninety-five percent (95%) 2-sided confidence intervals (CIs) were determined, where specified. No adjustment for multiplicity was done. A subset of patient samples was available for drug pharmacology analysis.
Clinical results:	**Cohort 1 results:** Data released online by the company *(2)* showed SER-155 was generally well tolerated and resulted in successful drug strain engraftment and a reduction in pathogen domination in the GI microbiome relative to a historical control cohort. **Cohort 2 results:** Online data further show that SER-155 was well tolerated, with no serious adverse events related to the drug *(4)*. It significantly reduced the incidence of bloodstream infections compared to placebo (10% vs. 42.9%; OR:0.15; 95% CI: 0.01–1.13, p=0.0423), and patients receiving SER-155 had a shorter duration of antibiotic use (9.2 days vs. 21.1 days). The incidence of febrile neutropenia was lower in the SER-155 group (65% vs. 78.6%; OR: 0.51; 95% CI: 0.07–2.99; p=0.4674), though this difference was not statistically significant *(4)*. There were six cases of gastrointestinal infections, with slightly more cases in the SER-155 group (20% vs. 14.3%). The rates of GvHD in the study were low, with two cases of grade 2 GvHD observed in each arm, and no cases of grade 3 or 4 GvHD were observed *(4)*.
Preclinical PK and safety:	Not yet publicly available.

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Annex 16
Non-traditionals – miscellaneous

Product name (INN or company code):	OligoG (CF-5/20)
Pharmacology: chemical class and MoA:	OligoG is an alginate oligosaccharide (G-block) fragment extracted and purified from the marine algae Laminaria hyperborea *(1)*.
Spectrum of activity:	OligoG shows anti-biofilm activity and inhibition of bacterial growth; it normalizes cystic fibrosis (CF) mucus by chelating calcium *(2)*. In a study using atomic force microscopy (AFM), OligoG was shown to modify the surface charge of MDR *P. aeruginosa*, resulting in cell aggregation and a reduction in motility *(3)*. In vitro, OligoG treatment reduced (by up to 512-fold) the MICs of a range of antibiotics, such as ceftazidime and macrolides, against MDR *P. aeruginosa (1)*.
Sought therapeutic indication:	It has been investigated in studies related to the treatment of *P. aeruginosa* lung infection in patients with CF. It has received orphan drug designation from both the US-FDA and the EMA.
Pharmaceutical form, route of administration:	Inhalation.
Phase of clinical development:	Phase 2b.

Product name (INN or company code):	OligoG (CF-5/20)
Clinical trial(s):	OligoG has been studied in six clinical trials. The most recent trial was terminated in October 2021. No positive results on clinical efficacy end-points are currently available for the drug. According to the company's communication to WHO, preclinical development has been re-started addressing both antimicrobial effects and drug delivery. The latest clinical trials performed with the drug are the following: **Phase 2/3:** A randomized, double blind, placebo-controlled study. The study has two parts: Dose-finding part, followed by longer term follow-up (6 months) (**NCT03698448**, withdrawn, determined not feasible). **Phase 2:** A double-blind, randomized, placebo-controlled cross over study of inhaled alginate oligosaccharide (OligoG) administered for 28 days in subjects with CF (NCT02157922, completed September 2017). **Study Population**: 65 consented male or females (on contraceptive) with confirmed CF and positive microbiological finding of *P. aeruginosa* treated for 28 days, three times per day with administration of Oligo G or placebo. **Time period:** October 2014 to September 2017. **Primary end-point:** An improvement in FEV1 during treatment with OligoG as compared to placebo (28 days). **Primary efficacy evaluation:** The ITT population (n=65) was defined as randomized to treatment with at least one administration of study medication and post-dosing evaluation. **Phase 2b:** A randomized, double-blind, parallel-group study of OligoG dry powder inhalation in addition to SOC compared to placebo in addition to SOC in 20 patients with CF. (NCT03822455: Status: terminated October 2021. No further information is available). **Study Population**: 65 consented males or females (on contraceptive) with confirmed CF and positive microbiological finding of *P. aeruginosa* treated for 28 days with 3 times/day administration of Oligo G at a lower dose compare to study NCT03822455 or placebo. **Time period:** October 2014–September 2017. **Primary end-point:** An improvement in FEV1 during treatment with OligoG as compared to placebo (28 days).
Clinical results:	The Phase 2 study (NCT02157922) did not meet its primary end-point *(4)*.
Adverse effects/ Preclinical PK and Safety:	The preclinical toxicity and PK studies from unpublished data were reported to demonstrate that doses at which OligoG is effective in vitro may be safely attainable in the lung in vivo *(1)*.

Product name (INN or company code):	PLG0206 (WLBU2)
Pharmacology: chemical class and MoA:	PLG0206 (WLBU2) is a 24-amino-acid engineered cationic antibiotic peptide (eCAP) *(5)*.
Spectrum of activity:	A broad spectrum against bacteria that cause biofilm-related infections including MDR and XDR *S. aureus*, *Enterococcus* spp., and aerobic Gram-negative bacilli *(6,7)*. As a systemic (UTI) and local (PJI) agent, PLG0206 exhibits activity in a variety of animal infection models *(7)*.
Sought therapeutic indication:	It has been investigated in the treatment of PJI occurring after total knee arthroplasty (TKA).
Pharmaceutical form, route of administration:	Irrigation.
Phase of clinical development:	Phase 1.

Product name (INN or company code):	PLG0206 (WLBU2)
Clinical trial(s):	**Phase 1b**: An open-label, dose-escalating study to evaluate the safety and tolerability of PLG0206 in patients undergoing debridement, antibiotics and implant retention (DAIR) for treatment of PJI occurring after total knee arthroplasty (TKA) (NCT05137314). **Study Population**: Patients with well-fixed prosthesis who have a pre- or intra-operative diagnosis of TKA-PJI will receive PLG0206 administered intraoperatively by local irrigation at the dose of 3mg/ml or 10 mg/ml. **Time period:** 31 March 2022- January 2024. **Primary end-point:** The percentage of treatment emergent AEs (1 year)
Clinical results:	Phase 1b (NCT05137314) topline results at 180 days *(7)*: In both patient cohorts followed for six months after PLG0206 treatment, there were: • No treatment-related serious adverse events. • No recurrence was observed in 13 of 14 (93%) treated patients at day-180 in contrast to reported 180-day success rate of 45%.
Adverse effects/ Preclinical PK and Safety:	In the now completed first-in-human study of 47 healthy participants, single iv infusion of PLG0206 resulted in linear PK at doses ranging from 0.05 to 1 mg/kg IV and was safe and well tolerated *(7)*. Most of the adverse events related to PLG0206 treatment were mild and similar between the PLG0206 treatment and placebo groups *(7)*. No severe adverse events, life-threatening events, or deaths occurred during the study.

Product name (INN or company code):	CAL02
Pharmacology: chemical class and MoA:	CAL02 is an antitoxin agent made up of liposomes. These liposomes create stable liquid-ordered lipid microdomains that function as traps for a range of bacterial virulence effectors (toxins) known to be inserted in cellular membranes *(8)*.
Spectrum of activity:	In vitro, artificial liposomes have been shown to protect mammalian cells against bacterial toxins during infection *(9)*. CAL02 proved to be efficacious in in vivo acute models of infection caused by Gram-positive (*S. aureus* and *S. pneumoniae*) *(9)*. When administered within 10 hours, it rescued mice with invasive pneumococcal pneumonia from septicaemia caused by *S. aureus* and *S. pneumoniae* in vivo *(9)*.
Sought therapeutic indication:	Severe CABP.
Pharmaceutical form, route of administration:	Intravenous.
Phase of clinical development:	Phase 2.

Product name (INN or company code):	CAL02
Clinical trial(s):	**Phase 2 trial:** A randomized, double-blind, placebo-controlled multicentre study to evaluate the efficacy and safety of CAL02 administered intravenously in addition to SOC in subjects with severe CABP (NCT05776004, recruiting). **Study population:** 276 participants with sCABP will receive either two intravenous infusions of CAL02 (13.7 to 24 mg/kg bracketed dose by weight), administered 24–26 hours apart or two intravenous infusions of placebo by a parallel assignment. **Time period:** Recruiting as of December 2024; estimated completion was Oct 2024. Pending updates. **Primary end-point:** clinical recovery, incidence of TEAE. **Phase 1 trial:** A randomized, double-blind, multicentre, placebo-controlled trial done in patients with severe CABP who required ICU admission and had been identified as being infected with *S. pneumoniae*. (NCT02583373, completed). **Study population:** 19 consented adults male or female patients ≥ 18 years and ≤ 80 years of age with confirmed severe pneumonia caused by *S. pneumoniae* managed in an ICU. **Time period:** March 2018 to February 2019. **Primary endpoint:** Frequency, severity, and characteristics of adverse events after two iv administrations of CAL02.
Clinical results:	During the Phase 1 clinical trial (NCT05776004), the group receiving a high dose of CAL02 showed better patient outcomes than the placebo group *(10)*. This was particularly evident in the initial stages of the infection when the level of bacteria is high *(10)*.
Adverse effects (From Phase 1 trial):	Adverse events occurred in 12 (86%) of 14 patients in the CAL02 treatment groups combined and all five (100%) patients in the placebo group *(9)*. Serious adverse events occurred in four (29%) of 14 patients in the CAL02 treatment groups combined and two (40%) of five patients in the placebo group. No adverse events were linked to local tolerability events *(11)*.

Product name (INN or company code):	AR-501 (Panaecin)
Pharmacology: chemical class and MoA:	Gallium citrate, which acts as an iron analogue to starve bacteria of iron. AR-501's inhibitory activity reaches bacteria growing in mature biofilms *(12)*.
Spectrum of activity:	Target bacterium in the Phase 2a clinical study is *P. aeruginosa*. However, AR-501 has broad anti-bacterial activity against Gram-negative and Gram-positive bacteria in vitro, including antibiotic-resistant strains *(12)*. In mouse models of bacterial lung infections reported (webpage data), a single inhalation exposure of aerosolized AR-501 protected the animal from morbidity and mortality. AR-501 was also protective when used in combination with antibiotics *(13)*. MIC testing demonstrates the efficacy of AR-501 against Gram-negative, Gram-positive and several species of mycobacteria of clinical isolates and the comparative antibacterial response with antibiotics *(14)*. Resistance testing showed that AR-501 exhibited lower propensity to develop resistance than the antibiotics tested. In vivo efficacy: AR-501 inhalation also increased the median survival time compared with iv dosing in the murine model. Bacterial clearance was increased when tobramycin and AR-501 are co-administered. Comparative analysis of AR-501 after inhaled route demonstrate increased gallium levels in bronchoalveolar lavage and reduced levels in the kidney in contrast to iv route *(14)*.
Sought therapeutic indication:	Treatment of bacterial lung infections in patients with CF.
Pharmaceutical form, route of administration:	Inhalation, to be dosed once weekly.

Product name (INN or company code):	AR-501 (Panaecin)
Phase of clinical development:	Phase 1/2a.
Clinical trial(s):	**Phase 1/2a:** A **r**andomized, double-blind, two-part (1 and 2a), dose-ascending (SAD and MAD), multicentre study of the safety and PK of inhaled AR-501 in healthy adults and *P. aeruginosa* infected CF subjects. CF MAD cohort to evaluate four different dose levels: once-per-week administration at 6.4mg (low dose cohort), 20mg (mid dose cohort), and 40mg (high dose cohort), 80mg Ga dose (top dose) (**NCT0366614**, recruiting). **Study population**: 48 subjects in healthy volunteer (HV) cohort, 54 subjects with CF and confirmed *P. aeruginosa* bacterial colonization. SAD and MAD HV cohorts: 3:1 randomization. The CF MAD cohort: sentinel subjects 2:1 ratio, expanded cohort 2:3:3:2 ratio, then top dose 2:1 ratio. **Time period:** 28 days for HV cohorts and 42 days for CF cohorts. **Primary end-point:** Evaluation of adverse events in HV and CF subjects. **The primary efficacy evaluation:** N/A.
Clinical results:	**Phase 1/2a trial (NCT0366614) results:** Topline results published online state that AR-501 was well tolerated with no serious adverse events and achieved high concentrations (50-fold higher than that required for inhibition of *P. aeruginosa*) in the respiratory tract *(13)*.

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Annex 17
Traditionals – CDI and *H. pylori*

Product name (INN or company code):	Ridinilazole
Pharmacology: chemical class and MoA:	Ridinilazole is a non-absorbable bis-benzimidazole compound. It acts as an antibiotic by binding to DNA, leading to dysregulation of transcription and cell death in *C. difficile* (1).
Spectrum of activity and potential resistance:	Early evidence indicates bactericidal activities and a decrease in toxin A and toxin B concentrations of *C. difficile* strains exposed to ridinilazole (2). It is hypothesized to lower risk for CDI recurrence while preserving the gut microbiome (3). No cross-resistance is reported.
Sought therapeutic indication:	Ridinilazole is being developed as a treatment option in non-fulminant CDI.
Pharmaceutical form, route of administration:	Oral 200 mg, bid, every q12h for 10 days.
Phase of clinical development:	Phase 3.
Clinical trial(s):	**Phase 3:** Two identical Phase 3 studies, Ri-CoDIFy 1 **(NCT03595553)** and Ri-CoDIFy 2 **(NCT03595566)**, combined in the Ri-CoDIFy Phase 3 trial, are complete. Ri-CoDIFy was an interventional, quadruple-blind, parallel assignment, randomized, active-controlled, non-inferiority study to compare the efficacy and safety of ridinilazole with vancomycin for treatment of CDI **(NCT04802837)**. **Study population:** Adult patients with signs and symptoms of CDI, including diarrhoea, such that in the investigator's opinion CDI antimicrobial therapy was required, and with presence of either toxin A and/or B of *C. difficile* in a stool sample determined by a positive free toxin test produced within 72 h prior to randomization. Excluded were all participants receiving effective antibacterial drug therapy (> 24 h prior to randomization), or participants with moderate or severe liver disease, severe neutropenia, a baseline QTc (corrected QT interval) of > 500 ms, known history of congenital long QT syndrome, uncompensated heart failure, uncorrected abnormal K+ or Mg++ blood levels or severe left ventricular hypertrophy. Patients were randomly parallel assigned to receive either oral ridinilazole (200 mg every 12 h) or oral vancomycin (125 mg every 6 h) for 10 days. **Time period:** January 2019 to November 2021. **Sites:** The study took place in over 180 sites in 28 countries. **Primary efficacy end-point:** Achievement of a sustained clinical response, defined as clinical cure at the TOC visit and no recurrence within 30 days post-EOT.

Product name (INN or company code):	Ridinilazole
Clinical trial(s):	**Primary efficacy evaluation** was done on the micro-MITT population (all individuals with CDI confirmed by the presence of free toxin in stool who were randomly assigned to receive one or more doses of the study drug). A non-inferiority margin of 15% was selected. **Ri-CoDIFy 3** (NCT04802837): a study evaluating the safety, tolerability, and PK of ridinilazole in adolescents, was terminated in alignment with a corporate decision to pursue further development of the drug candidate with a partner (as of an August 2023 update). **Phase 2 studies:** Conducted to evaluate the safety and efficacy of ridinilazole compared with two conventional antibiotics, fidaxomicin and vancomycin. **The first of these two Phase 2 studies (NCT02092935)** compared ridinilazole with vancomycin for the treatment of *C. difficile*-associated diarrhoea (CDAD). **Time period:** 26 June 2014 to October 2015. **Study design:** Randomized, double-blind, active-controlled, non-inferiority clinical study to investigate the efficacy and safety of ridinilazole 200 mg PO bid for 10 days (with alternating 200 mg placebo bid), compared with vancomycin 25 mg capsule qid for 10 days for treatment of CDAD. **Study population:** Participants with signs and symptoms of *C. difficile* infection and a positive diagnostic test result were recruited from 33 centres in the United States and Canada, and randomly assigned (1:1) to receive oral ridinilazole (200 mg every 12 hours) or oral vancomycin (125 mg every 6 hours) for 10 days. **Primary end-point:** Sustained clinical response, defined as clinical cure at EOT and no recurrence within 30 days, which was used to establish non-inferiority (15% margin). **The second of the two Phase 2 studies (NCT02784002)** compared ridinilazole with fidaxomicin for the treatment of CDI. **Time period:** December 2014 to August 2016. **Study design:** Randomized, open-label, active-controlled clinical study to investigate the safety and efficacy of ridinilazole (200 mg bid) for 10 days compared with fidaxomicin (200 mg bid) for 10 days for the treatment of CDI. **Study population:** 27 participants with clinical diagnosis of CDI plus laboratory diagnostic test. The study was conducted in three countries (Czechia, United Kingdom and the United States). Included in the study were adults (≥ 18 years of age) with clinical diagnosis of CDI confirmed by laboratory diagnostic test who had not received > 30 h antimicrobial treatment for their current CDI. Excluded were patients with life-threatening or fulminant CDI and those ≥ 2 episodes of CDI in the previous year and pregnant or breastfeeding women. **The primary end-poin**t was safety. Sustained clinical response at day 30 and clinical cure rates at day 12 were among secondary end-points.

Product name (INN or company code):	Ridinilazole
Clinical results:	**Ri-CoDIFy 1 and 2:** The study did not meet its primary end-point. Ridinilazole achieved sustained clinical response (SCR) in 73% of patients vs 70.7% of the vancomycin group (P = 0.4672). Ridinilazole resulted in a significant reduction in recurrent CDI (rCDI) rate (8.1% vs 17.3%, P = 0.0002) *(4)*. This was most notable in the pre-specified population of in-patients not receiving other antibiotics (rCDI 6.7% in ridinilazole vs 16.5% in vancomycin, P = 0.0005) *(4)*. Patients in the ridinilazole group presented with increased microbiome diversity compared with those in the vancomycin group at both 10 (P < .0001) and 30 (P ≤ .0007) days following treatment completion *(4)*. Note: *Upon consultation, the US-FDA requested additional evidence of efficacy from at least one additional clinical trial.* **Phase 2** (NCT02092935): Ridinilazole demonstrated an overall response rate (ORR) at TOC visit of 66.7% (n = 24/36) in the ridinilazole arm compared with 42.4% (14/33) of those in the vancomycin arm, for a percentage difference of 21.1% (90% CI: 3.1–39.1, P = 0.0004) *(5)*. The safety profile of ridinilazole was similar to that of vancomycin. Nausea (20%) and abdominal pain (12%) were the most commonly reported adverse reactions associated with ridinilazole *(5)*. **Phase** 2 (NCT02784002): The study reported comparable sustained clinical response rates on day 30 post-EOT: 50% for ridinilazole compared with 46.2% for fidaxomicin; treatment difference, 2.9% (95% CI: -30.8–36.7). The study also reported that ridinilazole preserved gut microbiome diversity to a greater extent than fidaxomicin during CDI treatment. The study concluded that this finding is consistent with low CDI recurrence rates.
Adverse effects/ Preclinical PK and safety:	According to a Phase 2 study that assessed the safety and efficacy of ridinilazole vs vancomycin for treatment of CDI in 100 patients, 82% of those treated with ridinilazole had adverse events (n = 41/50), mostly mild (40% GI tract related) *(5)*. One serious adverse event (hypokalaemia) was reported *(5)*.

Product name (INN or company code):	CRS3123
Pharmacology: chemical class and MoA:	CRS3123 is a diaryldiamine derivative that selectively inhibits Gram-positive bacterial methionyl-tRNA synthetase *(6)*.
Spectrum of activity and potential resistance:	CRS3123 is active against aerobic Gram-positive bacteria, including *C. difficile*, and inhibits toxin production in vitro *(6)*. It shows little activity against Gram-negative bacteria, including anaerobes, and no effect on human methionyl-tRNA synthetase enzyme *(7)*. In vivo evidence of efficacy for CDI treatment was obtained from the hamster model *(8)*.
Sought therapeutic indication:	Under development for the treatment of CDI.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 2:** A randomized, double-blind, comparator-controlled, multicentre study to evaluate the safety and efficacy of crs3123 compared with oral vancomycin in 108 adults with *C. difficile* infection (**NCT04781387**, currently recruiting). **Study population:** Approximately 100 adults 18 years or older diagnosed with a primary episode or first recurrence of CDI received either two dosages of CRS3123 (200 mg and 400 mg) administered twice daily, or vancomycin 125 mg administered four times daily. The duration of treatment for all study treatment arms is 10 days. Patients with clinically documented CDI were enrolled at up to 30 sites in Canada and the United States. **Primary end-point:** Rate of clinical cure at TOC in the ITT population. **Phase 1:** Randomized, double-blind, placebo-controlled, single ascending dose trial to determine the safety and PK of CRS3123 administered orally to healthy adults (**NCT01551004**, completed April 2014).

Product name (INN or company code):	CRS3123
Clinical results:	**Phase 2 (NCT04781387):** Topline results were published on the company's website. Among the 43 patients in the primary ITT analysis population, clinical cure rates at the day 12 test-of-cure visit were comparable in all three treatment groups, including 28/29 (97%) in patients receiving one of two dosages of CRS3123 versus 13/14 (93%) in those receiving vancomycin *(9)*. There were no clinical failures at the day 12 time point; the results in two patients were indeterminate. CRS3123 was generally safe and well tolerated *(9)*.
Adverse effects/ Preclinical PK and safety:	From the **Phase 1 study** (NCT01551004), CRS3123 was generally safe and well tolerated, with no serious adverse events or severe TEAEs reported *(7)*. Faecal concentrations were above the MIC90 value of 1 µg/mL at all dosages tested *(7)*. Subjects receiving either of the two lower doses of CRS3123 exhibited minimal disruption of normal gut microbiota after 10 days of twice-daily dosing *(7)*. CRS3123 was inactive against important commensal anaerobes, including *Bacteroides*, *Bifidobacteria* and commensal *Clostridia*. Beneficial microbiome effects were also observed *(7)*.

Product name (INN or company code):	Oxaquin (DNV3837, MCB-3837; prodrug of MCB-3681)
Pharmacology: chemical class and MoA:	Oxaquin (DNV3837/MCB-3837) is an oxazolidinone-quinolone hybrid and prodrug of MCB-3681 that is administered intravenously *(10)*.
Spectrum of activity and potential resistance:	Oxaquin has been reported to be active against Gram-positive gut microflora bacteria but to be sparing of Gram-negative organisms in human volunteer studies with iv administration over 5 days *(11,12)*. In in vitro studies, MICs of Oxaquin for *C. difficile* ranged from 0.008 mg/L to 0.5 mg/L *(11,12)*. There was no evidence of Oxaquin resistance from limited data *(11,12)*.
Sought therapeutic indication:	Under development for the treatment of CDI.
Pharmaceutical form, route of administration:	Intravenous.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 2:** An exploratory, open-label, oligo-centre study to evaluate the safety, efficacy and PK of iv DNV3837 in 40 subjects with *C. difficile* infection (**NCT03988855**, first part of the study completed, the status of the second part is unknown). **Time period:** January 2021-April 2024. **Study population:** Subjects with severe or non-severe CDI. DNV3837 is administered at a dose of 1.5 mg/kg actual body weight/day via iv infusion, for a total maximum daily dose of 120 mg in subjects with CDI. Infusions will be administered once a day for 10 consecutive days. The study will be conducted in two subsequent parts. In part 1 of the study, 10 subjects of either sex with severe or non-severe CDI will be enrolled to receive DNV3837. In part 2 of the study, up to 30 subjects with severe or non-severe CDI will be enrolled to receive DNV3837. **Primary end-points:** • Evaluate the safety of iv DNV3837. • Assess the PK of DNV3837 and DNV3681 in plasma and of DNV3681 in urine and faeces. • Assess *C. difficile* using microbiological assessments. **In the second part of the study:** Tate of clinical cure at TOC in the ITT population.
Clinical results:	In the first part of the study, by day 5, all 12 volunteers exhibited faecal concentrations of MCB3681 ranging from 98.9 to 226.3 mg/kg *(12)* caused no ecological changes in the skin, nasal or oropharyngeal microbiota; no new colonizing aerobic or anaerobic Gram-positive bacteria were found with MCB3681 MICs of ≥ 4 mg/L *(12)*. Faecal microbiota was normalized on day 19 *(13)*.

Product name (INN or company code):	Ibezapolstat (ACX-362E)
Pharmacology: chemical class and MoA:	Ibezapolstat (ACX-362E) is a first-in-class dichlorobenzyl purine analogue that binds to and inhibits bacterial DNA polymerase IIIC. DNA pol IIIC is essential for replicative DNA synthesis in Gram-positive bacteria with a low G + C content such as Clostridioides (new target and new MoA) *(14–16)*.
Spectrum of activity and potential resistance:	Ibezapolstat exhibits low MIC values against MDR *C. difficile* isolates. The overall MIC50/90 (mg/L) for ibezapolstat against *C. difficile* was 2/4, compared with 0.5/4 for metronidazole, 1/4 for vancomycin and 0.5/2 for fidaxomicin *(17)*. In vivo studies of ibezapolstat demonstrate minimal systemic absorption, and the drug was able to prevent recurrence when administered for 14 days. Its unique MoA is claimed to bypass cross-resistance with other frequently used antibiotics *(18)*.
Sought therapeutic indication:	Under development for the treatment of CDI.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2b.
Clinical trial(s):	**Phase 1**: A three-part, randomized, placebo-controlled study of the tolerability and safety of ibezapolstat in healthy male and female subjects of normal range body mass index (BMI) **(Midlands IRB# 220170383)** *(19)*. **Phase 2:** ACX-362E (ibezapolstat) for oral treatment of *C. difficile* infection: a Phase 2a open-label segment followed by a Phase 2b double-blind vancomycin-controlled segment **(NCT04247542)**. **Phase 2a:** An open-label study of up to 20 patients at six study centres and was terminated early at 10 patients based on the protocol-specified trial oversight committee's assessment of the compelling efficacy and safety data. Patients were treated with 450 mg of oral ibezapolstat bid for 10 days. **Phase 2b:** Designed to enroll 64 patients and is a randomized (1:1), non-inferiority, double-blind trial of oral ibezapolstat compared to oral vancomycin, an SOC to treat CDI. Subjects will receive either ibezapolstat 450 mg every 12 hours or vancomycin 125 mg orally every 6 h, in each case, for 10 days and followed for 28 + 2 days following the end of treatment for recurrence of CDI (not recruiting).
Clinical results/adverse effects:	From the **Phase 1 trial** (Midlands IRB# 220170383), multiple dose levels of ACX-362E were well tolerated with no reported adverse events *(19)*. Blood levels indicated poor oral absorption. Faecal concentrations at higher doses exceeded the inhibitory concentrations for *C. difficile* and were sustained throughout the treatment course *(19)*. Beneficial microbiome effects were also observed. **In the Phase 2a** (NCT04247542) **study:** All (10 of 10) patients were cured of CDI at end of treatment, and all (10 of 10) were sustained clinical cures 30 days after EOT. Ibezapolstat was well tolerated, with no reported serious adverse events *(20)*.

Product name (INN or company code):	MGB-BP-3
Pharmacology: chemical class and MoA:	MGB-BP-3 is a first-in-class, non-absorbable antibiotic with a novel chemical structure (distamycin derivative), a new target and antibacterial MoA (DNA minor groove binder). It acts on multiple binding sites and interferes with transcription *(21,22)*.
Spectrum of activity and potential resistance:	MGB-BP-3 is active against Gram-positive bacteria; resistance is found in Gram-negative bacteria through efflux pumps *(23)*.
Sought therapeutic indication:	Under development for the treatment of CDI.
Pharmaceutical form, route of administration:	Oral (not absorbed).
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 2a:** An exploratory, open-label study assessing the safety, tolerability and efficacy of incremental doses of MGB-BP-3 (**NCT03824795**, completed April 2020). **Study population:** Three sequential groups of 10 patients with *C. difficile*-associated diarrhoea (CDAD). Patients will be administered an oral dose of MGB-BP-3 for 10 days (day 1 to day 10). At the end of the treatment period, patients will be followed for up to 8 weeks to assess the incidence of disease recurrence. **Primary outcomes:** Number of participants with treatment-related adverse events assessed by the investigator, as per CTCAE (Common Terminology Criteria for Adverse Events), initial cure rate at 12 days post initiation of therapy. **Phase 1:** A single-centre, double-blind, placebo-controlled study in 40 healthy men to assess the safety and tolerability of single and repeated ascending doses of MGB-BP-3 (**NCT02518607**, completed).
Clinical results/ adverse effects:	**Phase 2a topline results published on the company website** *(23)***:** three dose levels were evaluated in the study with the maximum efficacy observed at 250 mg of MGB-BP-3, given twice daily for 10 days, achieving an initial cure and sustained cure of 100% *(24)*. This dosage regimen has now been confirmed for the next phase of clinical trials. In data from Phase 1 and 2 studies, MGB-BP-3 showed a good safety and tolerability profile with no serious adverse events reported *(24)*.

Product name (INN or company code):	Rifasutenizol (TNP-2198)
Pharmacology: chemical class and MoA:	Rifasutenizol (TNP-2198) is a stable conjugate of a rifamycin pharmacophore and a nitroimidazole pharmacophore *(25)*.
Spectrum of activity and potential resistance:	It is reported to show unique antibacterial activity against anaerobic and microaerophilic bacteria and against strains resistant to both rifamycins and nitroimidazoles *(25)*.
Sought therapeutic indication:	Under development for the treatment of *Helicobacter pylori* infection, CDI and bacterial vaginosis *(25)*.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 3.
Clinical trial(s):	**Phase 3:** To evaluate the efficacy and safety of rifasutenizol (TNP 2198) in combination with rabeprazole and amoxicillin in the primary treatment of 700 participants with *H. pylori* infection (**NCT05857163**, recruiting). **Study population:** 700 (estimated) adult patients with *H. pylori* infection with positive 13C-UBT results (≥ 4 delta over baseline), and confirmation of infection of *H. pylori* by gastroscopic biopsy histology, will be randomized 1:1 to be assigned to test group or control group stratified by study site, and will receive 400 mg, bid rifasutenizol, 2 mg bid rabeprazole sodium enteric-coated tablets, 1 g bid amoxicillin capsules combined with clarithromycin placebo tablets and bismuth potassium citrate placebo capsules (test group), or a bismuth-containing quadruple regimen of amoxicillin capsules, 250 mg bid clarithromycin, rabeprazole sodium enteric-coated tablets and 400 mg bid bismuth potassium citrate capsules combined with rifasutenizol placebo capsules (control group) for 14 consecutive days**.** **Time period:** May 2023 to October 2024. **Sites:** China, no further details. **Primary end-point:** Eradication rate of *H. pylori* strain 13C urea breath test will be performed 4 to 6 weeks after the last dose to evaluate the eradication effect of *H. pylori*.
Clinical results/ adverse effects:	**Phase 3 topline results published on the company website** *(26)*: Rifasutenizol triple therapy achieved >90% eradication rate, higher than bismuth-containing quadruple therapy (BQT), control in treating *H. pylori* infection. The company also claims that the rifasutenizol regimen showed a better safety and tolerability profile than BQT *(26)*. **Phase 1, Phase 1/2:** Three trials to evaluate the PK, efficacy, and safety of rifasutenizol have been completed in China. Results of these trials were summarized and published in 2024 by Li et al *(27)*.

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Annex 18 Non-traditional agents against CDI and *H. pylori*

Product name (INN or company code):	IM-01
Pharmacology: chemical class and MoA:	IM-01 is an egg-derived experimental polyclonal antibody targeting *C. difficile* toxins A, toxin B, spores and/or other virulent antigens responsible for the pathogenesis of CDI *(1)*.
Spectrum of activity:	A United States patent filing for IM-01 states that its antibodies inhibited >80% growth of three *C. difficile* isolates of hypervirulent NAP/B1/027 strains *(1)*. IM-01 is claimed to stimulate antibody production and cause toxin neutralization, reduction of spore burden, and inhibition of vegetative cell growth *(1)*.
Sought therapeutic indication:	Under development for the treatment of CDI in inflammatory bowel disease (IBD).
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.
Clinical trial(s):	**Phase 2:** To measure the clinical effectiveness of egg-derived polyclonal antibodies (IM-01) for the treatment of mild–moderate *Clostridium difficile* infection (CDI) (**NCT04121169**, unknown status)**.** **Study population:** 60 consented, 18 to 89 year-olds, males or females with CDI as per defined criteria (primary episode or relapse) in good general health. **Primary outcome:** Clinical response to IM-01 treatment for CDI for 14 days, *C. difficile* pathogen count, spore count, and *C. difficile* toxin titres in stool samples following IM-01 treatment.
Adverse effects/ Preclinical PK and safety:	In webpage data of results from a Phase 1 study: of the 106 *C. difficile*-infected patients were treated with IM-01, more than 94% showed improvement in clinical response and negative stool test results were measured *(1)*. There was no relapse of the disease reported during a 6-week follow-up period *(1)*.

Product name (INN or company code):	AZD5148
Pharmacology: chemical class and MoA:	AZD5148 is a monoclonal antibody; *C. difficile* toxin TcdB inhibitor *(2)*.
Spectrum of activity:	As an anti-toxin B neutralizing mAb, AZD5148 was shown to provide protection in a *C. difficile* gnotobiotic piglet model *(3)*.
Sought therapeutic indication:	Under development for the prevention of recurrent CDI.
Pharmaceutical form, route of administration:	Intravenous or intramuscular.
Phase of clinical development:	Phase 2.
Clinical trial(s):	AZD5148 is being evaluated in a series of Phase 1 trials: **Phase 1** (**NCT06469151**): A double-blind, placebo-controlled study is to measure safety, tolerability and PK of a single dose of AZD5148 administered via intravenous (IV) bolus or intramuscular (IM) injection in 84 healthy adults (active, not recruiting). **Phase 1** (**NCT06639997**, also jRCT2071240071): A double-blind, placebo-controlled study to measure safety, tolerability and PK of a single dose of AZD5148 administered via IV bolus or IM injection in 16 healthy Japanese participants (active, not recruiting).

Product name (INN or company code):	MTC01
Pharmacology: chemical class and MoA:	MTC01 is a live biotherapeutic product (LBP) *(4)*.
Spectrum of activity:	MTC01 is designed as an alternative to faecal microbiota transplantation (FMT). The LBP was isolated from known-successful FMT donors to compare the clinical response and the microbial engraftment of the FMT with that of the LBP *(4)*.
Sought therapeutic indication:	Under development for the treatment of recurrent CDI.
Pharmaceutical form, route of administration:	Endoscopic delivery.
Phase of clinical development:	Phase 1.
Clinical trial(s):	**Phase 1:** Open-label, randomized study with parallel assignment to compare four different interventions of MTC01 vs FMT for the treatment of recurrent *Clostridioides difficile* infection in 60 adult participants with history of recurrent CDI (**NCT05911997**, recruiting).

Product name (INN or company code):	EXL01
Pharmacology: chemical class and MoA:	EXL01 is a live biotherapeutic product; a single isolated unmodified strain of *Faecalibacterium prausnitzii*.
Spectrum of activity:	EXL01 is claimed to have immunomodulatory properties that enable synergistic effects when combined with standard therapies in a range of indications *(5)*. *F. prausnitzii* has also been identified as a key marker of response to immune checkpoint inhibitors *(6)*. In preclinical models, EXL01 stimulated response to existing anti-PD1/PD-L1 therapies *(6)*. EXL01 is currently being evaluated in patients with non-small cell lung cancer (NCT06448572), hepatocellular carcinoma (NCT06551272) and metastatic gastric cancer (NCT06253611).
Sought therapeutic indication:	Under development for the prevention of recurrent CDI.

Product name (INN or company code):	EXL01
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase ½.
Clinical trial(s):	Phase 1/2: A randomized open-label (Phase 1), double-blind (Phase 2) study with parallel assignment to evaluate EXL01 in the prevention of recurrence of *C. difficile* infection in 56 high-risk patients (LIVEDIFF) (NCT06306014, recruiting). The first phase of the study is designed to demonstrate the safety and tolerability of EXL01 in patients at high risk of recurrence previously treated with vancomycin. The second phase will assess EXL01's efficacy in preventing *C. difficile* recurrence after 8 weeks *(5)*.

Product name (INN or company code):	MET-2 (Microbial Ecosystem Therapeutic-2)
Pharmacology: chemical class and MoA:	MET-2 (Microbial Ecosystem Therapeutic-2) is a stool-derived oral capsule with a consortium of 40 lyophilized commensal bacteria species *(7)*.
Spectrum of activity:	MET-2 represents several bacterial phyla cultured from the stool of an intensely screened, single healthy donor to eliminate any potential risks posed by changes in donor health via subsequent manufacturing, reportedly conferring safety benefits over traditional FMTs *(8)*. It is also being investigated in psychiatric indications, specifically depression and anxiety *(9)*. Non-clinical publicly available data are limited.
Sought therapeutic indication:	Under development for the treatment of recurrent CDI.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 1.
Clinical trial(s):	Phase 1: An open label, single centre, multiple dose pilot study of 19 patients, designed to measure the resolution of diarrhoea, the feasibility of administration and safety of MET-2 for the treatment of recurrent CDI in patients who have experienced at least two prior episodes of CDI and have developed recurrence after having completed SOC oral antibiotic therapy to treat CDI. (NCT02865616, completed March 2020). Phase 1: A placebo-controlled, study of the safety and efficacy of MET-2 in 11 patients with ulcerative colitis (NCT03832400, completed March 2020). Phase 1: Investigates the safety, efficacy and tolerability of microbial ecosystem therapeutic-2 in 60 people with major depression (NCT04602715, unknown status). Phase 1: Investigates the safety, efficacy and tolerability of microbial ecosystem therapeutic-2 in 21 people with major depression and/or generalized anxiety disorder (NCT04052451, completed May 2020).
Adverse effects/ Preclinical PK and safety:	In its Phase 1 open-label trial, (NCT02865616) at day 40, 79% of patients receiving MET-2 did not have rCDI, which increased to 95% 40 days after receiving a second dose *(10)*. There were no serious adverse events or deaths *(10)*. At 130 days, 84% of patients did not have rCDI. Stool analysis showed increased microbiota diversity and increased abundance of MET-2–containing bacteria during final analysis when compared with baseline *(7,10)*.

Product name (INN or company code):	RBX7455
Pharmacology: chemical class and MoA:	RBX7455 is a live biotherapeutic product manufactured from a microbiota-based suspension prepared from human stool.
Spectrum of activity:	RBX7455 is designed to rehabilitate the human microbiome by delivering a broad spectrum of live microbes into a patient's intestinal tract via a ready-to-use and easy-to-administer format *(11)*. RBX7455 and Rebyota (RBX2660, enema) baseline participant microbiome health index (MHI) values were similar among the trials *(11)*. It is also under study in paediatric Crohn's disease (**NCT03378167**) and hepatic encephalopathy (**NCT04155099**).
Sought therapeutic indication:	Under development for the treatment of recurrent CDI.
Pharmaceutical form, route of administration:	Oral (capsules).
Phase of clinical development:	Phase 1.
Clinical trial(s):	**Phase 1:** To demonstrate the efficacy and safety of RBX7455 for the treatment of recurrent CDI in 30 subjects who have had at least one recurrence after a primary episode (i.e. at least two episodes) and have completed at least two rounds of SOC oral antibiotic therapy (**NCT02981316**, completed July 2020).
Adverse effects/ Preclinical PK and safety:	Nine of 10 group 1 patients (90%), eight of 10 group 2 patients (80%), and 10 of 10 group 3 patients (100%) were recurrence-free at the 8-week end-point with durability to 6 months *(12)*. There were no serious investigational product-related events. After treatment, responders' microbiomes showed increased *Bacteroidia* and *Clostridia (12)*.

Product name (INN or company code):	SYN-004 (ribaxamase)
Pharmacology: chemical class and MoA:	SYN-004 (ribaxamase) is a recombinant BLI enzyme orally administered with IV-administered β-lactams that degrades the excess of IV antibacterial agents in the proximal GIT, helping to preserve the gut microbiome *(13)*.
Spectrum of activity:	In in vitro studies, SYN-004 is reported to hydrolyse penicillins and cephalosporins *(13)*. In animal studies, SYN-004 was shown to degrade ceftriaxone in the GI tract of dogs and protected the microbiome of pigs from ceftriaxone-induced changes *(13)*.
Sought therapeutic indication:	SYN-004 is being investigated as therapy to mitigate predisposition to *C. difficile* in patients being treated with iv-administered β-lactams and in allogeneic haematopoietic cell transplantation (allo-HCT) recipients.
Pharmaceutical form, route of administration:	Oral.
Phase of clinical development:	Phase 2.

Product name (INN or company code):	SYN-004 (ribaxamase)
Clinical trial(s):	**Phase 1b/2a:** the evaluation of the safety and tolerability of SYN-004 in 36 adult allogeneic hematopoietic cell transplantation (allo-HCT) recipients (NCT04692181, currently recruiting). **Study population:** Consented adults, male or female, 18 years of age or older, undergoing myeloablative allo-HCT for a haematologic malignancy or myeloproliferative disorder. **Primary outcomes:** • SYN-004 systemic absorption; • systemic antibiotic concentrations; • bacteraemia; • bacterial intestinal infections; • grade 3 or 4 adverse events; and • overall survival. **Phase 2:** A double-blind, placebo-controlled, multicentre study of SYN-004 compared to placebo for the prevention of *C. difficile* in 413 patients with a diagnosis of a lower respiratory tract infection (**NCT02563106**, completed Nov 2016). **Study population:** Patients 50 years or older with clinical diagnosis of moderate to severe lower respiratory tract infection consisting of signs and symptoms of a lower respiratory tract infection and pneumonia severity index (PSI/PORT) score for CAP of 90-130, inclusive. (minimum hospital stay of 5 days and IV ceftriaxone >5 days). **Primary outcome:** Percentage of patients with CDI at four weeks of follow-up.
Clinical results/adverse effects	In interim (poster) results from the Phase 1/2 trial (NCT04692181), there were no SAEs attributable to SYN-004 *(14)*. In the Phase 2 trial (NCT02563106), for the period of study and 4 weeks after antibiotic treatment, two (1·0%) patients in the ribaxamase group and seven (3·4%) patients in the placebo group were diagnosed with an infection with *C. difficile* (risk reduction 2·4%, 95% CI: -0·6–5·9; one-sided p=0·045) *(15)*. Researchers found that adverse events were similar between groups. More deaths were reported in the ribaxamase group (11 deaths vs five deaths in the placebo group) *(15)*.

Product name (INN or company code):	ADS024 (formerly ART 24)
Pharmacology: chemical class and MoA:	ADS024 (ART24) is an orally delivered single strain live biotherapeutic product (SS-LBP) *(16)*.
Spectrum of activity:	The ADS024 cells were shown to kill *C. difficile* in vitro with limited impact on other commensal bacteria *(17)*. In addition to directly killing *C. difficile*, ADS024 also produces proteases capable of causing proteolytic cleavage of *C. difficile* toxins (TcdA, TcdB) *(16,17)*. In independent experiments, the lowest ratio of ADS024: *C. difficile* colony-forming units (CFU) that resulted in *C. difficile* killing (>3 log reduction in 24 h) was 275:1; lower ratios inhibited the growth rate of *C. difficile* without complete killing *(17)*. In a mouse model of CDI, oral gavage of ART24 cells demonstrated a protective effect with improved survival (90% in ART24 dosed groups versus 70% in the saline control group at Day 10), and a reduction in disease-related clinical observations *(18)*.
Sought therapeutic indication:	Under development for the prevention of recurrent CDI.
Pharmaceutical form, route of administration:	Oral.

Product name (INN or company code):	ADS024 (formerly ART 24)
Phase of clinical development:	Phase 1.
Clinical trial(s):	**Phase 1:** A randomized, placebo-controlled, double-blind, trial of ART24 in 36 subjects recently cured of CDI having completed a SOC course of CDI antibiotics. (**NCT04891965**, completed October 2020).
Clinical results/adverse effects	Not yet publicly available.

Product name (INN or company code):	MBK-01
Pharmacology: chemical class and MoA:	MBK-01 is a heterologous lyophilized faecal microbiota from healthy donors (for faecal microbiome transplant, FMT) acting through restoration of gut microbial diversity.
Spectrum of activity:	Is claimed to bring about modification of the microbiome to eliminate or prevent carriage of resistant or pathogenic bacteria (no data disclosed). Previous FMT studies with different products showed efficacy to prevent recurrent CD infections (CDIs) *(19)*, and three FMT products were recently approved for the prevention of recurrence of CDI (see Table 1b of the main report), whereas contrasting results were obtained for the eradication of intestinal colonization by MDR pathogens *(20–23)*.
Sought therapeutic indication:	Under development for treatment of primary or recurrent CDI and eradication of intestinal colonization by CREB.
Pharmaceutical form, route of administration and proposed posology:	A single dose of four capsules of MBK-01 orally.
Phase of clinical development:	• Phase 3 for the indication: primary or recurrent CDI. • Phase 2 (NCT04760665, terminated due to a lack of eligible population (last update July 2024)) for the indication: eradication of intestinal colonization by CREB.

Product name (INN or company code):	MBK-01
Clinical trial(s):	Phase 3 (NCT05201079, completed November 2023): A randomized, controlled, open-label trial in patients with primary or recurrent CDI, to evaluate the efficacy and safety of capsules of lyophilised faecal microbiota vs fidaxomicin. Study population: Adult patients that undergo an episode of CDI (either the first episode or subsequent recurrences), with an episode of diarrhoea defined as ≥3 stools/24 hours, at the beginning of the episode and confirmation of the presence of CD toxin A and/or B in faeces, by a direct toxin detection test or by the PCR technique for the detection of toxin/s producing genes, at the start of the episode that is going to be treated in the clinical trial (the toxin test must be positive within 7 days prior to the enrolment of the patient in the trial). Time period: October 2021 to June 2023. Sites: 21 sites in Spain. Primary end-point: Absence of diarrhoea. Number of episodes of diarrhoea (3 or more stools/24 hours) observed with different time frames: 1. Eight weeks after the start of the treatment. 2. 72 hours after the start of the treatment. 3. Three weeks after the start of the treatment. 4. Three months after the start of the treatment. 5. Six months after the start of the treatment. Diarrhoea resolution: <3 stools/24 hours for at least two consecutive days after the end of the treatment. Phase 2 (NCT04760665, terminated due to a lack of eligible population (last update July 2024)): The KAPEDIS trial is a single-centre, randomized, superiority, double blind controlled with placebo clinical trial, to demonstrate the effectiveness of faecal microbiota transplantation for selective intestinal decolonization of patients colonized by carbapenemase-producing *Klebsiella pneumoniae* (KPC) *(24)*. Study population: One hundred and twenty patients with a positive rectal swab for KPC within one week before randomization, with absence of active infection by KPC at the time of assessment as well as in the month prior to inclusion in the study, will be randomized 1:1 to receive encapsulated lyophilized FMT or placebo *(24)*. Time period: October 2021 to September 2024. Sites: Spain, number of sites not specified. Primary end-point: Percentage of patients with intestinal decolonization at 30 days after FMT. Decolonization will be considered as the absence of isolation of KPC in culture from rectal swab together with the absence of detection of carbapenemase by means of polymerase chain reaction assay. Primary efficacy evaluation will be performed in the ITT population (all randomized patients).
Clinical results/adverse effects	Phase 3 trial results have been submitted (to clinicaltrials.gov) but are not yet publicly available, as of 29 January 2025.

Product name (INN or company code):	LMN-201
Pharmacology: chemical class and MoA:	LMN-201 is a combination of a *C. difficile* targeting phage-derived endolysin and three toxin-binding proteins (5D, E3 and 7F) that all bind to *C. difficile* virulence mediator TcdB2 by different mechanisms *(25)*.
Spectrum of activity:	LMN-201 is reported to be 300- to 3000-fold more potent than bezlotoxumab, enhanced by a phage-derived endolysin that destroys the bacterium *(25)*.
Sought therapeutic indication:	LMN-201 is intended to be administered concomitantly with antibiotics and for eight weeks thereafter to provide protection from *C. difficile* reinfection while commensal bacteria recolonize the GI tract *(26)*.
Pharmaceutical form, route of administration:	Oral (capsules).
Phase of clinical development:	Phase 2/3.
Clinical trial(s):	**Phase 1:** An exploratory study to assess delivery of LMN-201 components via enteric capsules in the gut of 12 individuals with ostomies (**NCT04893239**, completed February 2022). **Phase 2/3:** A randomized, double-blind, placebo-controlled study of LMN-201 for prevention of CDI recurrence. A multisite study to evaluate the safety, tolerability and efficacy of LMN-201 in 375 participants recently diagnosed with CDI who are scheduled to receive or are receiving SOC antibiotic therapy against *C. difficile* (**NCT05330182**, recruiting expected completion 2026). **Study population:** Consented adults, 18 years or older, males or females, with a diagnosis of CDI who are scheduled to receive or planning to receive a ≤28-day course of SOC antibiotic therapy for CDI *(27)*. **Primary outcome measure:** Proportion of participants who achieve global cure.
Clinical results/adverse effects	Not yet publicly available.

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