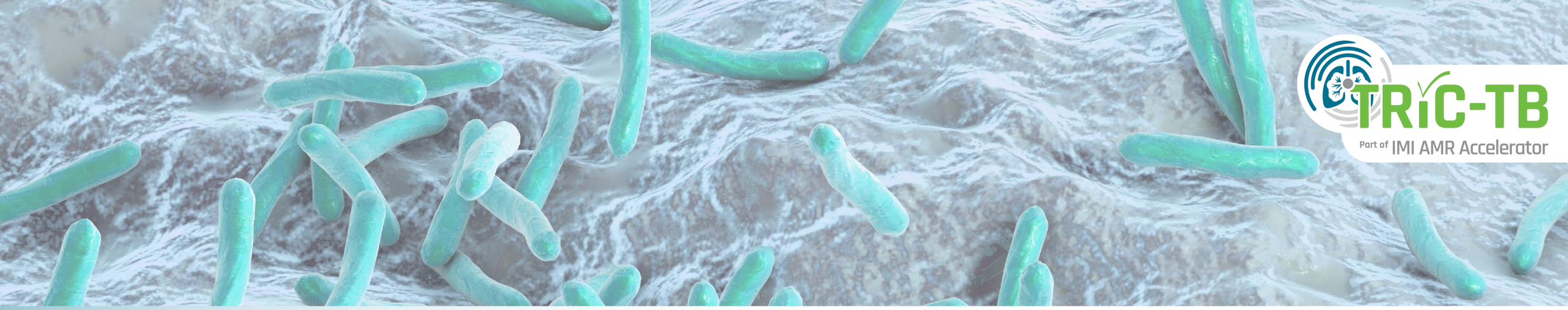


Reviving ethionamide. TRICky but possible

4th AMR Conference 2020

EU Project number 853800

Introduction: Tuberculosis is a global health burden

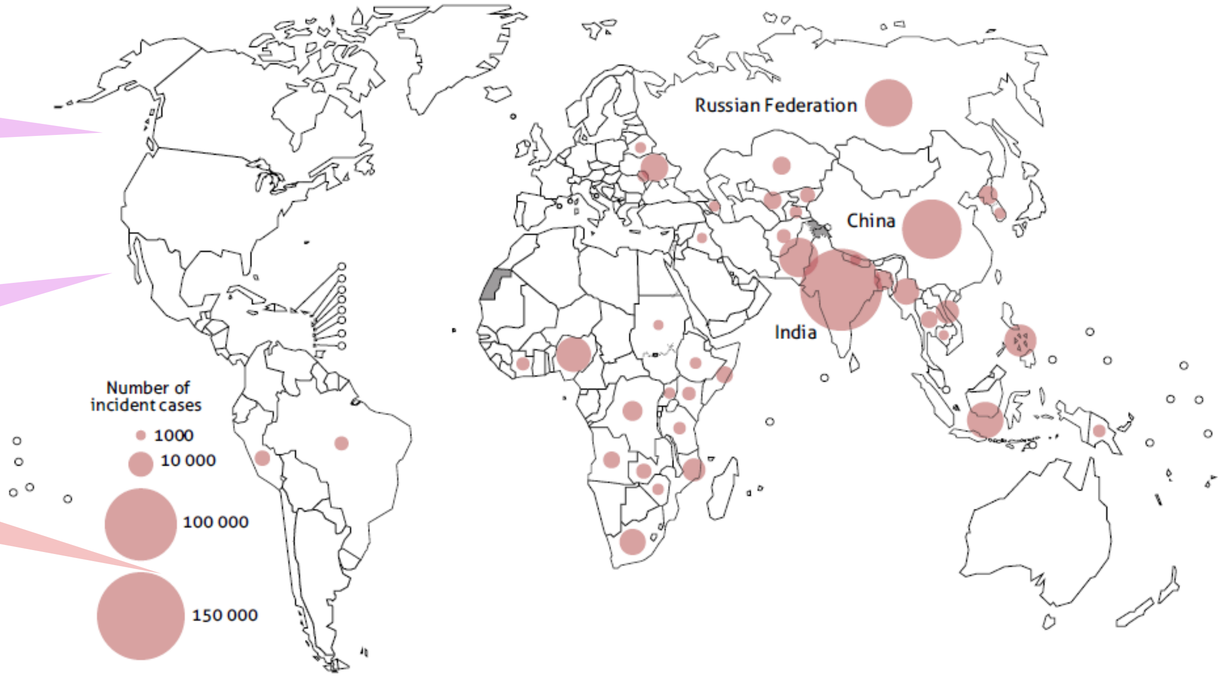
10.0 million
people in the world **developed** TB

1.5 million
people in the world **died from** TB

500 000 people developed MDR-TB

World Health Organization **WHO Global TB Report 2019**

Estimated incidence of MDR/RR-TB[a] in 2018, for countries with at least 1000 incident cases



[a] MDR-TB is a subset of RR-TB.

In 2014, TB surpassed HIV as the 1st infectious disease killer worldwide

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MDR/XDR-TB: Current treatments are long, inefficient and toxic

Disease	DS-TB	MDR-TB	XDR-TB
Drug	4 (INH, RIF, PZA, EMB)	≥5	≥5
Length (Months)	6	9-12	>24
Cure (%)	83	54	28

Main goals for novel TB drugs:

- **Overcome drug resistance**
- **Shorten treatment time**
- **Safer drug profile**

	MDR treatment*	Possible adverse effects
A	levofloxacin OR moxifloxacin bedaquiline linezolid	Well tolerated QT prolongation Peripheral neuropathy
B	clofazimine cycloserine OR terizidone	Skin discoloration CNS toxicity
C	**ethionamide OR prothionamide** ethambutol delamanid pyrazinamide amikacin *p*-aminosalicyclic acid	Nausea/vomiting Liver toxicity Kidney toxicity

* WHO guidelines 2019: MDR treatment

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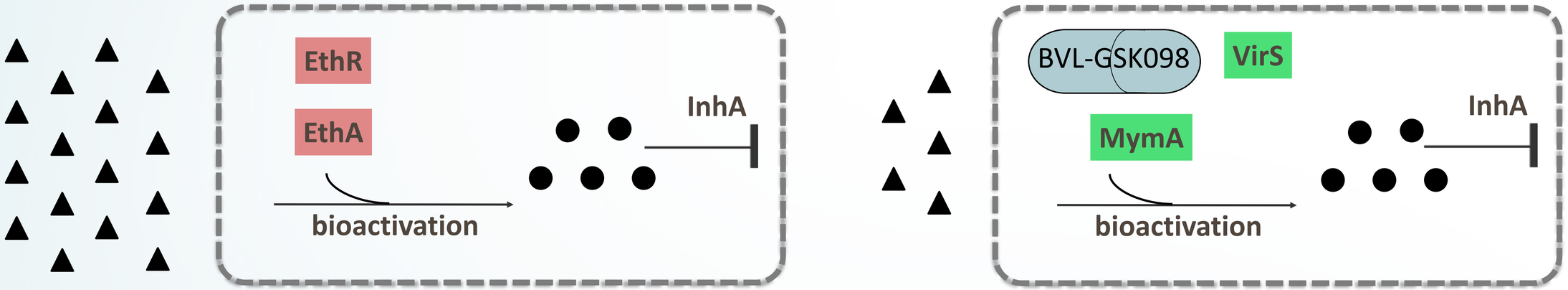
Background ethionamide (Eto) and prothionamide (Pto)



- Eto/Pto are pro-drugs ▲ that are converted inside *M. tb.* into the active form ● inhibiting InhA
- Bioactivation occurs through the enzyme EthA which is controlled by the transcriptional regulator EthR

- Due to limited bioactivation, high dosing of Eto/Pto is required causing GI disorders
- Resistance to Eto in clinical strains is observed in the bioactivation pathway (EthA mutations)

- BVL-GSK098 acts potently on VirS rendering MymA-mediated bioactivation of Eto/Pto complete
- BVL-GSK098 maintains the amount of the active form ● at lower doses of Eto/Pto ▲
- BVL-GSK098 overcomes Eto/Pto resistance

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BVL-GSK098 overcomes MDR-TB and Eto resistant isolates

MDR Clinical Strain ID	INH	RIF	MIC Eto (mg/L)	MIC Eto (mg/L) + BVL-GSK098 (0.02 mg/L)
B1602	R	R	256	≤0.8
B1304	R	R	32	≤0.8
B1196	R	R	32	≤0.8
07MY0066	R	R	>5	≤0.8
07MY1001	R	R	32	≤0.8
07MY1166	R	R	64	≤0.8
07MY1281	R	R	16	≤0.8
08MY0089	R	R	8	≤0.8
08MY0559	R	R	>4	≤0.8
08MY1099	R	R	16	≤0.8
09MY0467	R	R	64	≤0.8
09MY1304	R	R	32	≤0.8
10MY0992	R	R	>4	≤0.8
12MY1124	R	R	>4	≤0.8
L1094	R	R	2	≤0.8
H37Rv	S	S	2	≤0.8

Eto: Ethionamide: **INH**: Isoniazide: **RIF**: Rifampicin: **MIC:** Minimal inhibitory concentration: **MDR:** Multi-Drug Resistant: **R**: Resistant: **S**: Susceptible

- BVL-GSK098 overcomes Eto resistance and lowers Eto effective concentration on WT and MDR strains.
- MIC data based on 40 MDR/XDR clinical strains with bias towards Eto and INH resistance representing TB global lineages.
- MoA confirmed on > 100 strains.

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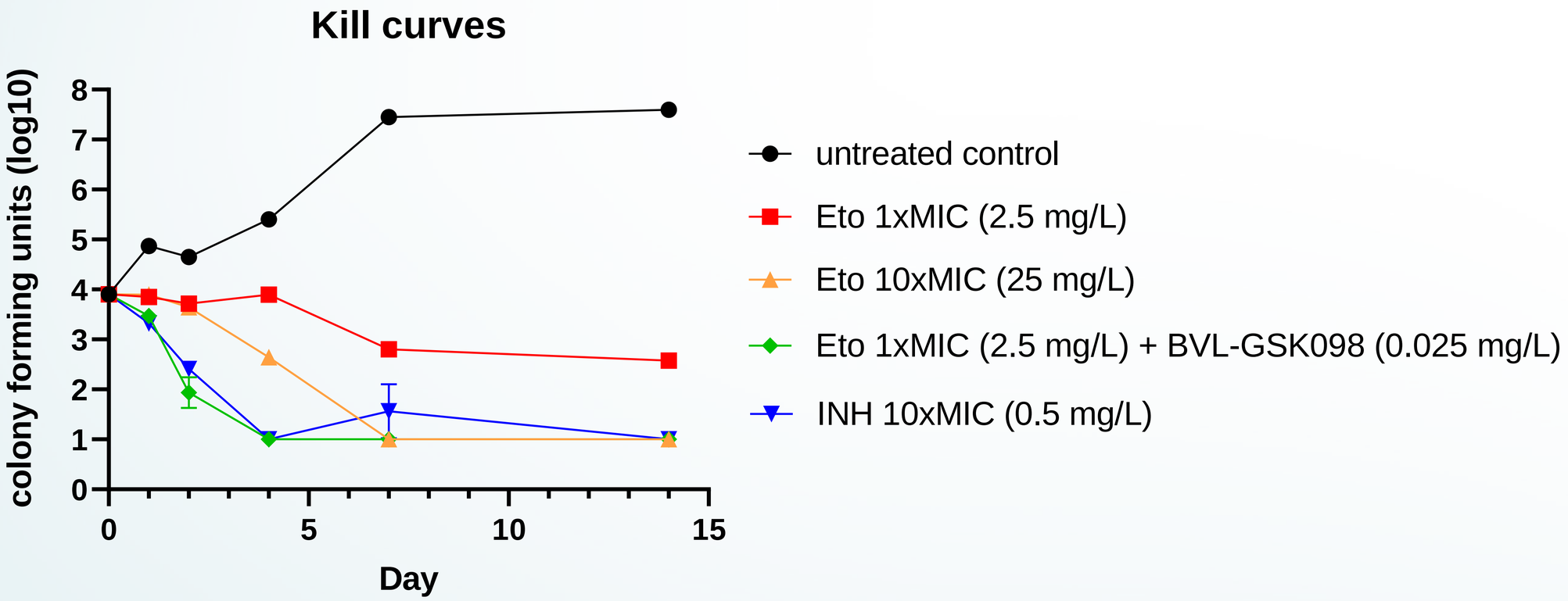
BVL-GSK098 renders Eto as rapidly bactericidal as INH



BVL-GSK098 renders Eto at 1x MIC as rapidly bactericidal as INH at 10x MIC

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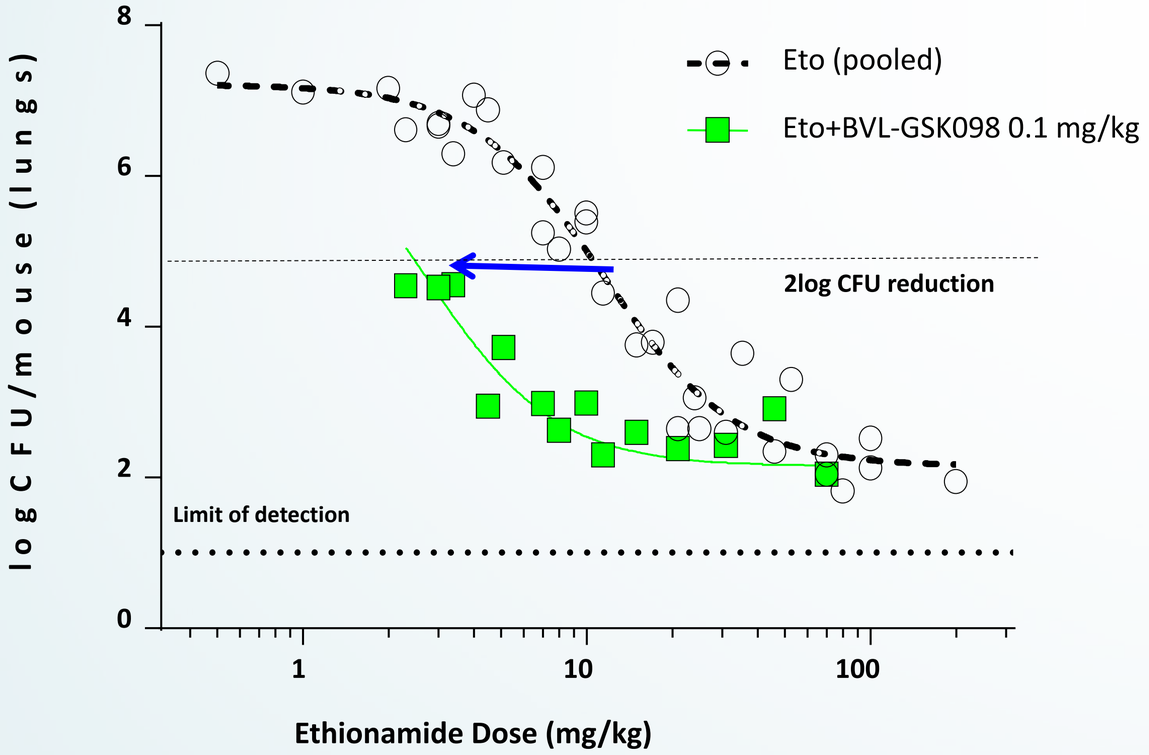
Potent *in vitro* activity translates into *in vivo* efficacy



Fast acute model of *M. tb* infection in C57BL/6 mice

- Infection IT with 10^5 CFU/mouse;
- Oral treatment for 8 consecutive days (once daily)

- ED_{99} is the dose of Eto resulting in a 2log reduction (dashed line) in lung CFUs compared to untreated control.
- In this model, BVL-GSK098 at 0.1 mg/kg boosts Eto efficacy based on the dose or on the AUC at least 3-fold

BVL-GSK098 boosts Eto efficacy *in vivo* by >3-fold, enabling full efficacy at lower Eto exposures

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BVL-GSK098 deploys the full potential to revive Eto/Pto

- ✓ Eto/Pto would be excellent drugs if their full action could be exploited at better tolerated human doses
- ✓ *In vitro* and *in vivo* data predict that the addition of BVL-GSK098 reduces the Eto efficacious dose, simultaneously optimizing its probability of target attainment and thus potentially lowering Eto dose-dependent side effects
- ✓ BVL-GSK098 overcomes Eto resistance in clinical strains (including MDR-TB) and makes Eto rapidly bactericidal at very low concentrations
- ✓ Addition of BVL-GSK098 to Eto/Pto regimens has the potential to play the role of INH in DS regimens in MDR/XDR regimens
- ✓ No cross resistance with current and development TB drugs
- ✓ Low risk of DDI: no inhibition/activation of CYP450s
- ✓ Simple synthetic route for API

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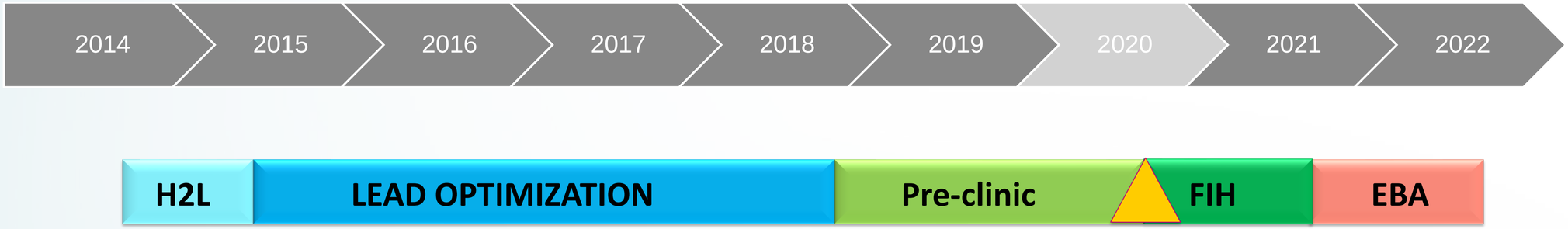
BVL-GSK098 development: next steps



- GMP-compliant manufacturing of capsules **completed**
- Pre-clinical safety evaluation in rodent and non-rodent species **completed**
- **CTA submitted and under evaluation**

Milestone: BVL-GSK098 ready for First in Human (FIH) studies in H2 2020

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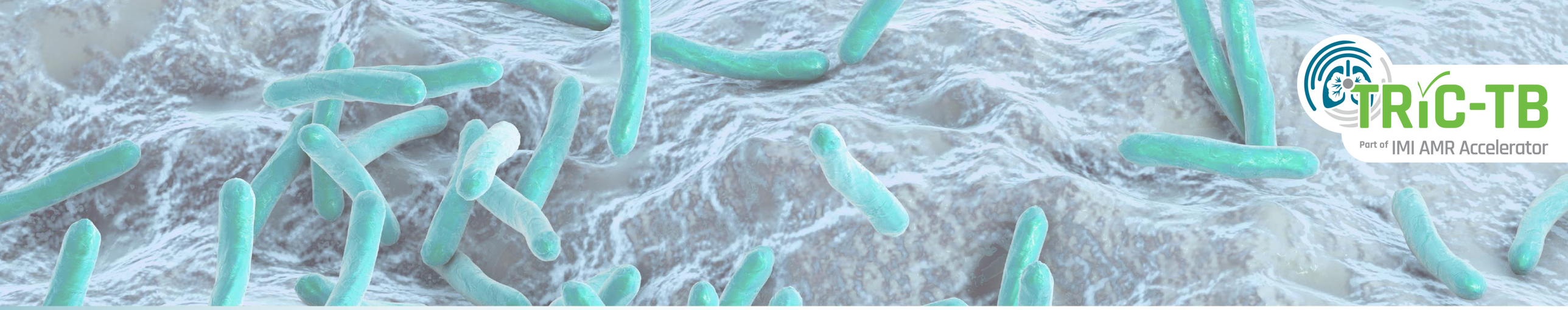

Thank you.

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