Murepavadin (POL7080)

A Pathogen-Specific, Novel Antibiotic for the Treatment of Infections due to *P. aeruginosa* in Patients with Nosocomial Pneumonia

FDA Public Workshop - Washington, March 1, 2017

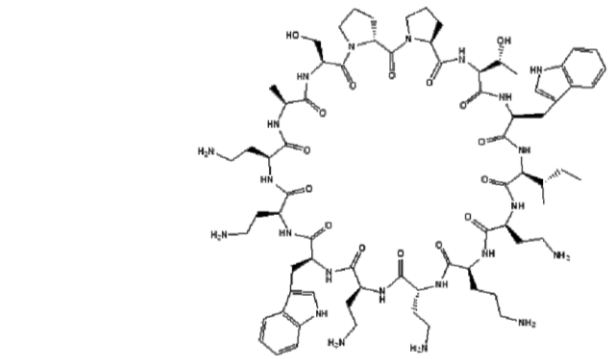
Andreas Wallnöfer
Acting Head, Polyphor Clinical Development

Disclosure Statement – Andreas Wallnöfer

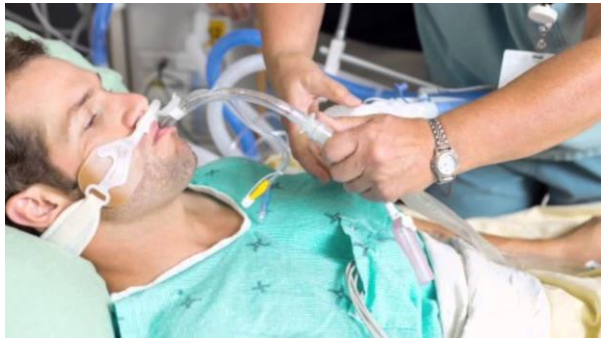
- **Partner at BioMed Partners, Basel, Switzerland.**
- **Founder of Wallnöfer Life Sciences Consulting Ltd.**
- **Consults Polyphor Ltd, Allschwil, Switzerland and acts *ad interim* as Head of Clinical Development.**
- **Previous Head of Clinical Research & Exploratory Development at F. Hoffmann La Roche, Basel, Switzerland.**

Murepavadin – A Member of a Novel Chemical Class of Outer Membrane Protein Targeting Antibiotic

- **Highly effective and pathogen specific**
  - Highly potent against clinical isolates of *P.aeruginosa* including MDR organisms
  - Bactericidal, activity not affected by lung surfactant
  - Favorable low liability resistance profile
  - No risk of resistance development of other pathogens such as *Clostridium difficile*
  - Highly active in murine lung infection models
- **High tissue distribution in the lung**
  - ELF concentration = free plasma concentration
- **Cyclopeptide**
  - Metabolized and excreted primarily in the kidney
  - Linear kinetics with $t_{1/2}$ of 6-8h
- **Acceptable safety profile**



indicates L-configuration at the chiral C atom
indicates D-configuration at the chiral C atom



Murepavadin has the potential to address an important unmet medical need in patients with nosocomial pneumonia due to P. aeruginosa

POLYPHOR Innovation in Drug Discovery

Murepavadin targets Selectively and Potently *Pseudomonas*

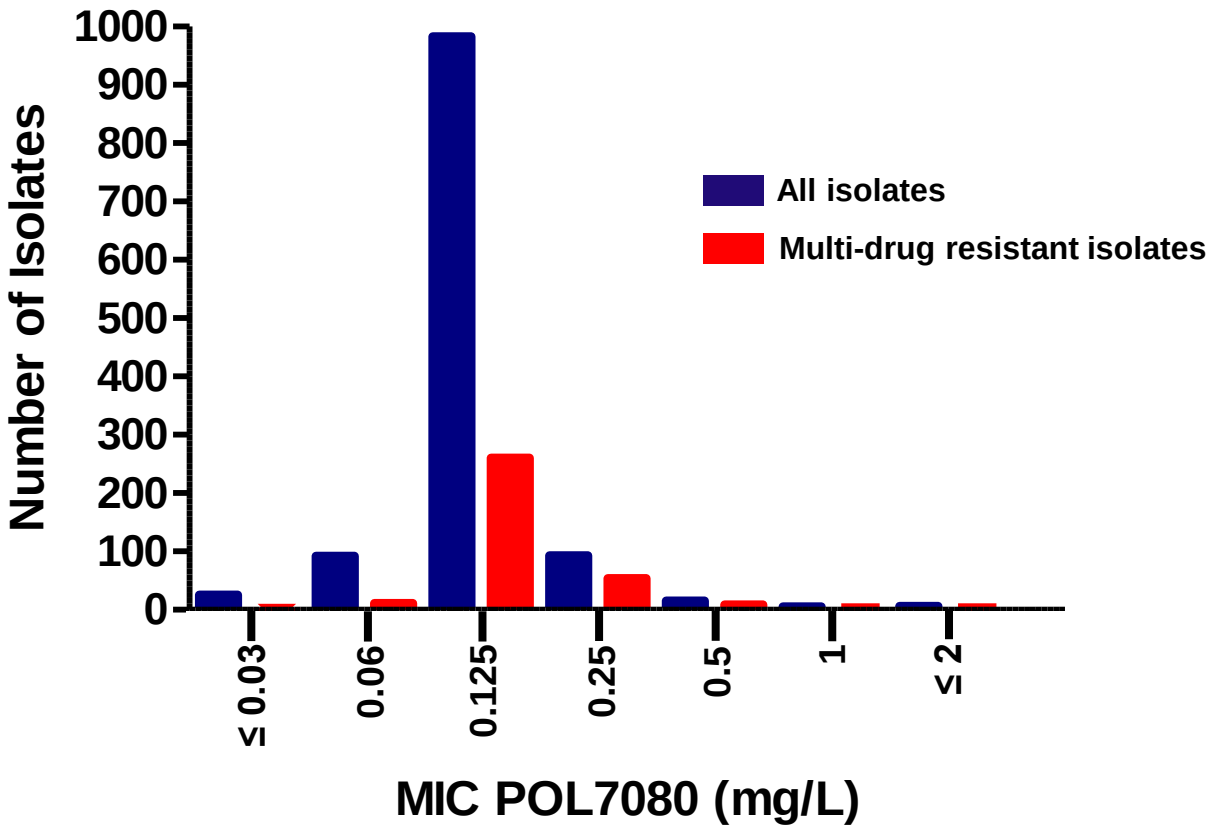
Potent *in vitro* activity against *Pseudomonas aeruginosa* strains

Type Strain	ATCC/DSM	MIC (µg/mL)
Pseudomonas aeruginosa	ATCC 27853	0.06
Pseudomonas aeruginosa	PAO1	0.25
Pseudomonas putida	DSM 291	0.06
Pseudomonas fluorescens	DSM 6147	0.06
Pseudomonas aureofaciens	ATCC 15926	0.06
Pseudomonas syringae	ATCC 12271	0.008
Escherichia coli	ATCC 25922	>64
Klebsiella pneumoniae	ATCC 13883	>64
Acinetobacter baumannii	ATCC 19606	>64
Burkholderia cepacia	ATCC 25416	>64
Stenotrophomonas maltophilia	ATCC 13637	>64
Staphylococcus aureus	ATCC 29213	>64

Murepavadin is a pathogen-specific antibiotic

Murepavadin MIC Data (1219 isolates; 28% MDR)

Distribution of POL7080 MICs by region and MDR

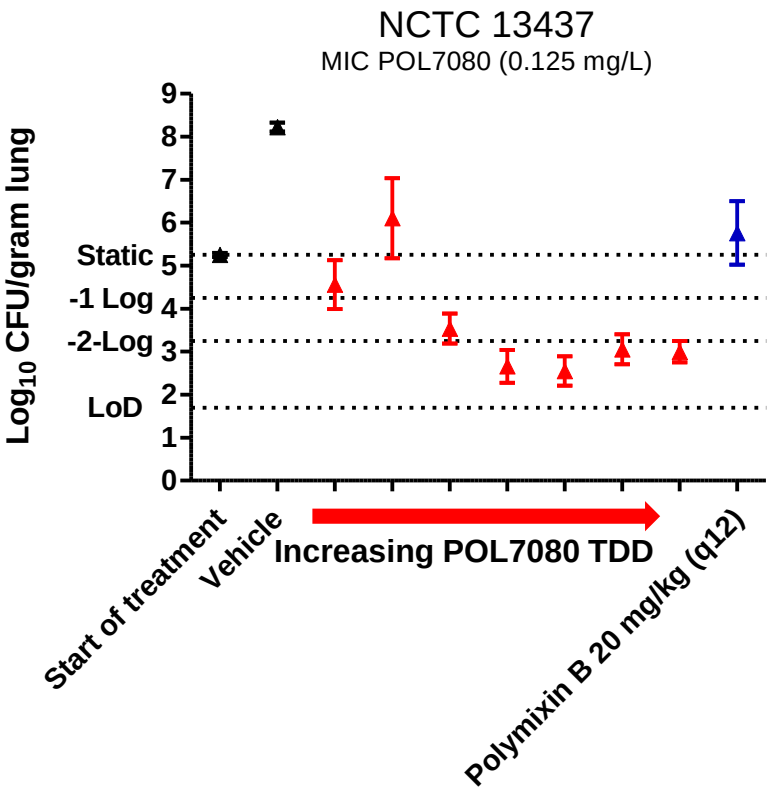


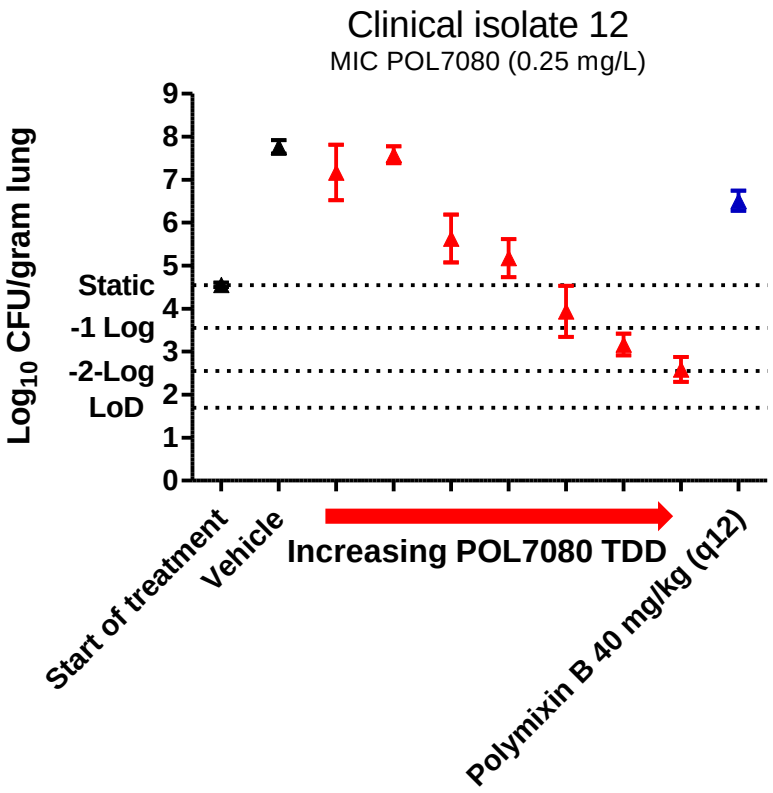
There is little difference between geographies or MDR and non-MDR MIC distributions

POLYPHOR Innovation in Drug Discovery

Murepavadin is active against XDR Isolates

Neutropenic mouse lung infection model





Murepavadin is effective against XDR* isolates whereas Polymyxin B shows little activity

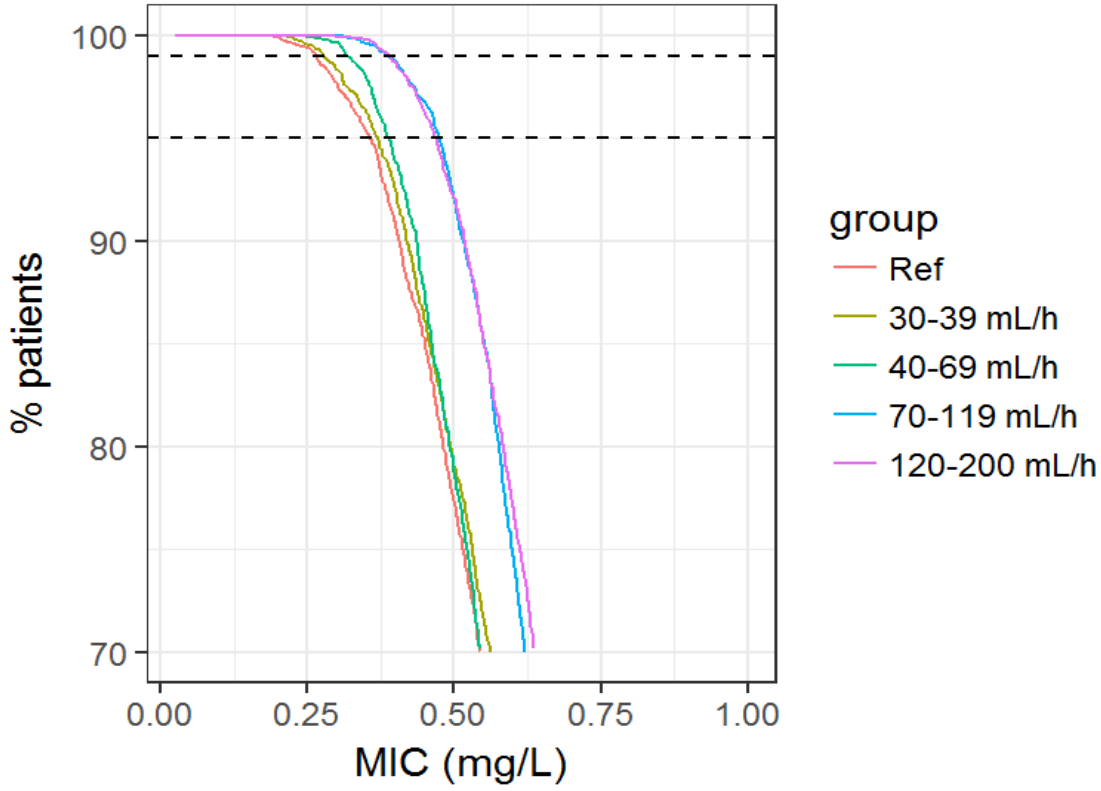
*** XDR defined by Magiorakos *et al*, 2012. Susceptibility based on EUCAST break points**

POLYPHOR Innovation in Drug Discovery

Tailored Dosing Regimen for Target Attainment

Robust PK/PD modeling used to optimize clinical dose for efficacy and safety

The PD target is AUC/MIC for a 1-log_{10} reduction



With the proposed dosing regimen, 100% of patients are predicted to achieve target attainment at a MIC 0.25 mg/L. Between 80 – 90% for MIC of 0.5 mg/L (MIC_{90} = 0.125 mg/L).

POLYPHOR Innovation in Drug Discovery

Summary Murepavadin Profile

- **Murepavadin has very potent anti-pseudomonal activity including MDR isolates**
  - Demonstrates a potent and rapid bactericidal activity at 2-4 times the MIC
  - Exhibits a low rate of resistance development (10^{-8} to10^{-9} by spontaneous mutations)
  - Demonstrates potent *in vivo* activity in animal models of infections, including XDR isolates
  - Has a high distribution into ELF and macrophages

- **Murepavadin could become a medicine that covers patients with nosocomial infections at risk of MDR pathogens, a condition associated with high mortality**
  - Well suited for stewarded de-escalation schemes for targeted therapy guided by confirmed culture

- **Murepavadin could become a medicine with limited risk of resistance dissemination to other pathogens**
  - The novel mechanism of action should result in no cross-resistance with commonly used antibiotics used for the treatment of Pseudomonas infections.
  - The pathogen-specific action should limit the drug pressure on the normal microflora and hence would reduce the risk of secondary infections such as *C. difficile* and the spread of resistance to other pathogens

Overview of Clinical Data Obtained to Date

- **Polyphor has conducted to date 8 studies**, including
  - 6 phase 1 studies in Healthy Volunteers, including potential DDI with colistin and amikacin as well as a PK/safety in renal impaired.
  - 2 patient phase 2 studies in NCFB and VABP patients

- **Outcome of Phase 2 PK/safety open-label study in VABP patients top of SOC**
  - 12 patients with microbiologically confirmed *P. aeruginosa* infection at baseline
  - 10 patients considered cured at ToC (92% at 7 days after EOT) and 11 /12 patients were alive at day 28
  - Mean SOFA score dropped from 4.8 to 3.7 at end of treatment
  - Mean CPIS score dropped from 9.5 to 4.5 at end of treatment
  - Median Improvement in PaO_2/FiO_2 ratio was 3 days
  - No resistance development towards POL7080 was observed
  - POL7080 was considered safe and well tolerated in this study

Although the data set is small and must be taken with caution, the outcome is promising and warrants further investigation

Challenges for Clinical Development in Nosocomial Pneumonia: Practical Experiences from Murepavadin Program

- **Traditional clinical study set-up is difficult to pursue in nosocomial pneumonia, including VAP/HAP with intrinsic high mortality with a pathogen-specific antibiotic**
  - Number of patients with confirmed Pseudomonas (miTT) for statistical evaluation of efficacy using mortality as endpoint (see JR intro).
    - At 22% incidence of P. aeruginosa and 10 % NI: need 3,064 patients in ITT
    - Superiority trials are hardly possible,
  - Availability of recruitable patients, particularly for attempted monotherapy comparison against Pseudomonas
  - Evaluability of drug efficacy in context of other antibiotics used and needed to complement pathogen specific spectrum
  - Obtaining consent within short period of onset

- **Different emphasis and direction given by EU and FDA regulatory Agencies for a global program**
  - FDA focus on demonstration of efficacy as monotherapy against P. Aeruginosa in centres with predominantly UDR etiology
  - MHRA focus on demonstration of efficacy on top of SOC against MDR pathogens.

The goal must be to reach, - together with clinical community and regulators - a scientifically and medically valuable <u>and</u> feasible way to demonstrate positive benefit/risk addressing a high medical need in nosocomial pneumonia

Constructive Dialogue with Agency and Clinical Community to Define the Way Forward to meet FDA Requirements

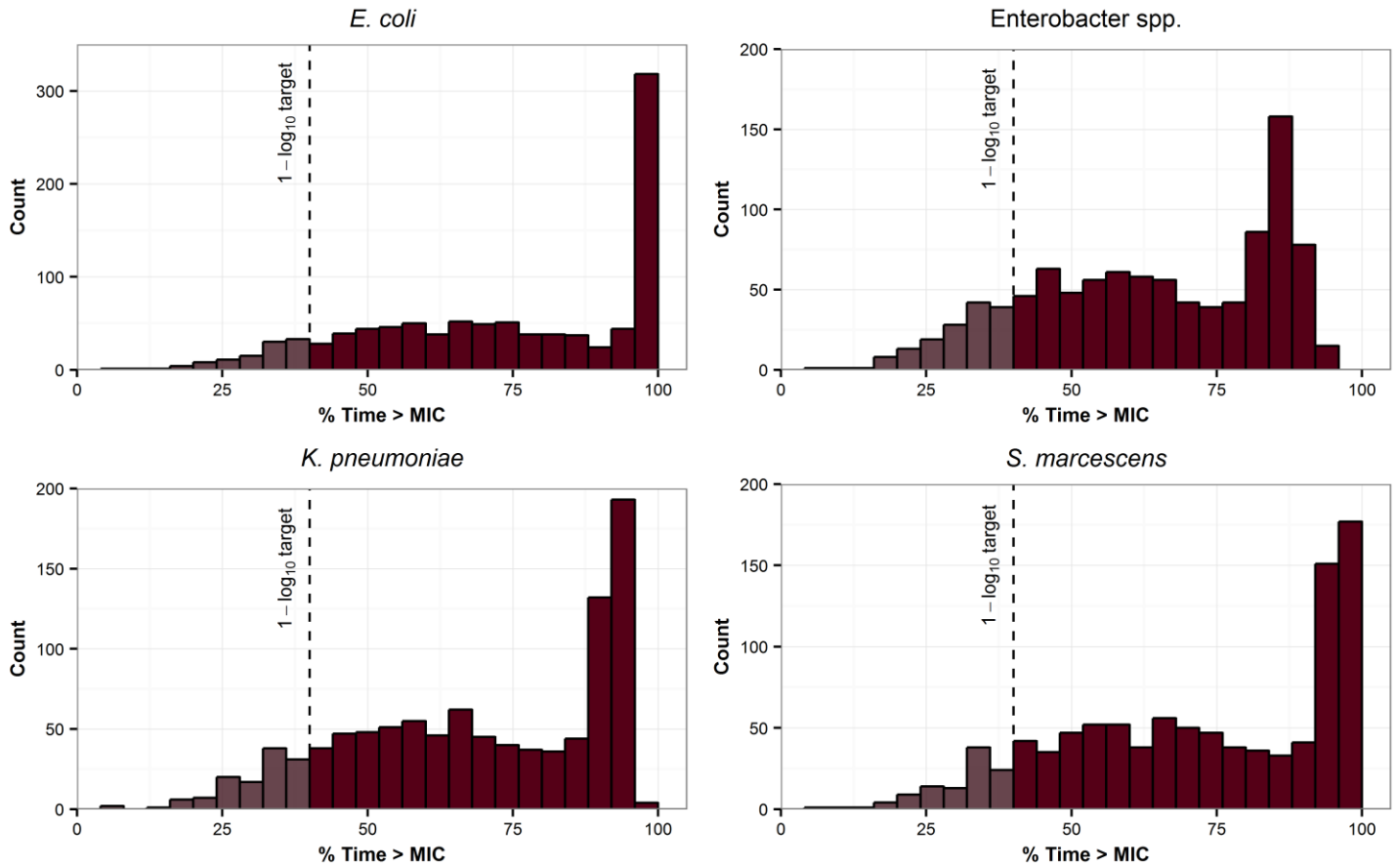
- **Multicenter, randomized, parallel group NI design study to evaluate the efficacy, safety, and PK of POL7080 in patients with nosocomial pneumonia due to suspected P. aeruginosa.**
  - Patients would be randomized 1:1 to the following treatment groups for single coverage against P. aeruginosa (Ertapenem does not cover P. aeruginosa)
  - Study arm: POL7080 + ertapenem
    Control arm: Meropenem
  - Non-inferiority 28-day ACM in the mITT population (confirmed P. aeruginosa)
- **A rapid diagnostic test will be used to identify patients with suspected *P. aeruginosa***
- **Empiric dual coverage will be allowed in both arms at the discretion of the investigators until culture and susceptibility results are available, for a maximum total duration of 72 hours.**
  - The Investigator will decide whether to administer dual coverage prior to randomization.
  - If the patient is randomized to the experimental arm, dual coverage must be POL7080 + ertapenem + amikacin
  - If randomized to the control arm, the dual coverage treatment will be meropenem + amikacin.

The proposed design is considered challenging but feasible in UDR environment based on the feedback from clinical KOLS.
Ertapenem coverage (1g QD) has been modeled with P. Ambrose

POLYPHOR Innovation in Drug Discovery

Modeling of Ertapenem TA for various Gram-negative Pathogens in VABP (Work done in collaboration with P. Ambrose)

Ertapenem 1 g IV q24h infused over 30 minutes may be an appropriate treatment modality for patients with ventilator-associated bacterial pneumonia



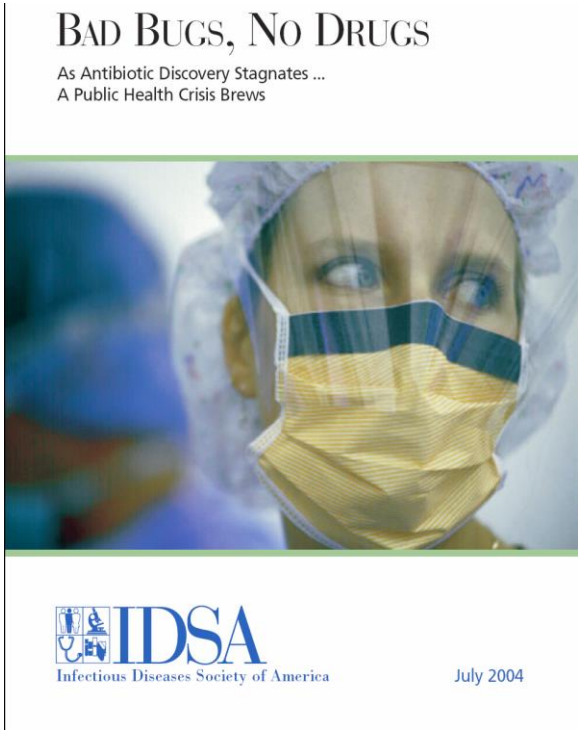
ELF %T>MIC were based on pathogen-specific weighted MIC distributions

POLYPHOR Innovation in Drug Discovery

Summary and Conclusions

The "**Ertapenem – Murepavadin combination design**" study should provide statistically powered evidence of **efficacy primarily in UDR** populations

- Clinical centres in centers with low level of MDR (<10%) which follow antibiotic stewardship (more in Northern Europe, few US).
- Few cases of MDR/XDR pathogens will be included and should allow extrapolation to MDR via susceptibility breakpoints
- Study implementation considered challenging but feasible



A continued, close collaboration and dialogue between the clinical community, regulators and research driven biotech companies is needed to develop the next generation antibiotics to address the increasingly challenging needs of patients and physicians

POLYPHOR
Innovation in Drug Discovery