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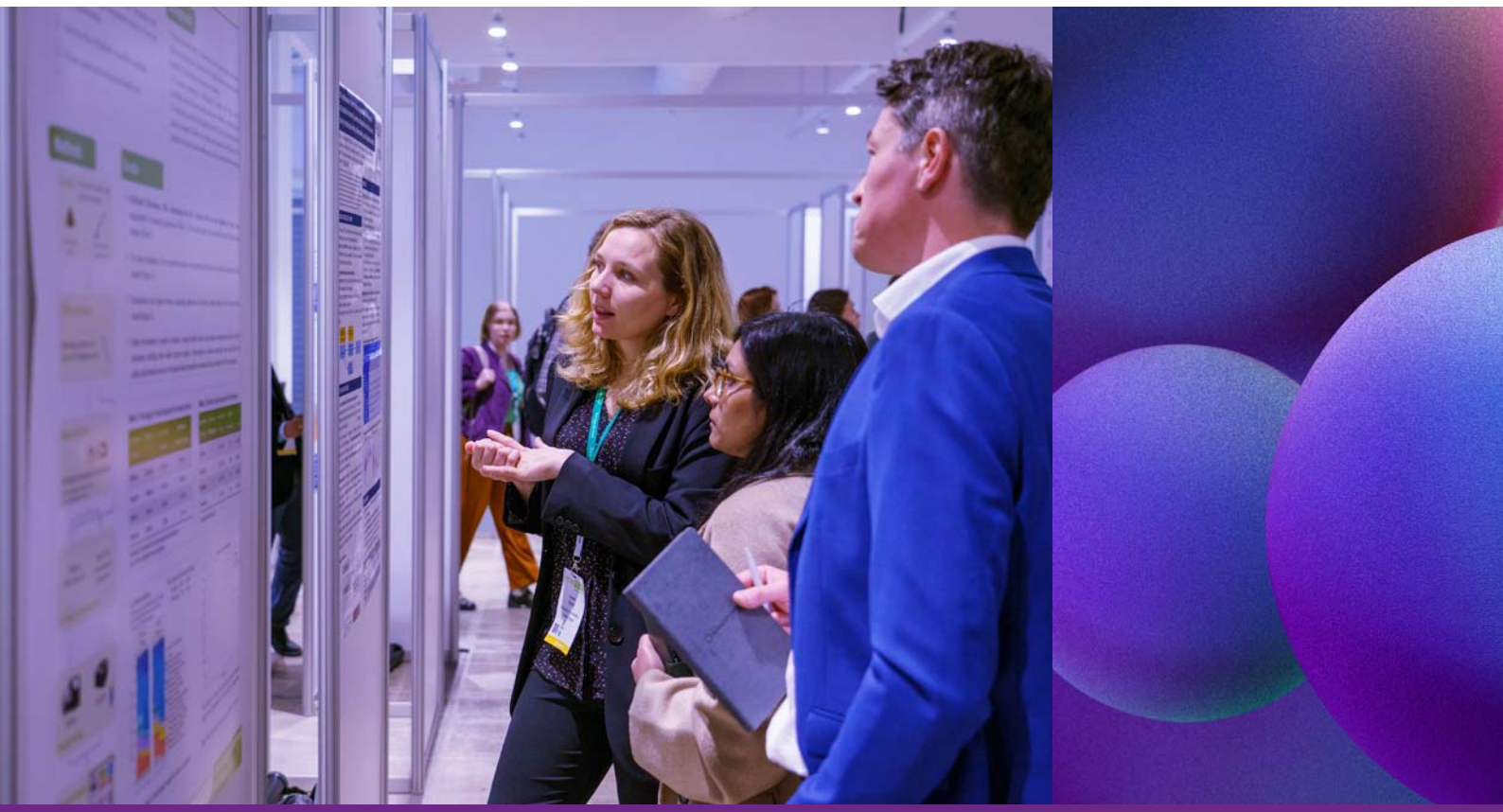

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Determination of the PK/PD driver for the LepB inhibitor, GDC-5780, a novel Gram-negative antibiotic against Enterobacteriaceae infections

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Background
GDC-5780 is a novel, small-molecule inhibitor of LepB, an essential type I signal peptidase encoded by gram-negative bacteria. GDC-5780 demonstrated high activity *in vitro* against the *Enterobacteriaceae* species, including multidrug resistant isolates, and bactericidal activity *in vivo* in multiple mouse infection models. Here, we describe the activity-exposure relationship determined by dose-fractionation studies (DFS) and dose-ranging studies (DRS) in the neutropenic mouse thigh infection model.

Methods
Neutropenic mice were intramuscularly infected with different *Enterobacteriaceae* isolates. For DFS, GDC-5780 was administered subcutaneously once, twice or four times in 24h at each dose level, starting 2h post infection. For DRS, a range of GDC-5780 doses were administered subcutaneously four times in 24h. For all studies, thigh muscle colony-forming units (CFUs) were determined at 26h post-infection. The PK/PD indices fCmax/MIC, fAUC/MIC, and %fT>MIC were calculated based on mouse PK and were correlated with CFU/thigh from DFS, and the PK/PD driver was determined through nonlinear least squares regression analyses. Furthermore, the magnitude of PK/PD driver (%fT>MIC) required to achieve stasis, 1-log kill, and 2-log kill for isolates tested in DRS was determined.

Results
GDC-5780 displayed dose-dependent antibacterial activity in the DFS with the two *Klebsiella pneumoniae* and one *Escherichia coli* isolate tested. Within the same total dose group, activity was dependent on the frequency of GDC-5780 administration and improved with greater frequency of administration. The most predictive PK/PD index was %fT>MIC. Efficacy was less well described by fAUC/MIC or fCmax/MIC as determined by the R2 values from the nonlinear fit analysis. The stasis and 1-log kill targets were narrowly distributed in DRS with ten *Enterobacteriaceae* isolates . The %fT>MIC required to achieve a 1-log kill ranged from 27% to 39% in *E. coli* and from 41% to 67% in *K. pneumoniae*.

Conclusions
GDC-5780 is active against multiple *Enterobacteriaceae* isolates in the neutropenic mouse thigh infection model. The *in vivo* PK/PD driver against *Enterobacteriaceae* is %fT>MIC. The mean value of %fT>MIC required to achieve a 1-log kill was 44% and the 90th percentile target was 56%, which will inform human dose selection.

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Hospital multiresistant strains of *Pseudomonas aeruginosa* sensitivity to newly synthesised compounds based on diindolylmethane

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Background
The growth of polyresistance of microorganisms is one of the problems of Ukraine. During the hostilities, the number of surgical interventions related to gunshot and shrapnel wounds increased, which were further complicated by the addition of hospital-acquired infection. *Pseudomonas aeruginosa* is classified by the World Health Organization as *a priori*ty pathogen responsible for the increasing level of multidrug-resistant bacteria. Therefore, the development of components of antibacterial drugs based on diindolylmethane is relevant and has practical significance

Methods
Identification of hospital *Pseudomonas aeruginosa* isolates done using MICRO-LA-TEST. The studied preparations are presented in the form of 0.5% solutions of 3,3′-diindolylmethane in: 1 – dimethyl sulfoxide, 2 - diethylene glycol monoethyl ether, 3 - N-methylpyrrolidone, 4 - propylene glycol. As a control used pure solvents.

Results
The test showed that the research components have a different antimicrobial effect on *Pseudomonas aeruginosa*, moreover, this effect depends on the period of use. The study of sample 1 showed that the lysis zone of *Pseudomonas aeruginosa* - 17±0.02 mm, increased by 2 mm in a compared to control. After a week and a month later, all strains became resistant. The study of sample 2 established high antimicrobial activity. The effect was stable even after 72 hours, after a week and a month did not differ from the initial one. Analyzing of sample 3, found the lysis zone of *Pseudomonas aeruginosa* was the largest and increased by 2 mm next 48 hours and by 1 mm - after 72. The study of sample 3 after a week and a month showed the same level of antimicrobial activity. The lysis zone of *Pseudomonas aeruginosa* of sample 4 reached 19 mm and became larger next days. However, over time, the effectiveness of the solution decreased and sample retained only bacteriostatic properties after a month.

Conclusions
Tested solvents containing 3,3′-diindolylmethane caused different antimicrobial activity against hospital multiresistant strains of *Pseudomonas aeruginosa*, 2, 3 and 4 samples have antiseptic properties, enhance and prolong the effect. These results prove the expediency of further testing solutions on bacterial biofilms.

References
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