# Meeting background document: antibacterial agents in clinical development

Table 1: Antibiotics and combinations containing a new chemical entity that are being developed against priority pathogens, approved by FDA 2017/2018

| Name (trade name) | Approved by (date) | Antibiotic class | Route of administration (Market authorization holder) | Indication | Expected activity against priority pathogens | | | | Innovation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CRAB | CRPA | CRE | OPP | NCR | CC | T | MoA |
| Delafloxacin (Baxdela) | FDA (6/2017) MAA | Fluoroquinolone | iv & oral (Melinta) | ABSSSI (CAP, sNDA) | ○ | ○ | ○ | ● | – | – | – | – |
| Vaborbactam + meropenem (Vabomere) | FDA (8/2017) EMA (11/2018) | Boronate BLI + carbapenem | iv (Melinta) | cUTI (*E.coli, K. pneumoniae*, *Enterobacter cloacae)* | ○ | ○ | ●[1] | / | ? | ✓ | – | – |
| Plazomicin (Zemdri) | FDA (6/2018) MAA (6/2018) | Aminoglycoside | iv (Achaogen) | cUTI | ○ | ○ | ● | / | – | – | – | – |
| Eravacycline (Xerava) | FDA EMA (9/2018) | Tetracycline | iv (Tetraphase) | | ? | ○ | ● | / | – | – | – | – |
| Omadacycline | FDA (10/2018) MAA (10/2018 | Tetracycline | iv & oral (Paratek) | | ○ | ○ | ○ | ● | – | – | – | – |
| Relebactam + imipenem/cilastatin (Recarbrio) | FDA (7/2019) | DBO-BLI + carbapenem/ degradation inhibitor | iv (MSD) | cUTI (E. cloacae, E. coli, K. aerogenes, K.pneumoniae, P.aeruginosa), cIAI | ○ | ? | ●[1] | / | – | – | – | – |
| Lefamulin (Xenleta) | FDA (8/2019) | Pleuromutilin | | iv & oral (Nabriva) | / | / | / | ● | ? | ✓[2] | – | ✓ |

[1] Active against *K. pneumoniae* carbapenemase (KPC) but not metallo-β-lactamase-producing Enterobacteriaceae
[2] First systemic formulation of this class, which has been used in animals and topically in humans previously

Table 2a. Antibiotics and combinations containing a new chemical entity that are being developed globally against priority pathogens

| Name (synonym) | Phase | Antibiotic class | Route of administration (developer) | Expected activity against priority pathogens | | | | Innovation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | CRAB | CRPA | CRE | OPP | NCR | CC | T | MoA |
| Iclaprim | NDA[1] | DHFR inhibitor | iv (Motif Bio) | / | / | / | ● | – | – | – | – |
| Cefiderocol | NDA[2] MAA | Siderophore-cephalosporin | iv (Shionogi) | ● | ● | ● | / | ? | – | – | – |
| | | | | | | | | | | | |
| Sulopenem, sulopenem etzadroxil/ probenecid | 3 | Penem | iv (Iterum) oral (Iterum) | ○ | ○ | ○[3] | / | – | – | – | – |
| Murepavadin (POL-7080) | 3[4] | Novel membrane targeting antibiotic | (iv & ) inhaled (Polyphor) | / | ● | / | / | ✓ | ✓ | ✓ | ✓ |
| Durlobactam (ETX2514)+ sulbactam | 3 | DBO-BLI /PBP2 binder + β-lactam-BLI/PBP1,3 binder | iv (Entasis) | ● | ○ | ○ | / | – | – | – | – |
| Taniborbactam (VNRX-5133) + cefepime | 3 | Boronate-BLI + cephalosporin | iv (VenatoRX) | ? | ? | ● | / | ? | ✓ | – | – |
| Enmetazobactam (AAI101) + Cefepime | 3 | β-lactam BLI + cephalosporin | iv (Allecra) | ○ | ○ | ○[5] | / | – | – | – | – |
| Zoliflodacin | 3 | NBTI (Spiropyrimidenetrione) | Oral (Entasis/GARDP) | / | / | / | ● | ✓ | ✓ | – | ✓ |
| Gepotidacin | 3 | NBTI (Triazaacenaphthylene) | iv & oral (GSK) | / | / | / | ● | ? | ✓ | – | ✓ |
| Contezolid Contezolid acefosamil | 2/3[6] | Oxazolidinone | oral (MicuRx) iv/oral (MicuRx) | / | / | / | ● | – | – | – | – |
| Afabicin (Debio-1450) | 2 | FabI inhibitor | iv & oral (Debiopharm) | / | / | / | ● | ✓ | ✓ | ✓ | ✓ |
| BOS-228 | 2 | Monobactam | iv (Boston Pharmaceuticals) | ○ | ○ | ● | / | – | – | – | – |
| Nafithromycin (WCK-4873) | 2 | Macrolide | Oral (Wockhardt) | / | / | / | ● | – | – | – | – |
| TNP-2092 | 2 | Rifamycin-quinolizinone hybrid | iv & oral (TenNor) | / | / | / | ? | – | – | – | – |
| Zidebactam + Cefepime | 1 | DBO-BLI/ PBP2 binder + cephalosporin | iv (Wockhardt) | ○ | ? | ● | / | – | – | – | – |
| Nacubactam + meropenem | 1 | DBO-BLI/ PBP2 binder + meropenem | iv (NacuGen Therapeutics) | ○ | ? | ●[7] | / | – | – | – | – |
| ETX0282+cefpodoxime | 1 | DBO-BLI + cephalosporin | oral (Entasis) | ○ | ○ | ●[7] | / | – | – | – | – |
| VNRX-7145+ceftibuten | 1 | Boronate-BLI + cephalosporin | oral (Venatorx) | ○ | ○ | ●[7] | / | ? | ✓ | – | – |
| SPR-741 + β-lactam | 1 | Polymyxin + β-lactam | iv (Spero) | ? | ? | ? | / | – | – | – | – |
| SPR-206 | 1 | Polymyxin | Iv (Spero) | ● | ● | ● | / | – | – | – | – |
| KBP-7072 | 1 | Tetracycline | oral (KBP BioSciences) | ? | ○ | ○ | ● | – | – | – | – |
| TP-271 | 1 | Tetracycline | iv & oral (Tetraphase) | ? | ○ | ○ | ● | – | – | – | – |
| TP-6076 | 1 | Tetracycline | iv (Tetraphase) | ● | ○ | ? | / | – | – | – | – |
| EBL-10031 (apramycin) | 1 | Aminoglycoside | Iv (Juvabis) | ? | – | ? | / | – | – | – | – |
| GT-1[8] | 1 | Siderophore-cephalosporine | Iv (Geom) | ● | ● | ○ | / | – | – | – | – |
| AIC-499 + unknown BLI | 1 | β-lactam + BLI | iv (AiCuris) | ? | ? | ? | / | – | – | – | – |
| TNP-2198 | 1 | Rifamycin-nitroimidazole conjugate | oral (TenNor) | / | / | / | ? | – | – | – | – |
| SPR-720 | 1 | GyrB inhibitor | oral (Spero) | ○ | ○ | ○ | /[9] | – | – | – | – |
| Delpazolid | 1 | Oxazolidinone | Legochem | ○ | ○ | ○ | ● | – | – | – | – |
| TXA709 | 1 | FtsZ inhibitor | Oral & iv (Taxis) | ○ | ○ | ○ | ● | ✓ | ✓ | ✓ | ✓ |
| BCM-0184 | 1 | ? | Oral (Biocidium) | ○ | ○ | ○ | ● | ? | ? | ? | ? |

**Pathogen activity:** ● active; ? possibly active; ○ not or insufficiently active; / activity not assessed as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods. The only agents assessed against OPP were those that are not active against critical

priority pathogens. OPP includes usually Gram-positive cocci, in the case of gepotidacin, zoliflodacin, solithromycin and delafloxacin, also *Neisseria gonorrhoeae*

**Innovation assessment**: ✓ criterion fulfilled; ? Inconclusive data or no agreement among the advisory group; - criterion not fulfilled; NCR, no cross-resistance to other antibiotic classes; CC, new chemical class; T, new target; MoA, new mode of action;

BLI, β-lactamase inhibitor; E, Enterobacteriaceae-, carbapenem- and third-generation cephalosporin-resistant; AB, *A. baumannii*, carbapenem-resistant; PA, *P. aeruginosa*-, carbapenem-resistant; DBO, diazabicyclooctane; DHFR, dihydrofolate reductase; iv, intravenous; NBTI, novel bacterial topoisomerase II inhibitor; NDA, new drug application (FDA), MAA, Marketing Authorization Application (EMA). OPP, other priority pathogens on the WHO PPL ("high" and "medium" priority); PBP, penicillin-binding protein

[1] NDA submission 14 June 2018, Complete Response Letter Feb 14 2019 (risk for liver toxicity)

[2] NDA submission Dec 2018, MAA submission March 2019. Accelerated assessment status in Europe for Gram-negative infections

[3] Active against extended-spectrum β-lactamase-producing cephalosporin-resistant but not carbapenem-resistant Enterobacteriaceae

[4] Current phase 3 trials for the iv formulation terminated due to nephrotoxicity

[5] Active against extended-spectrum β-lactamase-producing cephalosporin-resistant and some KPC producing carbapenem-resistant Enterobacteriaceae

[6] Contezolid acefosamil: Phase 2 in USA. Contezolid: Phase 3 in China, NDA in China expected in 2020

[7] Active against *K. pneumoniae* carbapenemase (KPC) but not metallo-β-lactamase-producing strains

[8] Maybe combined with BLI GT-055, a β-lactamase inhibitor to improve activity against CRE

[9] Developed for non-tuberculosis mycobacteria (NTM)

## Table 2b. Antibiotics and combinations containing a new chemical entity that are being developed regionally against priority pathogens

| Name (synonym) | Phase | Antibiotic class | Route of administration (developer, country) | Expected activity against priority pathogens | | | | Innovation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | CRAB | CRPA | CRE | OPP | NCR | CC | T | MoA |
| Lascufloxacin | NDA | Fluoroquinolone | iv & oral (Kyorin, Japan) | ○ | ○ | ○ | ? | - | - | - | - |
| Levonadifloxacin<br>Alalevonadifloxacin | 3 | Fluoroquinolone | iv (Wockhardt, India)<br>oral (Wockhardt, India) | ○ | ○ | ○ | ? | - | - | - | - |
| Cefilavancin<br>(TD-1792) | 3 | Glycopeptide-cephalosporine conjugate | iv (Theravance/R-Pharm, Russia) | / | / | / | ● | - | - | - | - |
| Solithromycin | 3 | Macrolide | iv & oral (Melinta/ Fujifilm Toyama Chemical, Japan) | / | / | / | ● | - | - | - | - |
| Benapenem | 2 | Carbapenem | Iv & oral (KBP Biosciences, China) | ○ | ○ | ○ | / | - | - | - | - |
| Benapenem | 1 | Carbapenem | Iv (XuanZhu Pharm, China) | ○ | ○ | ○ | / | - | - | - | - |
| PL-518 | 1 | Antimicrobial peptide | Iv (Jiangsu ProteLight Pharma, China) | ? | ? | ? | ● | ✓ | ✓ | ✓ | ✓ |

## Table 3. Biological antibacterial agents in clinical development

| Name (synonym) | Phase | Antibiotic class | Route of administration (developer) | Expected activity against priority pathogens | | | |
|---|---|---|---|---|---|---|---|
| | | | | PA | SA | CD | other |
| AR-301 (tosatoxumab, Salvecin) | 3 | Anti-*S. aureus* IgM monoclonal antibody | iv (Aridis) | / | ● | / | |
| CF-301 (exebacase) | 2 | Phage endolysin | iv (Contrafect) | / | ● | / | |
| SAL-200 (tonabacase) | 2 | Phage endolysin | iv (Roiant Sciences) | / | ● | / | |
| Suvratoxumab | 2 | Anti-*S. aureus* IgG monoclonal antibody | iv (MedImmune) | / | ● | / | |
| MEDI-3902 (Gremubamab) | 2 | Anti-*P. aeruginosa* IgG monoclonal antibody | iv (MedImmune) | ● | / | / | |
| AR-101 (Panobacumab, Aerumab) | 2[1] | Anti-P. *aeruginosa* serotype O11 IgG monoclonal antibody | Iv (Shenzhen Arimab Biopharmaceuticals) | ● | / | / | |
| AR-105 (Aerucin, panaecin) | 2 | Anti-*P. aeruginosa* IgG monoclonal antibody | iv (Aridis) | ● | / | / | |
| 514G3 | 2 | Anti-*S. aureus* IgG monoclonal antibody | iv (XBiotech) | / | ● | / | |
| DSTA-4637S | 1 | Anti-*S. aureus* IgG monoclonal antibody/rifamycin | iv (Genentech/Roche) | / | ● | / | |
| PolyCab | 1 | *C. difficile* polyclonal antibody | iv (MicroPharm) | / | / | ● | |
| IMM-529 | 1/2 | *C. difficile* polyclonal antibody | Oral (Immuron) | / | / | ● | |
| SAB-136 | 1 | Polyclonal antibody against Mycoplasma | iv (SAB Biotherapeutics) | / | / | / | ● |
| F598 | 1 | monoclonal IgG1 antibody against dPNAG in various pathogens | iv (Alopexx Pharmaceuticals) | / | / | / | ● |

**Pathogen activity:** ● active; / not applicable.
PA, *P. aeuruginosa*; SA, *S. aureus*; CD, *C. difficile*. These biologics are not influenced by conventional resistance mechanisms and the criterion of innovation was not applied.

[1] Developed only for China

## Table 4. Antibiotics for the treatment of tuberculosis in clinical development

| Name (synonym) | Phase | Antibiotic class | Route of administration (developer) | Innovation | | | |
|---|---|---|---|---|---|---|---|
| | | | | NCR | CC | T | MoA |
| Pretomanid (PA-824) | approved [1] | Nitroimidazole | Oral (+TB Alliance) | ? | – | – | ? |
| SQ-109[2] | 2/3 | Ethambutol derivative | Oral (Sequella/Infectex) | – | – | – | – |
| GSK070 (GSK-3036656) | 2 | Leu RS inhibitor (oxaborole) | Oral (GlaxoSmithKline) | ✓ | ✓ | ✓ | ✓ |
| Delpazolid (LCB01-0371)[2] | 2 | Oxazolidinone | Oral (LegoChem) | – | – | – | – |
| Sutezolid[3] | 2 | Oxazolidinone | Oral (TB Alliance/Sequella) | – | – | – | – |
| Telacebec (Q-203) | 2 | Imidazopyridine amide | Oral (Qurient/Infectex) | ✓ | ✓ | ✓ | ✓ |
| Macozinone (PBTZ-169) | 2 | DprE1 inhibitor (benzothiazinone) | Oral (Innovative Medicines for Tuberculosis Foundation) [4] | ✓ | ✓ | ✓ | ✓ |
| OPC-167832 | 1/2 | DprE1 inhibitor | Oral (Otsuka) | ? | ✓ | ✓ | ✓ |
| TBA-7371 | 1 | DprE1 inhibitor | Oral (TB Alliance, The Bill & Melinda Gates Medical Research Institute, Foundation for Neglected Disease Research) | ✓ | ✓ | ✓ | ✓ |
| TBI-166[5] | 1 | Riminophenazine (Clofazimine-analogue) | Oral (Institute of Materia Medica, TB Alliance, Chinese Academy of Medical Sciences & Peking Union Medical College) | – | – | – | – |
| TBI-223 | 1 | Oxazolidinone | Oral (TB Alliance/Institute of Materia Medica) | – | – | – | – |
| BTZ-043 | 1 | DprE1 inhibitor | Oral (University of Munich, Hans-Knöll Institute, Jena, German Center for Infection Research) | ✓ | ✓ | ✓ | ✓ |
| S 004992 | 1 | Nitroimidazole ? | Oral (Shionogi) | ? | ? | ? | ? |
| WX-081 | 1 | ATP synthase complex inhibitor | Oral (Shanghai Jiadan Pharmaceutical Technology) | ? | ? | ? | ? |
| YF-49-92MLS | 1 | Nitroimidazol | Oral (C & O Pharmaceutical) | ? | – | – | ? |

These agents are being developed for use against TB; their activity against other priority pathogens was not assessed.

**Innovation assessment:** ✓ criterion fulfilled; **?** Inconclusive data; – criterion not fulfilled

NCR, no cross resistance to other antibiotic classes; CC, new chemical class; T, new target; MoA, new mode of action; DprE1, decaprenylphosphoryl-β-D-ribose 2-epimerase

[1] Pretonamid, approved on August 14, 2019 in combination with bedaquiline and linezolid
[2] Delpazolid also completed a phase-1 trial as injectable for MRSA and vancomycin-resistant *Enterococcus* spp. infections
[3] Developed by Sequella and independently by the Global Alliance for TB Drug Development, non-exclusive patent held by Sequella and by The Medicines Patent Pool
[4] In Russia developed by Nearmedic Plus
[5] Clofazimine is approved for leprosy and used for TB

Table 5. Antibiotics (small molecules) for the treatment of *C. difficile* infections in clinical development

| Name (synonym) | Phase | Antibiotic class | Route of administration (developer) | Innovation | | | |
|---|---|---|---|---|---|---|---|
| | | | | NCR | CC | T | MoA |
| Ridinilazole | 3 | *Bis*-benzimidazole | Oral, not absorbed (Summit) | ✓ | ✓ | ✓ | ✓ |
| OPS-2071 | 2 | Quinolone | Oral (Otsuka) | – | – | – | – |
| DNV-3837 (MCB-3837) | 1 | Oxazolidinone-quinolone hybrid | iv (Deinove) | – | – | – | – |
| MGB-BP-3 | 1 | DNA minor groove binder (distamycin) | Oral, not absorbed (MGB Biopharma) | ✓ | ✓ | ✓ | ✓ |
| ACX-362E | 1 | DNA polymerase IIIC inhibitor | Oral, not absorbed (Acurx Pharmaceuticals) | ✓ | ✓ | ✓ | ✓ |
| Ramizol | 1? | targets MscL | Oral, not absorbed (Boulos&Cooper) | ✓ | ✓ | ✓ | ✓ |

**Innovation assessment:** ✓ criterion fulfilled; **?** Inconclusive data or no agreement by the advisory group; – criterion not fulfilled

**Abbreviations:** NCR, no cross-resistance to other antibiotic classes; CC, new chemical class; T, new target; MoA, new mode of action. These agents are being developed for *C. difficile* infections; their activity against PPL pathogens was not assessed.