Sulopenem Stewardship and Access Plan (SAP)

Iterum Therapeutics

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As per the requirements outlined in the CARB-X Portfolio Company Agreement, Iterum is providing an updated SAP after receiving FDA approval for marketing of oral sulopenem etzadroxil/probenecid (ORLYNVAH) on October 25, 2024. The purpose of this SAP is to help guide the introduction of ORLYNVAH into the community.

1. PRODUCT DESCRIPTION

Sulopenem is a broad-spectrum, parenteral β-lactam antibiotic of the thiopenem class that exerts its potent bactericidal activity by binding to and inhibiting key penicillin binding proteins in bacterial cell walls, thereby inhibiting cell division.

Sulopenem has broad spectrum activity against gram-positive and gram-negative aerobes and anaerobes consistent with that of ertapenem, a currently marketed carbapenem. Sulopenem is not expected to have activity against *Pseudomonas aeruginosa*, Enterococcus species, or methicillin resistant *Staphylococcus aureus.*

Sulopenem etzadroxil is an oral prodrug of sulopenem that, itself, has minimal *in vitro* antibacterial activity. Following absorption, it is rapidly hydrolyzed to generate the microbiologically active moiety, sulopenem, along with non-active moieties including formaldehyde and 2-ethylbutyric acid (2-EBA). Because sulopenem is the primary active circulating moiety following oral administration of the prodrug, the nonclinical and clinical effects are primarily attributable to sulopenem.

Sulopenem etzadroxil (500 mg) has been co-formulated with probenecid (500 mg), which prolongs the serum half-life and allows twice daily dosing in a bilayer tablet.

This bilayer tablet (ORLYNVAH) was approved by the FDA on October 25, 2024. Highlights from the package insert[1] are provided below.

Indications and Usage:

ORLYNVAH a combination of sulopenem etzadroxil, a penem antibacterial, and probenecid, a renal tubular transport inhibitor, is indicated for the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.

Limitations of Use:

ORLYNVAH is not indicated for the treatment of:

- Complicated urinary tract infections (cUTI) or as step-down treatment after intravenous antibacterial treatment of cUTI.
- Complicated intra-abdominal infections (cIAI) or as step-down treatment after intravenous antibacterial treatment of cIAI.

Usage to Reduce Development of Drug-Resistant Bacteria:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ORLYNVAH and other antibacterial drugs, ORLYNVAH should be used only to treat uUTI that are proven or strongly suspected to be caused by susceptible bacteria. Culture and susceptibility information should be utilized in selecting or modifying antibacterial therapy.

Dosage and Administration:

- The recommended dosage of ORLYNVAH is one tablet orally twice daily for 5 days.
- Administration of ORLYNVAH with food is recommended.

Contraindications:

- Patients with a history of hypersensitivity to the components of ORLYNVAH (sulopenem etzadroxil and probenecid) or other beta-lactam antibacterial drugs.
- Patients with known blood dyscrasias.
- Patients with known uric acid kidney stones.
- Concomitant use of ORLYNVAH and ketorolac tromethamine is contraindicated.

Warnings and Precautions:

- Hypersensitivity Reactions: Hypersensitivity reactions have been reported in patients treated with ORLYNVAH. Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis, have been reported with beta-lactam antibacterial drugs. Severe allergic reactions and anaphylaxis have been reported with the use of probenecid (a component of ORLYNVAH).
- *Clostridioides difficile*-Associated Diarrhea (CDAD): This has been reported with nearly all systemic antibacterial agents. Evaluate if diarrhea occurs.

- Exacerbation of Gout: When prescribing ORLYNVAH to patients with a known history of gout, ensure appropriate therapy of gout is instituted.

Adverse Reactions:

- The most common adverse reactions (≥2%) in patients treated with ORLYNVAH were diarrhea, nausea, vulvovaginal mycotic infection, headache, and vomiting.

Drug Interactions:

- Ketoprofen: Concomitant use is not recommended.

Microbiology:

Mechanism of Action

Sulopenem etzadroxil is a prodrug that is hydrolyzed to the active drug sulopenem after oral administration. Sulopenem has in vitro activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of sulopenem results from the inhibition of cell wall synthesis and is mediated through sulopenem binding to penicillin binding proteins (PBPs). In Escherichia coli, sulopenem demonstrated binding affinity for PBPs in the following order: PBP2 > PBP1A > PBP1B > PBP4 > PBP3 > PBP5/6.

Resistance

Resistance to sulopenem is caused by certain extended spectrum beta-lactamases (ESBLs) including carbapenemases, alteration of PBPs, over expression of efflux pumps and loss of outer membrane porins. Sulopenem demonstrated activity against Enterobacterales in the presence of certain beta-lactamases and ESBLs, e.g., AmpC, CTX-M, TEM, SHV. Sulopenem resistant mutants were selected in vitro at a frequency of 1×10-8.

Interaction with Other Antimicrobials

In vitro studies with sulopenem did not demonstrate antagonism with any of the following antimicrobials: amoxicillin, aztreonam, ceftriaxone, doxycycline, gentamicin, levofloxacin, nitrofurantoin, vancomycin or trimethoprim-sulfamethoxazole. The clinical significance of these in vitro findings is unknown.

Antimicrobial Activity

Sulopenem has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections:

Gram-negative bacteria:

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for sulopenem against isolates of similar genus or organism group. However, the efficacy of sulopenem in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria:

Staphylococcus saprophyticus

Streptococcus agalactiae

Gram-negative bacteria:

Citrobacter freundii

Citrobacter koseri

Enterobacter cloacae species Complex

Klebsiella aerogenes

Klebsiella oxytoca

Proteus vulgaris

Providencia alcalifaciens

Providencia stuartii

Susceptibility Testing For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see https://www.fda.gov/STIC.

2. IDENTIFY OBSTACLES AND CONSTRAINTS TO STEWARDSHIP AND ACCESS

As the first oral penem in the US, ORLYNVAH fulfils the unmet medical need for treatment of uUTI in patients with limited or no alternative oral treatment options. As with all antimicrobial agents, the appropriate clinical use of ORLYNVAH needs to occur simultaneously with basic antimicrobial stewardship activities to reduce the development of drug-resistant bacteria and maintain its effectiveness.

Obstacles and constraints to antimicrobial stewardship and access relative to ORLYNVAH include:

- Limited financial and human resources, preventing a small company like Iterum Therapeutics to plan commercialization and access activities in more than one country. Improvement of the current market and financial environment would allow Iterum to prioritize patients in other territories as well.
- Lack of a current consensus national guideline for the treatment of uUTI (last IDSA uUTI guideline was written in 2010[2])
- Prescriber lack of knowledge or sufficient training pertaining to antimicrobial resistance, and

antimicrobial stewardship as it relates to the diagnosis and treatment of patients with uUTI

- Inappropriate choice of first line empiric treatment of patients with uUTI
  - Using alternate oral treatment options in patients with uUTI proven or strongly suspected to be caused by bacteria resistant to such agents
  - Using ORLYNVAH in patients with uUTI when there are known or strongly suspected alternate oral treatment options
- Failure to use urine culture and susceptibility testing in the appropriate setting
- Inappropriate treatment of patients with asymptomatic bacteriuria
- Inappropriate use of urine culture to evaluate response to therapy

- Lack of an available rapid, point-of-care diagnostic tool to identify patients with uUTI due to drug-resistant pathogens and guide empiric therapy

Iterum's plan/activities to help address these obstacles and constraints include:

a. Prevent carbapenem resistance through the use of ORLYNVAH

When discussing the prevention of carbapenem resistance through the use of ORLYNVAH, It is important to understand the dynamic between improving patient treatment outcomes and maintaining a balance of susceptible organisms within the bacterial flora through antibiotic stewardship. A detailed discussion on this topic is provided as Appendix A below.

b. Work to develop relevant diagnostic tests

Iterum will work with diagnostic test manufacturers to help physicians identify organisms susceptible to sulopenem.

- 2 µg/mL discs for sulopenem

Iterum continued work initially started by Pfizer on the development of a 2 µg/ml susceptibility disk that was used in our Phase 3 clinical trials and will be produced and manufactured to enable *in vitro* susceptibility testing in the community. Iterum's 2 µg/ml disk development process has been published in a peer-reviewed journal[3].

- Ertapenem surrogate for broth microdilution

Given the delay in introduction of new antibiotics onto the automated antimicrobial susceptibility testing devices, Iterum has initiated research into the use of a surrogate penem antibiotic, ertapenem, already included in most of these panels, in order to allow physicians to judge susceptibility of pathogens isolated from patient samples to sulopenem, based on susceptibility to ertapenem. Results of this research were presented at a major medical meeting.

- Studying the urine dipstick for inefficiencies

Use of the urine dipstick has been a standard diagnostic test for identification of patients with urinary tract infections. We have compared the outcomes of a urine dipstick, as read manually by eye with outcomes read by an automated machine and found that the machine read tests correlate with positive urine culture more frequently than those that are manually read. This observation could help avoid the use of antimicrobials in patients who may not actually have a urinary tract infection.

- Studying use of PCR for rapid diagnosis of uUTI

During our first Phase 3 uUTI clinical trial, we partnered with a company that was developing a rapid PCR-based test for diagnosis of urinary tract infection to evaluate the correlation between the urine specimens sent to a central lab for culture with PCR analysis of the same specimen. Preliminary results from that endeavor were extremely promising. Since then, the partner we worked with changed its business focus. We continue to believe that a rapid point of care diagnostic test would be an extremely useful antibiotic stewardship measure. We would consider future collaborations with companies developing such a tool and would also consider using this PCR technology as an adjunct to our culture-based inclusion and outcome criteria in future clinical studies.

c. Collect and disseminate surveillance data

During the ORLYNVAH development program, Iterum worked with numerous third parties to better define the state of resistance to available antibiotics for treatment of urinary tract infection, both in the community as well as in the hospital.

- Sponsor collection of surveillance data and make it available to the public

Iterum has and will continue to sponsor the collection and analysis of surveillance culture data from numerous inpatient and outpatient sources, both controlled and uncontrolled populations, from organizations such as BD Insights (Becton Dickinson), the CANWARD project, JMI labs, IHMA, as well as data we will collect from any future clinical trials. To date, such surveillance data has been presented as posters at major medical meetings and has also been published in a peer-reviewed journal[4].

- Postmarketing surveillance

As part of its postmarketing requirements for ORLYNVAH, Iterum plans to conduct the following surveillance study:

- U.S. surveillance study over a five-year period after the introduction of sulopenem etzadroxil/probenecid (ORLYNVAH) to the market to determine if resistance or decreased susceptibility to ORLYNVAH is occurring in the target population of bacteria identified in the approved ORLYNVAH label.

- Availability of local susceptibility data to prescribers

A key antibiotic stewardship measure is for uUTI prescribers to understand and to utilize local susceptibility patterns for commonly prescribed oral antibiotics versus key Enterobacterales uropathogens. Iterum will promote this measure and work with laboratories to provide meaningful data to prescribers.

d. Understand social science and behavior

Feedback from practicing clinicians will be collected and analyzed in order to better understand the forces that drive the use of antibiotics, which, if not appropriately directed, could unnecessarily drive antimicrobial resistance.

- Survey physicians

Iterum has surveyed over 200 physicians and pharmacists to understand how oral antibiotics are empirically selected for treatment of a patient with an uncomplicated UTI, and what limitations they perceive relative to existing antibiotics. We then mapped their perceptions of resistance with actual resistance rates in their community to gauge knowledge of local resistance rates. Follow-up programs will be initiated to better understand the impact of awareness of local resistance patterns with the decision to prescribe a specific antibiotic.

e. Support research, including clinical studies conducted in accordance with relevant national and international governance arrangements, on treatments and prevention of common bacterial infections, especially in low resource settings

- Conducted five clinical trials

Iterum conducted four phase 3 clinical studies, two in the indication of uUTI, and one each in the indications of complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI), and a phase 4 study in treatment of uUTI with ciprofloxacin (to understand the consequences of quinolone resistance). Other clinical studies in related indications will be considered within the next five years.

f. Generate funding for infectious diseases through support of incentives, such as lump-sum payments, insurance models, tax credits and novel IP mechanisms that reflect the societal value of new antibiotics and vaccines and will attract further investment in R&D

- Within the public and private (venture) communities

Iterum will work with other biotech companies focused on infectious diseases in the Antibiotic Working Group to advocate for incentive packages which encourage venture investment in antibiotic discovery and development. We will work closely with the US Congress to understand the extent of governmental support and refine potential incentive options so as to provide a sustainable investment climate for efforts to combat resistance.

g. Engage in economic research, including the development of models to assess the cost of antimicrobial resistance and the costs and benefits of this action plan

- Examining the cost of treatment failure for urinary tract infections in the inpatient and outpatient setting (Becton Dickinson Insights)

Iterum collaborated with BD Insights to examine the costs in terms of re-prescriptions for antibiotics and hospitalizations related to mismatched treatment for uUTI. The results of this research were presented at major scientific meetings and published in a peer-reviewed journal[5].

- Looking at claims databases within a managed care program to understand the impact of failed empiric therapy of urinary tract infections

Iterum is working with a large US insurance company to explore the impact of incorrect empiric therapy, similar to the BD insights network, and specifically the reimbursement implications to the hospital for that initially mismatched therapy.

h. Support measures to reduce environmental impact from production of antibiotics and work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce environmental impact of manufacturing

- Supply chain management

Iterum has selected an EU (Italy)-based contract manufacturer for the supply of both the bulk active ingredient and drug product for Orlynvah. This manufacturer complies with national (Italy) and EU-wide environmental legislation.

Working with our contract manufacturer, and in view of their obligations to comply with national and EU-wide directives, we intend to follow responsible manufacturing processes and to meet the standards outlined in the AMR Industry Alliance Responsible Manufacturing Framework. We further intend to meet the discharge targets outlined in the AMR Industry Alliance's list of Predicted No-Effect Concentrations (PNECs) document. Unsold or unused product is returned to the manufacturer for appropriate disposal.

i. Support basic research and translational studies in the development of new treatments

- Optimizing the dosing of antibiotics

Iterum, building on work from Pfizer, has supported basic and translational phase 1 studies to optimize the dosing of sulopenem. A decision was made to co-administer sulopenem with a penem-sparing agent, probenecid, which reduces the amount of sulopenem required to be delivered to a specific patient and minimizes the subsequent amount of environmental exposure of sulopenem in the community. Taken together, this dosing approach may reduce the effect of sulopenem on the microbial flora, reducing the amount manufactured by as much as 50%, or tens of metric tons of drug per year, at peak utilization.

- Understanding mechanisms of resistance

Iterum has supported research to understand the likelihood of selection of resistance with sulopenem relative to other penems as well as *in vitro* studies to define the mechanisms that microorganisms use to evade the activity of antimicrobials, including sulopenem.

- Understanding the differences between colonizing flora and uropathogens that cause disease

After participating in FDA's June 3, 2022 virtual Public Workshop 'Development Considerations of Antimicrobial Drugs for the Treatment of Uncomplicated UTI[6], Iterum initiated discussions with researchers at the University of Michigan Medical School to collaborate on studies to characterize *E. coli* strains cultured from the urine of patients undergoing therapy for uUTI. The aim of the project was to focus on the subgroup of uUTI clinical trial patients who had *E. coli* identified as the causative pathogen at baseline as well as at the test of cure visit while all uUTI symptoms had resolved. *E. coli* strain characterization was to be performed to determine whether the initial *E. coli* persisted during treatment of uUTI or if new strains (non-pathogenic colonizers) were acquired. This collaboration was paused due to financial constraints, but Iterum remains keenly interested in continuing this research as the

findings may impact the primary endpoint for uUTI clinical trials and the ability for companies to combat antimicrobial resistance by developing novel replacement antibiotics.

j. Support new ways of working such as open collaborations between industry and public researchers to overcome the scientific challenges of creating new antibiotics and diagnostics

- Collaborate in public-private partnerships

Iterum is collaborating in a number of public private partnerships, including CARB-X and NIAID.

k. Education

Iterum supports the need for ongoing education to assure that prescribers:

- Know how to find current local antimicrobial susceptibility patterns
- Know how to interpret antimicrobial susceptibility results
- Understand the principles of antimicrobial stewardship
- Know how to diagnose uUTI
- Know how choose empiric therapy for a given patient with uUTI, including those patient characteristics that warrant the use of ORLYNVAH
- Know the correct dose and duration of therapy for the treatment of patients with uUTI
- Know when and how to use urine culture in the diagnosis and treatment of patients with suspected and confirmed uUTI
- Understand the importance of not treating asymptomatic bacteriuria
- Understand that a 'test of cure' urine culture should not be obtained for patients with appropriate clinical response to therapy

3. STRATEGIES TO ENSURE MARKETING APPROVALS ARE RECEIVED IN A TIMELY MANNER IN THE TARGETED TERRITORIES

- As part of its postmarketing requirements, Iterum plans to carry out the following pediatric studies:
  - Open label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of sulopenem etzadroxil/probenecid in pediatric patients aged 12 years to less than 18 years with bacterial infection and receiving background antibacterial therapy.
  - Open label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of sulopenem etzadroxil/probenecid in pediatric patients aged 2 years to less than 12 years with bacterial infection and receiving background antibacterial therapy.
  - Randomized, controlled study to evaluate the safety, tolerability, and efficacy of sulopenem etzadroxil/probenecid in pediatric patients aged 2 years to less than 18 years with uncomplicated urinary tract infections (uUTI).
- In addition, Iterum plans to conduct the following bioavailability study:

- Relative bioavailability study in healthy adults comparing the oral granule formulation and the bilayer tablet formulation of sulopenem etzadroxil/probenecid.

- As part of its postmarketing requirements, Iterum plans to conduct the following surveillance study:
  - U.S. surveillance study over a five-year period after the introduction of sulopenem etzadroxil/probenecid to the market to determine if resistance or decreased susceptibility to sulopenem etzadroxil/probenecid is occurring in the target population of bacteria identified in the approved sulopenem etzadroxil/probenecid label.

- Iterum is currently focussing its initial commercialization and access activities in the United States. As financial and human resource environments improve, we plan to expand our commercialization efforts to other territories.

4. STRATEGIES TO SUPPORT STEWARDSHIP AND ACCESS AND FOR EXPLOITING PROJECT IP RIGHTS IN THE OTHER TERRITORIES

Iterum is committed to supporting stewardship activities and access in other territories. Specifically, Iterum promotes strengthening the knowledge and evidence base through surveillance and research, optimizing the use of antimicrobial medicines in humans, developing the economic case for sustainable investment that takes into account the needs of all countries, and increasing investment in new medicines, diagnostic tools, and other interventions. At this time, however, financial constraints prohibit Iterum from making ORLYNVAH available in other territories and devising specific stewardship and access plans related to ORLYNVAH for other territories. Once it is feasible, Iterum will consider the following actions to increase local availability of ORLYNVAH in lower and middle-income nations (LMICs):

- Product registration in local markets (LMICs)
- Tiered pricing
- Voluntary licensing agreements
- Technology transfers
- Public-private partnerships
- Patient assistance programs
- WHO pre-qualification

Pending a successful launch of ORLYNVAH in the United States and the related availability of adequate financial resources, Iterum will initiate conversations with relevant partners, including CARB-X, its funders and other public-private partnerships, to facilitate stewardship and access in the other territories.

Iterum stresses the importance for governments and funders to recognize the difficulty of achieving a return on investment when developing and marketing an innovative antibiotic like ORLYNVAH. The current market dynamics prevent small companies like Iterum to raise enough capital to dedicate appropriate resources to plan for access outside a small number of geographies.

5. STRATEGIES FOR MONITORING EFFECTIVENESS OF STEWARDSHIP AND ACCESS ACTIVITIES

Iterum believes that it is essential to monitor the effectiveness of stewardship and access activities. We plan to establish a relationship with a partner, such as the Access to Medicine Foundation (ATMF), to develop a strategy for reporting the actual implementation and effectiveness of our stewardship and access activities. We would plan to cooperate with this partner so that our metrics could be part of publicly available benchmark data for antibiotic companies.

Iterum recognizes that this Stewardship and Access Plan has limitations given the importance and urgency for the company to focus on the launch of ORLYNVAH in the United States to ensure its own survival and sustainability. If product sales in the United States allow for us to expand our attention to other geographies, Iterum commits to update this Stewardship and Access Plan to include details about such other geographies.

References

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Appendix A: Sulopenem Stewardship and Access Plan, Iterum Therapeutics, July 2018. Iterum Response to Follow-up Question
CARB-X Follow-up Question from JOC:

The CARB-X JOC would like to see more information on your company's proposed plan to prevent carbapenem resistance through the use of your oral penem.

Iterum Response:

Resistance to antibiotics has become an issue of global importance. In recent years the development of new antibacterial agents has occurred primarily in response to resistance in existing classes, and frequently from which the new antibiotic is derived. Sulopenem will address resistance which has developed in multiple other classes by extending the clinical relevance of carbapenems which, to date, remain effective against the vast majority of offending pathogens. Though uncommon, threats to this class do exist today, making it important to understand the dynamic between improving patient treatment outcomes and maintaining a balance of susceptible organisms within the bacterial flora through antibiotic stewardship.

To best approach this topic, a review of resistance to carbapenems already in the market will be provided, followed by a proposed sulopenem development plan which will address the evolving underlying medical need while minimizing any impact on the existing flora.

Carbapenem Susceptibility

Since the introduction of imipenem in 1985, extensive efforts have been made to track the development of resistance to carbapenems through *in vitro* surveillance studies and, subsequently, identify mechanistic explanations for the observed changes in susceptibility.

The MIC_{90} for imipenem based on isolates obtained in 1980-1982 was described in a paper published in 1985 (Table 1) [Birnbaum]. The MIC_{90} for *E. coli* and Klebsiella species was 0.26 µg/mL and 0.41 µg/mL, respectively.

Table 1. Susceptibility of Gram-Negative Aerobes to Imipenem

Pathogen	Isolates (N)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Escherichia coli	1,122	0.14	0.26
Enterobacter species	1,276	0.34	1.3
Klebsiella species	952	0.18	0.41
Serratia species	805	0.76	1.93
Proteus species	1,655	1.3	2.9
Pseudomonas aeruginosa	2,278	1.57	3.54
Carbenicillin-resistant	142	1.7	3.7
Aminocyclitol-resistant	317	2.1	3.8
Acinetobacter species	436	0.22	0.47
Alcaligenes species	86	0.97	2
Brucella melitensis	98	1	2
Eikenella corrodens	56	0.15	0.22
Hemophilus influenzae	302	0.95	1.82
Moraxella species	37	0.08	0.37
Neisseria gonorrhoeae	387	0.1	0.3

Neisseria meningitidis	266	0.05	0.11
Shigella species	33	0.17	0.27
Yersinia enterocolitica	234	0.23	0.44
Citrobacter species	370	0.3	0.62

In a recent surveillance study conducted at IHMA, sponsored by Iterum, we can see that after 30 years the MIC_{90} for imipenem for these two organisms has not changed, remaining at 0.25 µg/mL and 0.5 µg/mL for *E. coli* and Klebsiella species, respectively (Table 2) [data on file].

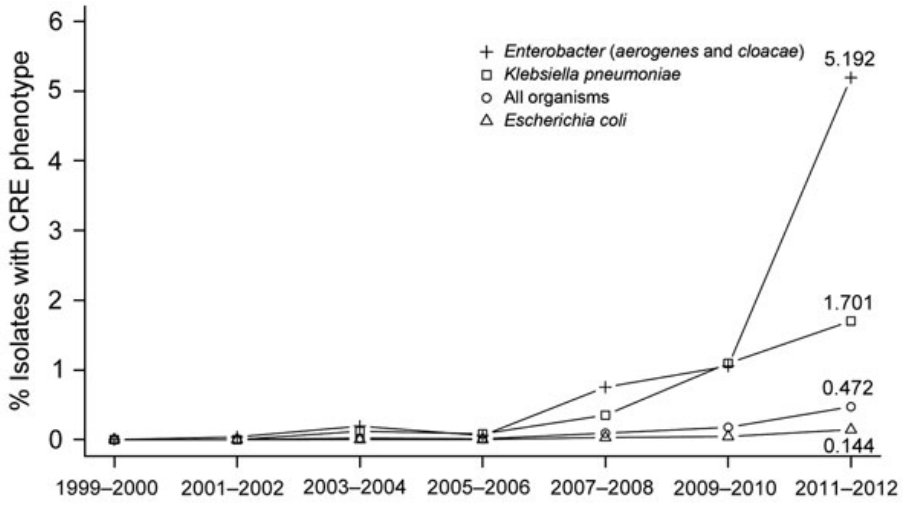
Table 2. Antimicrobial Susceptibility of Sulopenem and Other Carbapenems

Organism	N	MIC_{90} (µg/mL)				
		Sulopenem	**Ertapenem**	**Meropenem**	**Imipenem**	**Doripenem**
E. coli	189	0.06	0.015	0.03	0.25	0.03
K. pneumonia	65	0.12	0.12	0.06	0.5	0.12
K. oxytoca	61	0.06	0.03	0.03	0.25	0.06
B. fragilis	73	0.25	1	1	0.25	0.5

For carbapenems introduced after imipenem, such as meropenem, ertapenem and doripenem, the distribution of MIC_{50} and MIC_{90} for these Enterobacteriaceae would also demonstrate little change over time. Such cannot be said for *Pseudomonas aeruginosa* and the Acinetobacter species, where resistance has progressively increased (Walters, Xu).

Even though the MIC_{90} for Enterobacteriaceae has not changed substantially, resistance to carbapenems has increased, most evident since 2000. The frequency of these carbapenem-resistant Enterobacteriaceae (CRE) remains low at <1% overall but, given the importance of carbapenems in treatment of resistant infections, much attention has been paid to documenting the epidemiology of this group of pathogens and identifying the reasons for resistance. Figure 1 describes the increase in CRE in a pediatric population; similar trends can be seen in adults [Logan; CDC website].

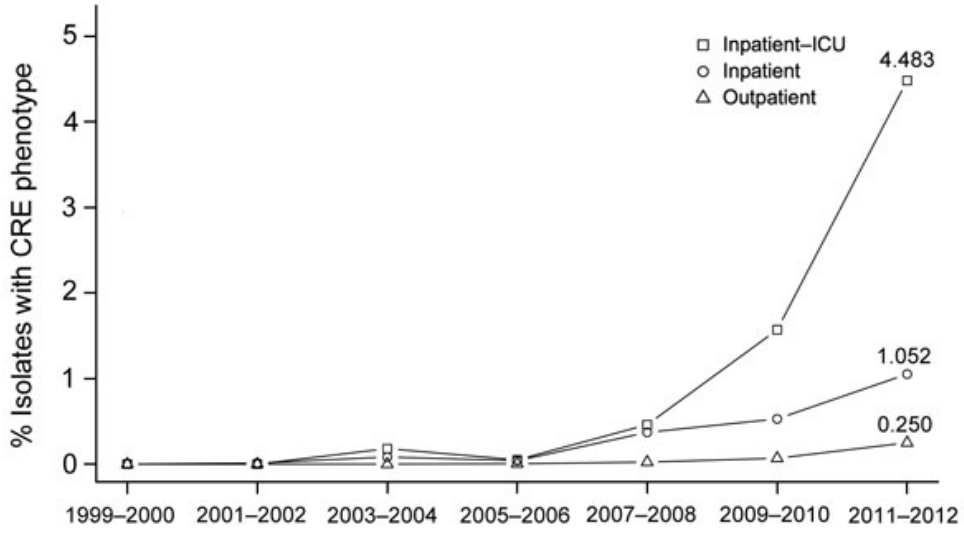
Figure 1. National Trends in Prevalence of Carbapenem-resistant Enterobacteriaceae (CRE) Isolates from Children



Among these Enterobacteriaceae the rate of resistance is low, approaching 0.5%. Among these three species, the rates are also inversely proportional to the frequency with which the pathogen contributes to human infection.

As often with emergence of resistance, these organisms are also concentrated within the hospital setting (Figure 2). In this series, the percentage of isolates with carbapenem resistance is concentrated by 20 fold within the intensive care unit relative to the outpatient sector, likely a consequence of the preponderance of hospital acquired pneumonia and instrumentation or catheter associated disease.

Figure 2. Prevalence of Carbapenem-resistant Enterobacteriaceae (CRE) Isolates from Children by Health Care Setting



Mechanisms of Resistance

The mechanisms of resistance for CRE organisms fall into three categories: changes in penicillin binding proteins, changes in outer membrane proteins including porins on the cell surface, and

the emergence of carbapenemases. Organisms with a change in penicillin binding proteins are infrequently identified in clinical isolates though they can be selected *in vitro*. Changes in the expression of porins on the surface of the bacteria have been identified in clinical isolates and can result from either a frame shift mutation effecting the production of that protein or from mutations in the promoter sequences that drive the production of these outer membrane proteins [Chow, Kaczmarek, Tangden]. If these outer membrane mutations occur in an organism that also produces an extended spectrum beta-lactamase, especially Amp-C, it is more likely that elevations in MIC's will occur. While these mutations do affect susceptibility, it appears that only a minority of the organisms that have these mutations will have an MIC above the susceptible range.

The more important type of resistance mechanism is the production of carbapenemases [Antunes; Pratt], which account for at least 50% of all CRE, as described in the Tables 3-5 below [Guh, Castanheira , Deshpande].

Table 3. Occurrence of Carbapenem–resistant and Carbapenemase-producing *E. coli* and Klebsiella spp. During 2007-2009.

Table 1. Occurrence of carbapenem-resistant and carbapenemase-producing *E. coli* and *Klebsiella* spp. during 2007–09

	Number (%) by organism		Number (%) by year/period				
Phenotype/genotype	*E. coli*	*Klebsiella* spp.	2007	2008	2009	2007–09	*P* [OR (95 CI %)][a]
Carbapenem resistance[b]	29 (0.3)	294 (5.3)	97 (1.8)	97 (1.9)	129 (2.4)	323 (2.0)	0.0467 [0.76 (0.58–1.01)]
Carbapenemase producer (MHT+PCR)	16 (0.2)	213 (3.8)	63 (1.2)	65 (1.3)	100 (1.8)	228 (1.4)	<0.0001 [0.52 (0.37–0.72)]
KPC-like	2 (<0.1)	156 (2.8)	52 (1.0)	38 (0.7)	68 (1.2)	158 (1.0)	0.1767 [0.78 (0.53–1.14)]
OXA-48	14 (0.1)	24 (0.4)	3 (<0.1)	8 (0.2)	27 (0.5)	38 (0.2)	<0.0001 [0.11 (0.03–0.39)]
MBL	0 (0.0)	32 (0.6)	8 (0.1)	19 (0.4)[c]	5 (0.1)	32 (0.2)	0.3836 [1.64 (0.49–5.74)]
Total	10432	5516	5355	5122	5471	15948	—

[a]*P* values were calculated by χ^2 for trend test; *P* values <0.0001 were considered statistically significant. OR and respective 95% CI values refer to comparisons between the years 2007 and 2009.
[b]Carbapenem resistance was as defined by CLSI document M100-S20-U.[5]
[c]The vast majority (85.0%) of MBL isolates originated from two Greek medical centres; however, they did not participate in the surveillance programme in 2007 and 2009.

Table 4. Summary of Results for the Evaluation of Enterobacteriaceae (37,557 isolates) Displaying Decreased Susceptibility (MIC values >2 mg/L) to Carbapenems

Organism (no. tested)	*No. (%) with elevated carbapenem MICs*	*MIC range (mg/L)*[a]		*No. of isolates PCR+*
		Imipenem	*Meropenem*	
Escherichia coli (20,138)	4 (0.02)	2–8	4–8	2
Klebsiella spp. (8,977)	46 (0.51)	2–> 8	2–> 8	23
Enterobacter spp. (5,206)	57 (1.09)	2–> 8	2–> 8	19
Citrobacter freundii (1,061)	3 (0.28)	2–4	2–4	2
Serratia marcescens (2,175)	9 (0.41)	8–> 8	2–> 8	5

Table 5. Carbapenem-Resistant Enterobacteriaceae (CRE) Organisms and Carbapenemase-Producing Isolates by Emerging Infections Program Site 2012-2013.

Table 1. Carbapenem-Resistant Enterobacteriaceae (CRE) Organisms and Carbapenemase-Producing Isolates by Emerging Infections Program Site, 2012-2013

Emerging Infections Program Site	Total No.	CRE Organism or Isolate, No. (%)						
		Enterobacter aerogenes	*Enterobacter cloacae* Complex	*Escherichia coli*	*Klebsiella pneumoniae*	*Klebsiella oxytoca*	Isolates Submitted for Carbapenemase Testing	No. of Carbapenemase-Producing Isolates/Total No. of Isolates Submitted forTesting (%)[a]
Colorado[b]	27	7 (25.9)	10 (37.0)	3 (11.1)	7 (25.9)	0	16 (59.3)	5/16 (31.3)
Georgia	356	22 (6.2)	38 (10.7)	56 (15.7)	235 (66.0)	5 (1.4)	75 (21.1)	48/75 (64.0)
Maryland[b]	92	8 (8.7)	6 (6.5)	9 (9.8)	69 (75.0)	0	17 (18.5)	13/17 (76.5)
Minnesota	71	29 (40.8)	16 (22.5)	10 (14.1)	16 (22.5)	0	58 (81.7)	17/58 (29.3)
New Mexico[b]	6	2 (33.3)	0	3 (50.0)	1 (16.7)	0	[c]	[c]
New York[b]	27	3 (11.1)	2 (7.4)	5 (18.5)	17 (63.0)	0	9 (33.3)	5/9 (55.6)
Oregon	20	4 (20.0)	7 (35.0)	3 (15.0)	6 (30.0)	0	13 (65.0)	2/13 (15.4)
Total	599	75 (12.5)	79 (13.2)	89 (14.9)	351 (58.6)	5 (0.8)	188 (31.4)	90/188 (47.9)

[a] Only *K pneumoniae* carbapenemase was detected among the submitted CRE isolates.

[b] Only 2013 data are available.

[c] New Mexico did not submit any CRE isolates during 2012-2013 for molecular characterization.

Recent reviews of carbapenemases can be found that provide a good overview of the topic [Gupta] but, briefly, carbapenemases were first identified in clinical specimens in 2001. Carbapenemase genes can be found on transposable elements and plasmids and clonal spread has been documented. Different carbapenemases have different structures and are consequently grouped into four classes. Because of these inherent differences, carbapenemase inhibitors on the market and under development do not cover all carbapenemases in circulation today.

Carbapenemase production may have variable effects on the subsequent MIC of a pathogen but the effect is generally similar for all carbapenems and results in MIC's generally >16 μg/mL. Occasionally, clinically important differences can be seen within the class, with some compounds remaining fully susceptible and others fully resistant.

Identification of the origin of these carbapenemases has been the subject of significant investigation. Given that carbapenemases are not the result of a single point mutation but rather the transfer of significant genetic material on plasmids or other transposable elements, the source of the genetic code is likely to have come, in fact, from another organism. Metallo-β-lactamases, for example, are considered to be part of an ancient superfamily of metallo-hydrolases with diverse functions, known as the MBL superfamily and are found in many bacteria [Meini; Daiyasu]. Carbapenemases have been identified in waterborne environmental organisms such as *Schewanella oneidensis* and are likely to have existed for billions of years. Interactions between these organisms and pathogenic Enterobacteriaceae in the environment is a plausible source for the observed evolution. Of interest, the OXA-48 carbapenemase, recently increasing in importance, can be found in *E.coli* identified in the waterways around Wisconsin as well as in clinical samples, an environment where organisms such as *Schewanella* spp. are likely to be found [Kappell]. Similarly, an aquatic *Serratia marcescans* in Morocco was also found to have the *bla*OXA-48 gene on a plasmid, suggesting that this organism, as both an environmental organism and a human pathogen, could be a source of carbapenemases in circulation in clinical specimens [Rieber].

New agents for treatment of carbapenemase producing organisms have been recently approved and others are in development. Approved agents include ceftazidime-avibactam, ceftolazone-tazobactam and tigecycline. Compounds in development which will have activity against CRE, include plazomicin, relebactam-imipenem-cilastatin, vaborbactam combinations and

eravacycline. Given that carbapenemases in human pathogens are already widely distributed in the hospital setting, further selection of CRE is likely to occur given even the existing use of carbapenems today. The availability of the newer agents that employ different mechanism of action may help to mitigate the selective pressure on these organisms.

Sulopenem

After the introduction of every antibiotic discovered to date, there has been a subsequent change in the flora leading to an increasing percentage of organisms which are non-susceptible. 'When new agents do get used eventually, emergence of resistance at some point is almost inevitable' [Gould]. After 30 years, the carbapenems have selected for a small population of organisms with reduced susceptibility to this class. The question being raised is focused on the extent to which sulopenem may contribute to the selection pressure driving carbapenem resistance and what measures can be taken to minimize that pressure.

There are three elements of the sulopenem program which will serve to minimize any impact of its introduction on the development of resistance: optimizing the dose to take into account it's *in vitro* potency and pharmacokinetic parameters, identifying the patient who will benefit the most by designing clinical studies to define the risk and benefit of sulopenem treatment and monitoring for resistance in the community after launch.

Optimize dosing

As with all antibiotics in development, efforts are underway to optimize target attainment with sulopenem using typical PKPD analysis and Monte Carlo simulations. Target attainment will be presented both using the MIC distribution of the organisms anticipated in the indications we are studying as well as using a 'fixed' exposure, with the highly conservative assumption that all organisms will have that MIC, essentially a 'margin of error' assessment. The PKPD Parameter of interest with sulopenem, like other carbapenems, is the time>MIC.

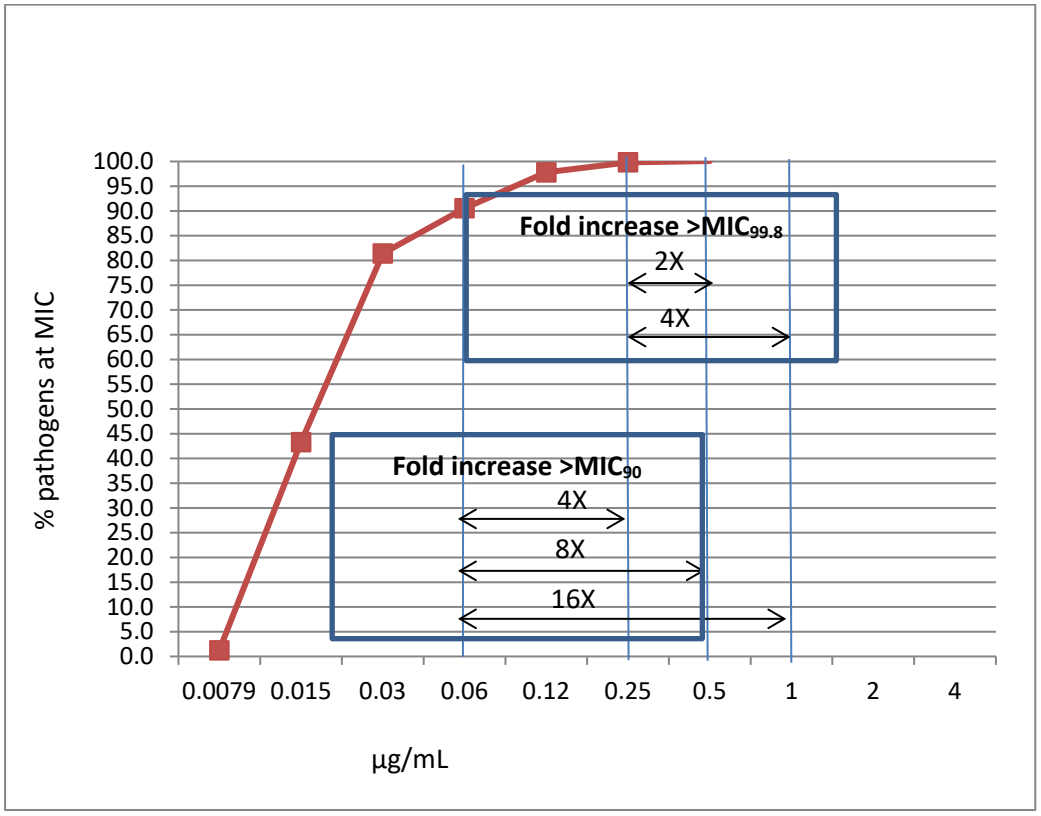
Sulopenem MIC's for organisms anticipated to be found in the infections of the urinary tract are provided in the table below, along with the frequency of their distribution; other pathogens may be identified, of course, but their frequency is expected to be low and their MIC distribution will be similar to the more common organisms.

Table 6. Distribution and Frequency of MIC's of Key Pathogens Associated with Urinary Tract Infection

MIC (µg/mL)	*E. coli*	*K. pneumoniae*	*P. mirabilis*	*E. cloacae*	%MIC coverage with serum exposure at given concentration
0.0079	0.012				1.2
0.015	0.415	0.006			43.3
0.03	0.302	0.071		0.008	81.4
0.06	0.051	0.018	0.015	0.008	90.5
0.12	0.051	0.012	0.007	0.003	97.8
0.25			0.015	0.005	99.8
0.5				0.003	100
Incidence	0.830	0.107	0.037	0.027	

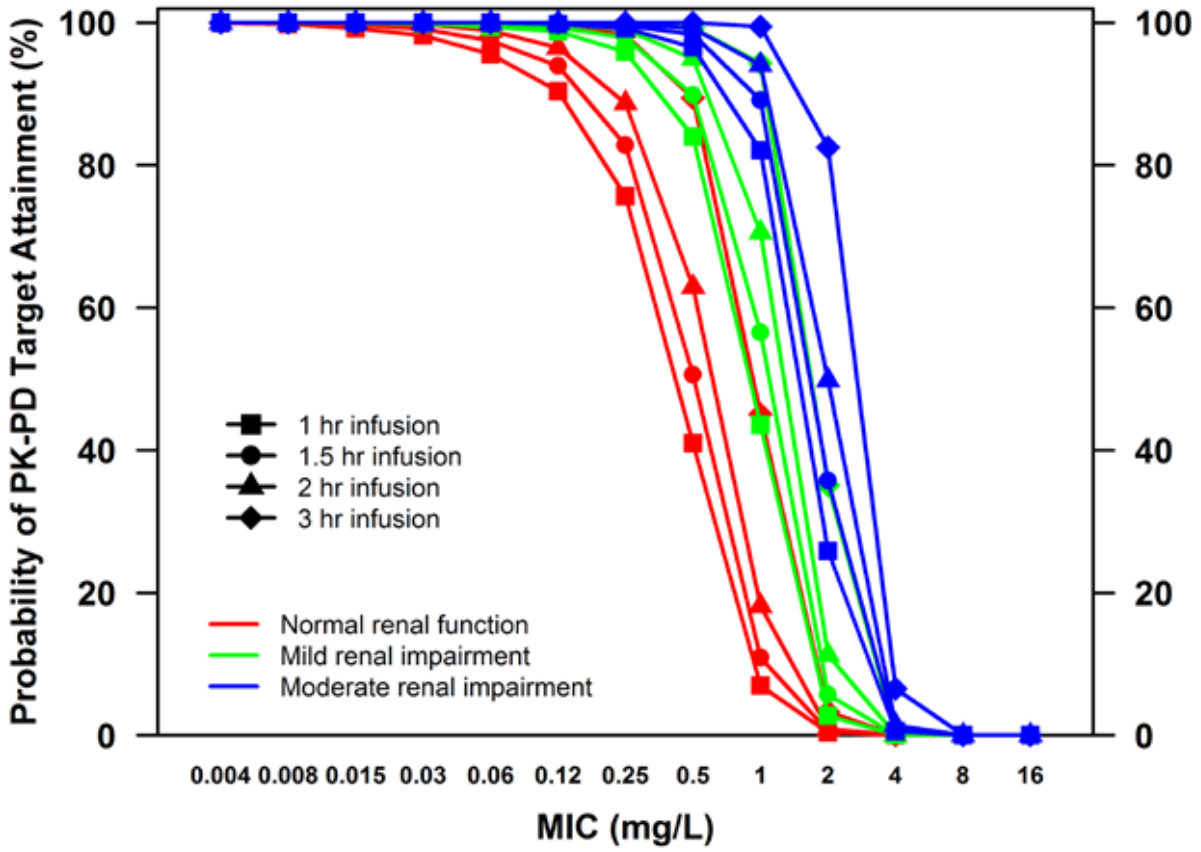
The column labelled '%MIC coverage with serum exposure at given concentration' can also be viewed as a graph**.** The extent to which serum exposure, which can also be read off the x-axis, exceeds the MIC_{90} (0.06 µg/mL) or $MIC_{99.8}$ (0.25 µg/mL) for all potential organisms, the worst case scenario, is displayed in figure 3.

Figure 3. Percentage of Pathogens Associated with UTI at a Given MIC



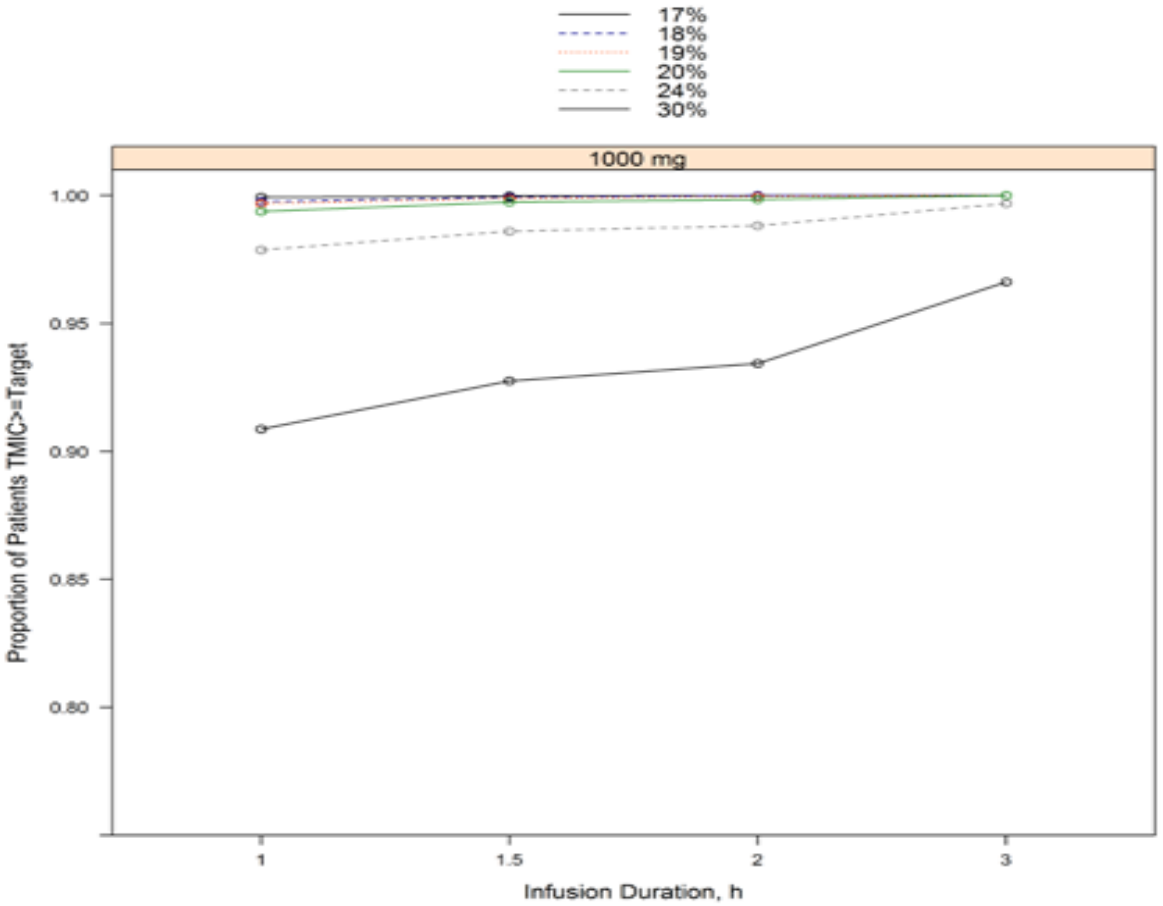
Monte Carlo modelling then allows us to examine different %Time>MIC scenarios for target attainment using actual PK from the phase 1 studies. Iterum is presently collecting data from a phase 1 study to confirm the anticipated PK of the oral formulations, building on data collected by the previous sponsor. We do, however, have data from the IV studies that allows us to run Monte Carlo simulations on proposed IV dosing regimens. Target attainment for one such regimen of 1000mg IV q24 hours infused over various durations using a T>MIC of 20% is displayed below (Figure 4).

Figure 4. Monte Carlo estimation of Probability of Target Attainment



If all organisms had an MIC of 0.25 µg/mL, one would expect nearly 100% target attainment with this dosing regimen. Alternatively, using various %T>MIC values and the actual distribution of MIC's for the organisms anticipated in these infections, target attainment >90% can be expected for all the scenarios studied (Figure 5).

Figure 5. Monte Carlo Estimation of the Probability of Target Attainment with Various %T>MIC



These analyses will be applied to the oral agent in order to optimize dosing in that setting.

Optimizing the dose is the first step in avoiding the possibility that under-dosing will encourage overgrowth of pathogens at the margin of those exposures. In other words, if exposures in the target tissue reach only 0.12 µg/mL, then there is the potential for organisms with MIC's of 0.25 µg/mL or greater to persist and either colonize the patient or contribute to the underlying infection. Given the modelling work above, we do not anticipate that such a scenario will occur with sulopenem, just as it has not occurred with the other carbapenems.

It's worth noting that, like ertapenem, sulopenem does not have activity against Pseudomonas, Acinetobacter, Stenotrophomonas and some other non-fermenters. As a result we do not expect that sulopenem will exert any significant pressure on pre-existing carbapenem resistance in those organisms. Overgrowth is certainly possible, as it is with any antibiotic that does not cover a particular part of the flora, but this will not influence carbapenem resistance, per se, and any organisms which persist should retain their original susceptibility to the other carbapenems. It is also worth noting that since sulopenem is not active against CRE organisms, it will produce no pressure to select for organisms resistant to the new carbapenemase inhibitor combinations, such as ceftazidime-avibactam, therefore not impacting the utility of this new 'last line of defense.'

Define the appropriate patient population

One of the critical components of the broader stewardship strategy to avoid the inadvertent development of antibiotic resistance is the development of 'evidence-based optimal standards for routine antimicrobial use [Ashiru-Oredope].' Iterum plans on defining the patient population

where the medical need is greatest and, after consultations with global regulatory bodies, executing phase 3 clinical studies that will inform the practitioner as to how to best use sulopenem.

The medical need for sulopenem is driven by the lack of good empiric options for treatment of infections impacted by the growing rate of ESBL and quinolone resistance among Enterobacteriaceae. Resistance is especially problematic among the urinary tract pathogens, making empiric treatment of these infections very challenging. As noted recently in JAMA 'Even uncomplicated cystitis in adults is increasingly difficult to treat, requiring individualized assessment of risk factors for resistant uropathogens and acceptance of potentially reduced clinical efficacy of empirical regimens [Grigoryan].' The focus of sulopenem development will therefore be in complicated and uncomplicated urinary tract infections. The inclusion and exclusion criteria define the patients in whom benefit has been established and safety data collections will inform any needed adjustments to dose or patient populations.

Reduction in the use of other classes of agents, such as β-lactams and quinolones, due to resistance is driving an increase in use of existing carbapenems. The selection of resistance by either the oral or IV use of sulopenem in complicated UTI is not expected to be significant, relative to that generated by the anticipated increasing use of existing carbapenems, for two reasons. First, as sulopenem is very similar to ertapenem, but will be introduced at branded pricing in the US and Europe, it seems that its use relative to other carbapenems will be limited on economic grounds due to formulary restrictions and primarily be attractive to those practitioners who like to treat an infection with both an IV and oral agent of the same molecule. Secondly, the step down from IV therapy to sulopenem is most likely to come from patients who have previously been exposed to a carbapenem, either initially as part of the empiric therapy or after the cultures confirm the need to switch to this class. If that is the case, no new selective pressure is anticipated to occur. Step down therapy is also a hallmark of good stewardship as it allows patients to be discharged from the hospital environment and neither be further exposed, nor contribute to, the pool of resistant pathogens. With regard to the hospital setting, it should also be noted that sulopenem will not be indicated for empiric treatment of hospital-acquired or ventilator-associated pneumonia, given that, like ertapenem, it does not cover Pseudomonas or MRSA. Since the ICU is the most common source of CRE, no further selection pressure on the flora of the ICU should occur due to sulopenem. Overall, no new pressure on the flora should occur in the hospital or step down environment.

Selection for resistance is likely to be limited in the outpatient setting as well. Treatment of uncomplicated UTI is very sensitive to cost pressures. Cultures, for example, are not taken prior to initiation of treatment, consistent with IDSA guidelines, because it adds to the cost of care as well as the inconvenience. It is very likely that physicians will prescribe a typical generic antibiotic and expect that, if bacterial clearance has not occurred and symptoms persist, they can move to another generic agent. Given the availability of low cost generics in this price sensitive environment, the use of sulopenem is likely to be as a second or, more likely, a third line of treatment, reserved for patients who do not respond to older agents. Based on our analysis of AMR data, the percent of patients receiving third line therapy is approximately 1-2% of the total uUTI patient population [data on file]. The medical need in uUTI, however, is not limited to third line treatment of persistent infections resistant to existing classes of antibiotics. There are patients who have, for example, significant comorbidities such as Diabetes mellitus, for whom repeated and persistent cystitis increases the risk that they will progress to more significant disease, including pyelonephritis, or creates a situation in which their underlying comorbidity

becomes more difficult to manage. These patients are likely to have access to relatively more expensive agents such as sulopenem, sooner than third line. If even a small fraction of these patients, however, can avoid hospitalization and prolonged exposure to intravenous carbapenems, again, a reduction in the overall selective pressure within the hospital can be expected. We estimate that these patients represent another 1-2% of the uUTI population. Overall, the use of sulopenem in the outpatient setting is expected, both on the basis of medical need as well as cost constraints, to represent a small increase in the overall exposure of patients to the penem class.

Monitoring for the effect on the bacterial population

As part of the development program, Iterum will sponsor yearly national surveillance studies on the susceptibility of key pathogens to sulopenem in various patient populations. These studies provide practitioners with the data they need to decide on the appropriateness of empiric therapy with sulopenem and these data will be made public in the form of presentations at scientific meetings and publications in the scientific literature. Iterum will endeavor to support those medical education opportunities that can disseminate the data to the target audiences. In parallel, Iterum plans to partner with the Centers for Disease Control and participate in its initiatives directed at limiting antimicrobial resistance such as the "National Strategy to Combat Antimicrobial Resistance" and "Get Smart: Know when antibiotics work".

In addition to data collected and summarized at a national level, we will also work to collect resistance data at the local level, specifically down to the zip code. This kind of information, for example on the rates of ESBL and quinolone resistance in *E. coli* taken from local outpatient cultures, will further enable clinicians to understand the likelihood of microbiologic success in the treatment of uUTI's in their own geographic region with existing generic antibiotics but, just as importantly, help insure that sulopenem is introduced into those areas where the medical need, as defined specifically by the rates of multi-drug resistance, is highest. Similar types of studies have been done in Europe based on other geographic criteria (Galvin). Wherever possible we will look to partner with organizations that can perform this kind of testing locally. Resistance testing and reporting is an essential part of antibiotic stewardship and Iterum is committed to ensuring that the introduction of sulopenem takes advantage of all the potential opportunities to focus its use where it will do the most good.

Other points to consider

An additional challenge facing the introduction of a penem relates to the complexities of manufacturing, summarized recently by the CMC staff from Pfizer [Pfizer CMC presentation]. Penems, as members of the family of β-lactams, require a separate facility for API production, for IV vial manufacture as well as for tableting. As a consequence, a pharmaceutical company with an interest in developing a penem, even if they presently manufacture penicillins or cephalosporins, must invest heavily and up front in equipment and physical facilities which are segregated from other production lines. Given the cost of the raw materials, the requirement for sterile intermediates and the number of steps in the synthetic process, the cost of goods initially is quite significant. Early first runs of commercial and registration batches are equally as expensive and costs will not approach the range seen with generic drugs until volumes reach beyond 5 metric tons, an amount that presently exceeds the base case market projections. Initially it will cost > $40,000 to produce one kilogram of sulopenem API, as outlined in Table 7, below.

Table 7. Rough Estimate of the Cost of One kilogram of CP-70,429 (Sulopenem)

Estimated Raw Starting Material Costs			
Compound	**$/batch**	**batch scale**	**$/kg**
A	$ 130,000	770	169
B	$ 752,560	980	768
C	$ 882,560	980	900
D	$ 106,250	8.5	12,500
E	$ 21,000	4.2	5,000
F	$ 28,900	3.4	8,500
G	$ 623,650	350	1,782
H	$ 211,850	50	4,237
Estimated cost contribution to 1kg API of CP-70429			
Compound		**kg**	**$**
C		10.3	9,276
G		4.5	8,018
D		0.109	1,366
E		0.054	270
F		0.044	372
Manufacturing cost of CP-70429 from C		1.0	24,840
Total		**1.0**	**$ 44,142**

Over time it is anticipated that cost of goods will come down but these compounds will always be more expensive to manufacture than antibiotics in other classes. Coupled with the complexity of production, the number of manufacturers interested in this business is expected to be limited.

Indirectly, another factor related to cost which will influence its uptake, and therefore the proportion of its use relative to the class as a whole, is the initial pricing of the sulopenem, expected to be consistent with other branded agents. As is typical for new agents, formulary restrictions are likely to be put in place by hospitals and medical reimbursement plans, in the US and Europe. In other areas of the world, the initial cost of goods and other societal restrictions will also limit its introduction.

Probenecid, co-administered with the oral prodrug, is known to reduce renal clearance and increase systemic exposure of the active moiety, sulopenem, allowing for an improved %T>MIC with a reduction in the amount of administered prodrug. For patients, this will mean enhanced efficacy and reduced exposure in gastrointestinal tract limiting GI adverse events. A related consequence is the added advantage of decreasing the total environmental exposure to sulopenem, thus decreasing any impact on organisms present in the environment, that harbor carbapenem resistance determinants.

In summary, the sulopenem clinical program will follow essential practices consistent with good antibiotic stewardship in order to avoid any unintended antibacterial resistance which could limit the utility of carbapenems as a class. This will be accomplished by optimizing the dose in the intended patient population, providing the essential clinical trial data to build an evidence base to support its use and monitoring the bacterial environment for any changes in susceptibility to the class.

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