1232. Efficacy and Safety of Intravenous Sulopenem Followed by Oral Sulopenem etzadroxil/Probenecid Versus Intravenous Ertapenem Followed by Oral Ciprofloxacin or Amoxicillin-clavulanate in the Treatment of Complicated Urinary Tract Infections (cUTI): Results from the SURE-2 Trial

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Session: P-56. New Drug Development

Background. Sulopenem is a broad-spectrum IV and oral penem antibiotic being developed for the treatment of infections caused by multidrug-resistant bacteria to allow for earlier discharge of hospitalized patients.

Methods. 1,395 hospitalized adults with pyuria, bacteriuria, and clinical signs and symptoms of cUTI were randomized to sulopenem IV once daily for 5 days followed by a bilayer tablet of sulopenem-etzadroxil and probenecid bid or ertapenem IV once daily for 5 days followed by either oral ciprofloxacin or amoxicillin-clavulanate bid, depending on susceptibility of the baseline uropathogen. The primary endpoint was overall (clinical and microbiologic) response at Day 21 [Test of Cure (TOC)] in the micro-MITT population.

Results. The sulopenem and ertapenem treatment arms were well-balanced at baseline.

The difference in overall response was driven by a difference in asymptomatic bacteriuria occurring between the end of treatment (EOT) and TOC in the subgroup of patients with a ciprofloxacin susceptible uropathogen at baseline who received ertapenem IV followed by oral ciprofloxacin. No difference in overall response was identified at EOT [86.7% vs 88.9%, sulopenem and ertapenem, respectively; difference, 95% CI: -2.2% (-6.5, 2.2)].

19% of patients remained on ertapenem IV as the baseline pathogen was both resistant to quinolones and ESBL positive; overall response for patients with these resistant pathogens on IV sulopenem who stepped down to oral sulopenem was higher [64/80 vs 55/84 on sulopenem IV/oral and ertapenem IV, respectively; difference, 95% CI: 14.5% (0.8, 27.8)].

Treatment emergent adverse events (all, 14.8% vs 16.1%; related, 6.0% vs 9.2%) and serious adverse events (2.0% vs 0.9%) were similar for patients on sulopenem and ertapenem, respectively.

Overall Response at Test of Cure, micro-MITT Population

Outcome	Sulopenem n (%) N=444	Ertapenem n (%) N=440	Difference (%), (95% CI)
All patients			
Overall response	301 (67.8)	325 (73.9)	-6.1 (-12.0, -0.1)
Clinical success	397 (89.4)	389 (88.4)	1.0 (-3.1, 5.1)
Microbiologic success	316 (71.2)	343 (78.0)	-6.8 (-12.5, -1.1)
Patients with ciprofloxacin susceptible isolates			
	Sulopenem IV/ oral Sulopenem n (%) N=248	Ertapenem IV/ oral Ciprofloxacin n (%) N=215	
Overall response	168 (67.7)	186 (86.5)	-18.8 (-26.1, -11.0)
Patients with all other isolates			
	Sulopenem IV only or Sulopenem IV/ oral Sulopenem n (%) N=196	Ertapenem IV only or Ertapenem IV/ Amoxicillin-clavulanate n (%) N=225	
Overall response	133 (67.9)	139 (61.8)	6.1 (-3.1, 15.1)

Conclusion. Sulopenem followed by oral sulopenem-etzadroxil probenecid was not non-inferior to ertapenem followed by oral step-down therapy for the treatment of cUTI driven by a lower rate of asymptomatic bacteriuria in patients receiving oral ciprofloxacin. Sulopenem, both IV and oral, was well-tolerated; its oral formulation allowed patients with baseline pathogens resistant to both quinolones and β-lactams an opportunity to successfully step down from IV therapy.

Disclosures. Michael W. Dunne, MD, Iterum Therapeutics (Employee, Shareholder) Steven I. Aronin, MD, Iterum Therapeutics (Employee, Shareholder)

1233. Identification of Novel Inhibitors of Clostridioides difficile Enoyl-Reductase II (FabK) by High-Throughput Virtual and Experimental Screening

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Session: P-56. New Drug Development

Background. *Clostridioides difficile* is one of only three bacteria categorized as an 'urgent' drug-resistant threat by the CDC. This pathogen is responsible for nearly 500,000 hospital-acquired infections and 29,000 deaths per year at a cost of nearly $4.8 billion. There is a critical need for the identification of novel, anti-difficile agents with narrow-spectrum activity that can spare the human microbiome. We previously reported the essentiality of the FAS-II enzyme, enoyl-ACP reductase (FabK) in *C. difficile*, and the narrow-spectrum activity of a series of phenylimidazole inhibitors. We present here experimental and virtual compound screening studies that identified novel FabK inhibitors with sub-micromolar activity and follow-up SAR and structural studies.

Methods. Using a novel luminescence assay, 20K diverse compounds from the St. Jude drug-like and lead-like libraries were screened. In parallel, a ligand-based virtual screen was performed against 2.4 million lead- and drug-like compounds from commercial libraries. Hit compounds were confirmed using an orthogonal fluorescence-intensity assay and SAR studies were performed by testing commercially available hit analogs. The most potent inhibitor was advanced into co-crystallography structural studies.

Results. The compound screening campaigns resulted in the identification of several confirmed hit compounds with low to sub-micromolar activity and novel scaffolds relative to the known phenylimidazole inhibitors. Importantly, the first confirmed nanomolar inhibitor of *C. difficile* FabK was identified and validated with an IC_{50} of 0.35 μM. SAR studies of the hits along with a high-resolution co-crystal structure have allowed new insights into the key binding determinants and structural requirements for activity as well as the structural requirements for species specificity.

Conclusion. The *C. difficile* FabK enzyme offers a promising narrow-spectrum drug target that can potentially spare the human microbiome. The known activity of the phenylimidazole inhibitor series supports the druggability of this target. The newly discovered inhibitor class presented here further demonstrates the potential of FabK inhibition and will facilitate the development of clinically relevant, narrow-spectrum anti-difficile agents.

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1234. Increasing private sector investment in neglected tropical disease (NTD) research and development: a mixed methods study

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Session: P-56. New Drug Development

Background. This study explores the drug development environment for Human African Trypanosomiasis and Chagas disease and investigates ways to stimulate greater investment in the small molecule drug pipeline for NTDs.

Methods. We conducted qualitative case studies of successful public-private partnerships (PPPs) that have supported the research pipeline for treatment of HAT (Fexinidazole & Acoziborole) & Chagas disease (Benznidazole). We conducted semi-structured interviews with 21 key informants. We then performed an economic modeling analysis to evaluate the development costs compared to estimates of potential revenue in order to identify expected private investment returns, inclusive of the contribution of the Priority Review Voucher (PRV) program. We also investigate under what circumstances one can expect positive returns if R&D for NTDs was executed by a private biopharmaceutical firm. We calculate the net present value of R&D costs both for an average NTD drug and use the specific features of these three candidates to estimate the private ROI that would have prevailed for each drug had they been developed by a for-profit entity.

Results. The major themes that emerged from the case studies were: (1) the importance of pre-existing philanthropic efforts for a given disease, (2) the desire to align the social goals of the company with its actions, (3) the vital role of PPPs in coordinating development and reducing private-sector risk & (4) the limited role that the PRV played in motivating these activities. Overall, the current NTD R&D landscape is driven by PPPs. The modeling analysis shows why: although the PRV is an important incentive for drug development, it is not sufficient to generate a positive private return for novel drug development when adjusting for capitalized costs and failure risk. However, for a pre-existing, unapproved drug such as Benzinadozole, returns are positive in the current environment (Table 1). We find that both a restricted PRV supply & better estimates of approval probabilities would generate positive returns (Fig 1 + 2).

Table 1: Return on investment by small molecule drug

	OOP costs per investigational drug	Capitalized costs per approved drug			Return on Investment	
	Total	Pre-clinical	Clinical	Total	Current	Restricted
Avg. Drug	339	1098	1460	2558	-98.4%	-92.2%
Avg. NTD Drug	207	752	1120	1872	-97.9%	-89.4%
Fexinidazole	43	32	298	330	-88.0%	-39.7%
Acoziborole	55	106	240	347	-88.5%	-42.6%
Benzinadozole	9	N/A	28	28	41.1%	607.3%

Sources: Authors calculations, DNDi, DiMasi et al. (2016), and Ridley and Regnier (2016). The estimated PRV value given current market supply is $40 million and estimated PRV value given restricted supply $ 200 million. OOP refers to out-of-pocket (not capitalized) costs. Costs in million $US.