BioVersys AG
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BioVersys: saving lives in resistant times

The Swiss pharmaceutical company BioVersys is developing next-generation antimicrobial drugs with unique modes of action targeting a range of multidrug-resistant bacteria.

Antimicrobial resistance (AMR) is predicted to cause 10 million deaths by 2050 and is widely recognized as the biggest threat to human health by the World Health Organization (WHO) and the G7 and G20 Group of Nations. A lack of effective antibiotics for harmful bacteria such as *Acinetobacter baumannii* and *Mycobacterium tuberculosis* has resulted in common infections becoming lethal. Moreover, the global antibiotic pipeline is dangerously thin, with only 43 in development in 2020 and only a fraction of them representing new drug classes or having novel mechanisms of action.

In prime position to tackle this global public health crisis is BioVersys AG, a privately owned clinical-stage, multi-asset Swiss pharmaceutical company that is researching and developing next-generation antimicrobial drugs for multidrug-resistant bacterial infections. The company has four distinct antibacterial programs in development, each with a new mode of action. Its pipeline is innovative, diverse, de-risked and focused on addressing the highest unmet medical needs of the WHO and US Centers for Disease Control and Prevention (CDC) priority pathogens.

BV100: carbapenem-resistant *A. baumannii* pneumonia

Mortality rates for pneumonia caused by carbapenem-resistant *A. baumannii* (CRAB)—a Gram-negative pathogen—are above 50%, and more than half of *A. baumannii* infections are resistant to carbapenems, with up to 95% of strains resistant in some countries.

BioVersys's lead product, BV100 (rifabutin for infusion), is in clinical development for infections caused by CRAB. Rifabutin is a rifamycin antibiotic, a group of antibiotics that were first isolated in the 1950s. They are still widely used to treat mycobacteria and Gram-positive infections, but uptake into Gram-negative bacteria is usually poor.

> **Investing in BioVersys is advancing the fight against AMR, improving patient outcomes and saving lives in fighting AMR using innovation**
>
> Marc Gitzinger, CEO & co-founder, BioVersys

"It turns out that rifabutin is different, and it was a minimal-media screen at the University of Southern California that unmasked its potent activity at really low doses against CRAB," explained Glenn Dale, Chief Development Officer.

"We licensed BV100 and elucidated that the exceptional activity is facilitated by an active uptake into CRAB that is mediated by hijacking its iron uptake system" (Fig. 1).

BioVersys then developed a proprietary intravenous formulation of rifabutin (BV100), suited for dosing of patients in intensive care and achieving higher and more predictable exposures. BV100 is currently in phase 1 trials and being prepared for a single phase 2/3 registration trial in ventilator-associated pneumonia and bloodstream infections caused by CRAB. The active pharmaceutical ingredient is already known to be a fast bactericidal agent, distributing well into lungs, and safe for adults and children treated for 6–18 months. The US Food and Drug Administration has granted Qualified Infectious Disease Product Designation for BV100, providing the possibility of fast-track approval and an extra 5 years of market exclusivity.

BVL-GSK098: multidrug-resistant tuberculosis

Tuberculosis (TB) is the world's largest infectious disease killer; approximately 10 million people were infected by TB in 2018, and 1.5 million were killed. The WHO estimates that there were 484,000 new cases with resistance to rifampicin, the most effective first-line drug, of which 78% had multidrug-resistant TB (MDR-TB). TB usually affects the lungs, but may also affect other parts of the body, including the brain. TB meningitis is another very important unmet medical need with high mortality rates and a devastating impact on patients, often children.

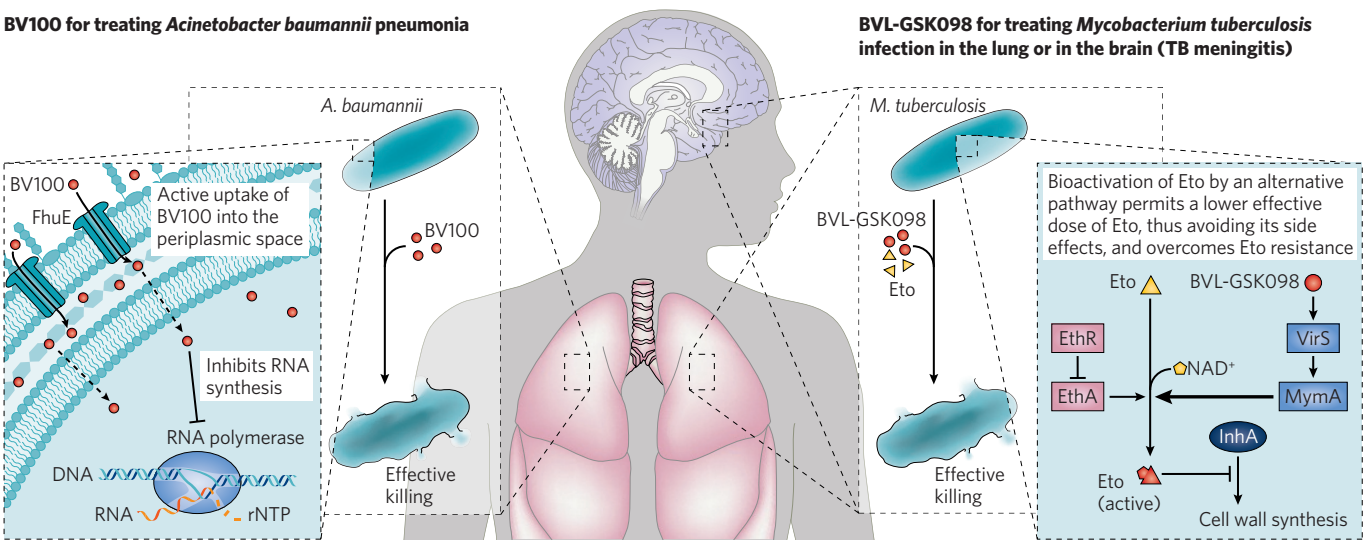

Fig. 1 | Modes of action of BV100 and BVL-GSK098. BV100 acts inside the lung to treat *Acinetobacter baumannii* pneumonia, whereas BVL-GSK098 acts in the lung and in the brain to treat *Mycobacterium tuberculosis*. Eto, ethionamide; TB, tuberculosis.

Some key TB antibiotics, including the second-line drug ethionamide/prothionamide (Eto/Pto), are prodrugs that are activated inside the mycobacterium. Expression of the enzyme (EthA) responsible for bioactivation of Eto/Pto is repressed by transcriptional regulation, and resistance also develops within this bioactivation pathway (Fig. 1). BioVersys specifically targets bacterial transcriptional regulation with its transcriptional regulator inhibitory compound (TRIC) platform.

> **BVL-GSK098 has a unique mode of action that essentially reverses existing resistance to Eto/Pto and potentiates its efficacy. This allows for lower, well-tolerated doses of Eto/Pto with similar or higher efficacy**
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> Glenn Dale, Chief Development Officer, BioVersys

Preclinical studies show that Eto in combination with BVL-GSK098 (a TRIC in clinical development) has a fast bactericidal activity by interfering with a transcriptional regulator in *M. tuberculosis*, triggering an alternative bioactivation pathway (MymA) for Eto/Pto (Fig. 1). In addition, because it also crosses the blood–brain barrier, BVL-GSK098 has the potential to treat both pulmonary TB and TB meningitis.

"BVL-GSK098 has a unique mode of action that essentially reverses existing resistance to Eto/Pto and potentiates its efficacy. This allows for lower, well-tolerated doses of Eto/Pto with similar or higher efficacy," explained Dale. "This is the first example of a small molecule targeting bacterial transcriptional regulators in human clinical trials, a ground-breaking approach with the potential to create a paradigm shift in treatment options for AMR."

Discovered and developed jointly by BioVersys, GSK and University of Lille, the clinical phase 1 program is funded by the EU Innovative Medicines Initiative. A phase 2a early bactericidal activity study is planned for 2022 with TASK, a clinical research institute and social enterprise in South Africa, and funded by the European and Developing Countries Clinical Trials Partnership.

BV200: disarming *Staphylococcus aureus*

Atopic dermatitis (AD) is a highly prevalent chronic inflammatory skin disease affecting 7–10% of the adult population and 25% of children aged <7 years. *Staphylococcus aureus* (*S. aureus*) commonly colonizes the lesions in patients with AD (60–100%), producing toxins that cause inflammatory flare ups and irreversible necrotic damage.

BV200, a small-molecule preclinical TRIC asset against *S. aureus*, inhibits the transcriptional regulator responsible for the expression of major *S. aureus* toxins and virulence factors without killing the bacteria (Fig. 2). "Topical BV200 has the potential to reduce or treat flares in patients with AD and helps to restore a healthy skin microbiome," explained Sergio Lociuro, CSO. "BV200 can also be used as an adjuvant in superficial skin infections or administered systemically with an antibiotic in skin and lung infections to speed up treatment and protect tissues from the toxin-induced necrotizing effects during *S. aureus* infections."

BV200 for treating *Staphylococcus aureus*-induced exacerbation/flares of atopic dermatitis and superficial skin infections

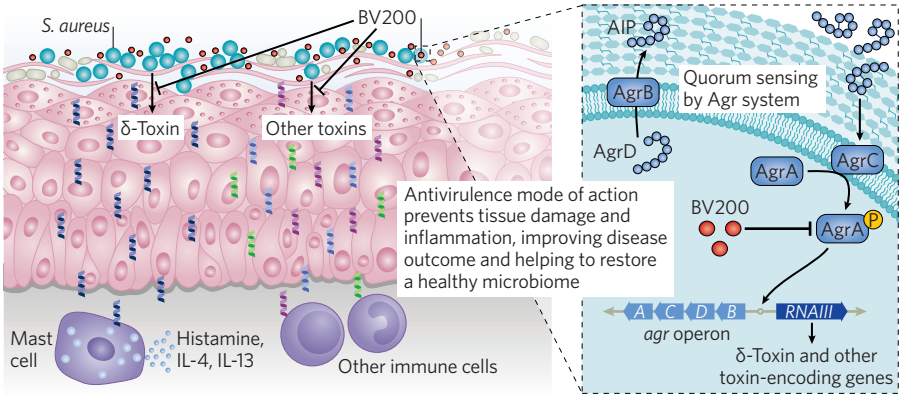

Fig. 2 | BV200 in action. BV200 acts upon the skin to treat *Staphylococcus aureus*-induced atopic dermatitis and skin infections, by blocking *Staphylococcus aureus*-toxin production.

BV200 is in preclinical candidate selection for toxicology studies in AD and in lead optimization for skin infections and pneumonia. The BV200 development for pneumonia and severe *S. aureus* infections is supported by Combating Antibiotic-Resistant Bacteria Accelerator (CARB-X) funding.

> **Our de-risked and diversified pipeline, a streamlined development and regulatory strategy, and the clear commercial positioning of our clinical assets make us the most compelling investment opportunity in the AMR space**
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BV300: a new class of broad-spectrum antibiotics

BV300 is a pyrrolocytosine, a novel class of broad-spectrum antibiotics acquired from Melinta Therapeutics and funded by CARB-X. BV300 targets a new and unexploited binding site of the bacterial ribosome and has demonstrated in vitro and in vivo activity against multidrug-resistant Gram-positive and Gram-negative bacteria. These include *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species—the so-called ESKAPE pathogens, the leading cause of drug-resistant nosocomial infections.

"Novel classes of broad-spectrum antibiotics with demonstrated in vitro and in vivo activity against all ESKAPE clinical isolates are like rare gems," said Lociuro. "If successfully developed, this will be the first new class of truly broad-spectrum antibiotics in decades."

BioVersys has focused its lead optimization campaign for this highly promising compound class on pneumonia caused by extremely difficult-to-treat drug-resistant Gram-negative pathogens that are on the WHO and CDC priority list.

Partnering for progress

With a diverse portfolio of innovative, first-in-class and best-in-class assets designed to address the highest unmet medical needs of priority pathogens, BioVersys is well on its way to a leadership position in AMR. BioVersys also has a world-leading team of experts with extensive scientific and clinical experience in AMR, mixed with entrepreneurial thinking and a strong business sense.

Collaborations are an essential part of its operational philosophy, and BioVersys works with some of the world's leading academic, industry and funding institutions to progress its pipeline. In addition, the company is looking for licensing and late-stage partners to co-develop and commercialize its pipeline products. "Our de-risked and diversified pipeline, a streamlined development and regulatory strategy, and the clear commercial positioning of our clinical assets make us the most compelling investment opportunity in the AMR space," said CEO and co-founder Marc Gitzinger. "Investing in BioVersys is advancing the fight against AMR, improving patient outcomes and saving lives in fighting AMR using innovation, saving lives and improving patient outcomes."

CONTACT
Marc Gitzinger, CEO
BioVersys AG
Basel, Switzerland
Tel: +41 61 633 22 50
Email: marc.gitzinger@bioversys.com