

|                         |                   | Novelty                         |  |   |   |   | Development Stage   |                   |                   |                      |         |                                    |                         |                              |                                   |  |  |
|-------------------------|-------------------|---------------------------------|--|---|---|---|---|-------------------|-------------------|----------------------|---------|------------------------------------|-------------------------|------------------------------|-----------------------------------|--|--|
| AMR Accelerator Project | Asset Owner       | Programme                       | New Class  | New MoA   | Mode of Action (MoA)  | Description   | Discovery   | (Pre)-Hit to Lead | Lead to Candidate | Candidate to Phase I | Phase I | Phase 2a - alone or in combination | Phase 2b - Dose ranging | Phase 2b - Regimen selection | Phase 2c - Duration randomization |  |  |
| ERA4TB<br>€208 m        | GSK               | Gepotidacin tissue distribution | ✓  | ✓   | Topoisomerase type II inhibitor   | Demonstrating penetration of gepotidacin in tonsillar and prostate tissues.   |   |                   |                   |                      |         | ➡                                  |                         |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-01  | ✓   | ✓   | Cholesterol catabolism.   | Molecule targeting mycobacterial cholesterol cycle.   |                   |                   |                      |         | ➡                                  |                         | *                            |                                   |  |  |
|                         |                   |                                 | ERA4TB-02  | ✓   | ✓   | <i>Mycobacterium tuberculosis</i> tryptophan synthase   | Compound targeting <i>Mycobacterium tuberculosis</i> tryptophan synthase, enzyme that catalyses the final two steps in the biosynthesis of tryptophan.        |                   |                   | ➡                    |         |                                    |                         |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-03  |   |   | Electron chain transport.   | Compounds targeting energy metabolism.  |                   |                   |                      |         |                                    | ➡                       |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-04  | ✓   | ✓   | Lysine transfer RNA synthase  | Compound targeting lysine transfer RNA synthase (Rv3598c), which is an essential gene as assessed by transposon mutagenesis.                                  |                   |                   | ➡                    |         |                                    |                         |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-06  | ✓   | ✓   | Mycobacterial membrane protein Large 3 (MmpL3)  | Potent in vitro inhibitory and bactericidal activity against <i>Mycobacterium tuberculosis</i> .  |                   |                   | ➡                    |         |                                    |                         |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-09  | ✓   | ✓   | Unknown.  | Natural product analogs active against <i>Mycobacterium tuberculosis</i> .  |                   |                   | ➡                    |         |                                    |                         |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-10  | ✓   | ✓   | Targets and covalently inhibits the enzyme Decaprenyl-phosphoryl-ribose 2'-epimerase (DprE1).   | Derivative of piperazinobenzothiazinone that acts as an anti-mycobacterial compound.  |                   |                   |                      |         |                                    | ➡                       |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-11  | ✓   | ✓   | Inhibits leucyl tRNA synthetase (LeuRS)   | Small molecule oxaborole.   |                   |                   |                      |         |                                    | ➡                       |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-13  | ✓   | ✓   | Cholesterol catabolism.   | Targets cholesterol cycle in <i>Mycobacterium tuberculosis</i> .  |                   |                   |                      |         |                                    | ➡                       |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-14  | ✓   | ✓   | Inhibits the mycobacterial cytochrome bc1 complex in the cellular respiration pathway.  | Small molecule compound that leads to the depletion of ATP in three mycobacterial species, <i>M. tuberculosis</i> , <i>M. leprae</i> , and <i>M. ulcerans</i> |                   |                   |                      |         |                                    | ➡                       |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-15  | ✓   | ✓   | Covalently inhibits the acyl transferase domain of Mtb Pks13, a polyketide synthase involved in mycolic acid biosynthesis via a novel mode of inhibition.   | A novel class of small-molecule antibiotics shown to inhibit new targets within the <i>M. tuberculosis</i> mycolic acid biosynthesis pathway.                 |                   |                   | ➡                    |         |                                    |                         |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-16  | ✓   | ✓   | Covalently inhibits the acyl transferase domain of Mtb Pks13, a polyketide synthase involved in mycolic acid biosynthesis via a novel mode of inhibition.   | A novel class of small-molecule antibiotics shown to inhibit new targets within the <i>M. tuberculosis</i> mycolic acid biosynthesis pathway.                 |                   |                   | ➡                    |         |                                    |                         |                              |                                   |  |  |
|                         |                   |                                 | ERA4TB-17  | ✓   | ✓   | Inhibits FadD32, a key enzyme at the interface between the fatty acid synthase and polyketide synthase biosynthetic pathways and is involved in mycolic acid biosynthesis.  | A novel class of small-molecule antibiotics that targets several Mtb biosynthesis pathways.   |                   |                   | ➡                    |         |                                    |                         |                              |                                   |  |  |
| ERA4TB-18               | ✓                 | ✓                               | Inhibits FadD32, a key enzyme at the interface between the fatty acid synthase and polyketide synthase biosynthetic pathways and is involved in mycolic acid biosynthesis. | A novel class of small-molecule antibiotics that targets several Mtb biosynthesis pathways. |   |   | ➡   |                   |                   |                      |         |                                    |                         |                              |                                   |  |  |
| GNA NOW<br>€21.6 m      | GSK               | Gepotidacin                     | ✓  | ✓   | Topoisomerase type II inhibitor   | Gepotidacin is a first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a novel mechanism of action and binding site by inhibition of two different Type II topoisomerase enzymes. Thanks to positive PhIII results for other indications (uUTI & gonorrhoea) is investigated by GNA NOW for its suitability to treat severe enteric infections in low- and middle income countries. |   |                   |                   |                      | ➡       |                                    |                         |                              |                                   |  |  |
| RespiriTB<br>€9 m       | JANSSEN           | BC1 back up                     | ✓  | ✓   | Cytochrome bc1 complex in the cellular respiration pathway.   | Lead optimisation program on BC1 inhibitors.  |   |                   | ➡                 |                      |         |                                    |                         |                              |                                   |  |  |
|                         |                   |                                 | MenG   | ✓   | ✓   | Inhibits menG, a product of which catalyses methylation of demethylmenaquinone.   | "H2L medChem for novel menaquinone biosynthesis inhibitors."  |                   | ➡                 |                      |         |                                    |                         |                              |                                   |  |  |
|                         |                   |                                 | BDQ LAI  | ✓   |   | ATPase.   | Novel long-acting injectable formulation of bedaquiline for Tb preventive therapy.  |                   |                   |                      |         | ➡                                  |                         |                              |                                   |  |  |
|                         |                   |                                 | PASA   | ✓   |   | Dihydrofolate reductase (DHFR).   | Novel para-Aminosalicylic acid (PAS) analogues.   |                   | ➡                 |                      |         |                                    |                         |                              |                                   |  |  |
|                         |                   |                                 | HDT  | ✓   | ✓   | Various.  | Exploring known host-directed therapies for TB treatment.   | ➡                 |                   |                      |         |                                    |                         |                              |                                   |  |  |
|                         |                   |                                 | Mtr  | ✓   | ✓   | <i>Mycobacterium tuberculosis</i> transcription regulator (Mtr).  | Target exploration of <i>Mycobacterium tuberculosis</i> transcription regulator (Mtr) complex.  | ➡                 |                   |                      |         |                                    |                         |                              |                                   |  |  |
| RespiriNTM<br>€8 m      | TBA               |                                 |  |   | Unknown.  | Novel assets (one first-in-human start) that may synergise with bedaquiline and cytochrome bc1 drugs.   |   | ➡                 |                   |                      |         |                                    |                         |                              |                                   |  |  |
| TRIC-TB<br>€8.3 m       | BioVersys and GSK | Alpibectir                      | ✓  | ✓   | Bacterial transcriptional regulation.   | Boosts ethionamide efficacy and lowers the dose with small molecule transcriptional modulators to overcome multi-drug resistant tuberculosis infections.  |   |                   |                   |                      |         | ➡*                                 |                         |                              |                                   |  |  |
| UNITE4TB<br>€185 m      | GSK               | GSK656                          | ✓  | ✓   | Suppresses protein synthesis in <i>Mycobacterium tuberculosis</i> by inhibiting the enzyme leucyl t-RNA synthetase (LeuRS). | A first-in-class investigational antitubercular agent is being developed to treat tuberculosis as part of a future combination regimen.   |   |                   |                   |                      |         |                                    |                         |                              | ➡                                 |  |  |
|                         | Leibniz-HKI/ LMU  | BTZ-043                         | ✓  | ✓   | Inhibits an essential enzyme for cell wall synthesis in <i>Mycobacteria tuberculosis</i> .                                  | A first-in-class investigational antitubercular agent is being developed to treat tuberculosis as part of a future combination regimen.   |   |                   |                   |                      |         |                                    | ➡                       | ➡                            |                                   |  |  |

### Accelerating scientific discoveries in the antimicrobial resistance (AMR) field

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|-------------------|---|
| COMBINE<br>€25 m  | Providing learnings derived from shared vaccine and/or antibacterial clinical trial data, and improving understanding of variability and translatability of animal models of bacterial infection. |
| PrIMAVeRa<br>€9 m | Developing a decision-making tool accessing health and economic outcomes of vaccines on the reduction of AMR.   |

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