Development of the natural product Corallopyronin A to treat filarial nematode infections and antibiotic-resistant staphylococci infections

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Corallopyronin A (CorA) inhibits bacterial RNAP, including rifampicin-resistant bacteria. Funded by the DZIF, EU Horizon 2020 and GHIT Fund, we are developing CorA to treat infections with filarial nematodes and antibiotic-resistant staphylococci.

Filarial nematodes affecting >72 Mio. people cause onchocerciasis (river blindness) and lymphatic filariasis (elephantiasis). Depleting their essential *Wolbachia* endosymbionts causes worm sterility, blocked development, and worm death. In the *Litomosoides sigmodontis* infection model, a 2-week regimen depleted *Wolbachia* >2-logs and was adulticidal. CorA was also adulticidal in an onchocerciasis mouse infection model (*Onchocerca ochengi*).

Non-GLP *in vitro* toxicity tests demonstrated CorA is nontoxic and safe. Seven-day repeated dose studies demonstrated no prohibitive *in vivo* safety issues: dog NOEL=150 mg/kg; rat LOAEL=250 mg/kg; predicted HED=4 mg/kg.

CorA was effective in three different *in vivo* murine *S. aureus* infection models: lung, thigh and foreign body. CorA was detected in several tissues using LC-MS/MS with particularly high levels in bone.

For 103 strains, CorA had an MIC_{90} of 0.5 mg/L (*S. aureus*) to 1 mg/L (coagulase negative strains). Crystal violet and MBEC biofilm assays showed that CorA efficiently inhibits (0.06-4 µg/ml) and eradicates (0.125-2 µg/ml) biofilms (equal to- or better than dalbavancin and rifampicin, respectively).

The fermentation and purification processes were upscaled to industrial-scale, producing CorA API with >90% purity (impurities are CorA isoforms, <1% each). These processes were established at the GMP-certified CMO Phyton Biotech, Germany.

We developed solid oral formulations with increased stability (>3 months at 30 °C, >6 months at 5 °C) and oral bioavailability (mouse >59%, rat >90%, dog >53%). Excipients increased CorA stability, with no loss after 4 weeks of stress testing (40 °C, 75% rh,

closed with desiccant, air environment). PBBM predicts a safety margin for the predicted HED that supports clinical trials. Administering the CorA QD, BID or TID showed that a consistent plasma concentration, either via trough concentration or time above threshold, improved efficacy.
With our partner Eisai Co., Ltd., we will complete pre-clinics for a phase I clinical trial in 2026, and plan to progress CorA through phase 2 and phase 3 trials against onchocerciasis to registration.

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