SPR994: Oral Carbapenem for the Treatment of Complicated Urinary Tract Infections

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Disclosure: Dr. Jain is a full-time employee of Spero Therapeutics

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UTI Isolates of *E. coli* from USA are Increasingly Resistant to Oral Antibiotics (SENTRY USA, 2017)

<table>
<thead>
<tr>
<th>Agent</th>
<th>MIC (µg/mL)</th>
<th>%S</th>
<th>%I</th>
<th>%R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤0.03 - &gt;4</td>
<td>&gt;4</td>
<td>73.9</td>
<td>25.8</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>≤0.03 - &gt;16</td>
<td>&gt;16</td>
<td>74.2</td>
<td>24.3</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>≤0.5 - &gt;8</td>
<td>&gt;8</td>
<td>67.9</td>
<td>32.1</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>≤0.12 - &gt;64</td>
<td>&gt;64</td>
<td>63.2</td>
<td>15.9</td>
</tr>
<tr>
<td>Doripenem</td>
<td>≤0.06 - 1</td>
<td>≤0.06</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≤0.008 - 2</td>
<td>0.03</td>
<td>99.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤0.12 - 1</td>
<td>0.25</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤0.015 - 1</td>
<td>0.03</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>


Critchley et al. ASM 2019, Poster AAR-602
ESBL-producing UTI *E. coli* from USA Exhibit Co-Resistance to Oral Antibiotics (SENTRY USA, 2017)

![Bar chart showing percent resistant to various antibiotics. Cefuroxime is 93.6%, Ciprofloxacin 71.8%, Levofoxacin 67.9%, TMP-SMX 59.2%, Cefepine 56.1%, Ceftazidine 54.4%, Pip-Tazo 4.5%, Ertapenem 1.4%, Doripenem 0%, Imipenem 0%, Meropenem 0%. Only the carbapenems retain activity.](image-url)
Management of cUTIs caused by ESBL-producing Pathogens

Problem
• Eroding utility of oral antibiotics
• Triple Resistance; *You Lose One, You Lose All*
• Agents that retain activity are IV administered

Impact
• Limited treatment options for patients and treatment providers outside the walls of hospital
  • *Stay in Hospital*
  • *Go to Hospital*

Opportunity
• Oral agent with the activity of IV Carbapenem
• New treatment option
  • *Go Home*
  • *Stay Home*
SPR994: Oral Carbapenem

**Oral pro-drug of Tebipenem**
- ~60% oral bioavailability

**Expected properties of a Carbapenem**
- **Mode of action**: cell wall biosynthesis inhibitor; primarily targets PBP2
- **Spectrum**: Enterobacteriaceae (ESBL, AmpC, FQ-R), Gram + (No MRSA)
- **PD**: Time dependent antimicrobial effect
- **Safety**: Consistent with iv carbapenems

**10 years of prior clinical experience in Japan**
- Orapenem® fine granules for pediatric respiratory tract infections (Meiji)

**In Phase 3 trial for cUTI (ADAPT-PO)**
- Head to head comparison of oral SPR994 vs. iv ertapenem
- Dose linear PK and well-tolerated at predicted therapeutic dose x14 days (Phase 1 trial)
- Dosing regimen (600 mg PO q8h) chosen to match the PD efficacy of iv carbapenems
MIC distribution: Tebipenem vs. Meropenem
Predominant cUTI pathogens

E. coli (N = 101)

K. pneumoniae (N = 208)
In Vivo Efficacy: Oral SPR994 vs. IV Meropenem
E. coli (CTX-M-15) in Murine Thigh Infection model

<table>
<thead>
<tr>
<th>Agent</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBP</td>
<td>0.03</td>
</tr>
<tr>
<td>MEM</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Corbett et al. ASM Microbe 2018, Poster 564**
ADME Properties

SPR994
TBPM-PI-HBr
(oral prodrug)

Tebipenem
(parent drug)

~60% Oral Bioavailability
Half life of ~1hour
Renally excreted
Plasma protein binding 45%
Low potential for DDIs

Oral Absorption
SPR994-101: Phase 1 SAD/MAD Study

Key Objective: To establish the safety, tolerability and PK (including Food Effect) of SPR994 following administration of single and multiple ascending doses in healthy volunteers
Dose linear PK and No Food Effect at Predicted Therapeutic Dose

Plasma PK of Tebipenem following single ascending doses of of SPR994 (fasted)

Plasma PK of Tebipenem following 600mg dose of SPR994 in fasted vs. fed state

Eckburg et al. ASM 2019, Poster 779
Plasma and Urine Levels at Predicted Therapeutic Dose Adequately Cover Predominant UTI pathogens

Free Plasma Concentration of Tebipenem (600mg MAD Day 1)  
Urine Concentration of Tebipenem (600mg MAD Day 1)

Eckburg et al. ASM 2019, Poster 779
SPR994 is Well-tolerated in Healthy Adult Subjects at Predicted Therapeutic Dose

Well tolerated in single or multiple doses
- No SAEs or deaths
- No severe TEAEs
- No premature discontinuation of IP

GI events were most common category of TEAEs
- Typically single episodes of loose stool (diarrhea) on Day 1; all self-resolved despite continued TID dosing x 14 days
- No cases of *C. difficile* infection
- No TEAEs of vomiting; 1 case of mild nausea

Elevations in serum aminotransferases uncommon
- 3 SPR994-treated subjects had TEAEs of asymptomatic increase of ALT (2 mild, 1 moderate)
- No premature discontinuation of IP
- No case met Hy’s law

Eckburg et al. ASM 2019, Poster 779
Safety Profile Consistent with Clinical Experience in Japan

• **Meiji evaluated safety in nearly 1,200 subjects for NDA**
  – 496 adult subjects across 5 trials (Phase 2 and Phase 3, including 2 open label cUTI trials)
  – 245 adult subjects across 12 Phase 1 trials
  – 440 pediatric subjects across 6 trials (including a pivotal double-blind, comparator-controlled Ph3 trial)

• **Meiji Post marketing safety surveillance (>3,500 patients)**
  – No specific concern has been raised in Spero studies in comparison to existing Meiji experience in > 3,500 Japanese people
Phase 3 Dose Selection

Key Objective: To identify a therapeutic dose and dosing regimen for oral SPR994 with high probability of target attainment against predominant cUTI pathogens
Phase 3 Dose Selection Approach

**Pop PK model**
- PK from SPR994-101 Phase 1 study

**PD assessment**
- Mouse neutropenic thigh model and hollow fiber infection model (HFIM)
- Assessed across wild-type strains and ESBL producing pathogens
- $f_AUC/MIC \times 1/\tau$ best expresses the time dependent PD
- Resulting target of $f_{AUC0-8ss}/MIC > 23$ – stasis in mouse and bacterial killing in HFIM

**PTA analysis**
- Simulation of 5,000 patients
- Inflated variance on clearance
- MIC distribution against *E. coli* and *K. pneumoniae*

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1 Das et al. ECCMID 2019, Poster 1950, 2 McEntee et al. AAC, May 2019, accepted online, 3 Lakota et al. ICPD, ID Week 2017, Poster 831
SPR994 Predicted Human Exposures Achieve Non-clinical Targets for Bacterial Killing

Human $fAUC_{0-8\,ss}/MIC$

\[
\text{Log}_{10}\text{CFU/g thigh} = fAUC:MIC*1/\tau
\]

- ESBL negative
- ESBL positive
Probability of Target Attainment: Oral SPR994 vs. IV Ertapenem

SPR994 600mg po q8h

Ertapenem 1g iv q24h

Das et al. ECCMID 2019, Poster 1950, McEntee et al. ECCMID 2019, Poster 7676
ADAPT-PO Single Phase 3 Study to Demonstrate Oral-IV Equivalency and Support Approval

**Screening**
- Patients ≥ 18 years with cUTI / AP
- 1:1 Randomization Double-blind, double-dummy
  - N=1,200
  - 10% NI margin
- Stratified by age and type of infection (pyelonephritis vs. complicated lower tract UTI)

**Phase 3 with lead-in PK**
- Up to 10 days total therapy
- **SPR994 600 mg TiD + placebo IV**
- Lead-in PK* to confirm dose n=70
- **Ertapenem IV + placebo oral**

**Follow-Up**
- TOC: Test-of-Cure Visit
- LFU: Long-term Follow-up Visit
  - 19 ± 2 days from 1st dose of study drug
  - 25 ± 2 days from 1st dose of study drug

* Masked individual and composite PK data will be reviewed by an IDMC after enrolling the first 70 patients to confirm the SPR994 dose; trial will remain blinded.
Summary

Unmet need for an ORAL agent with potency of IV carbapenem

- Eroding efficacy of oral options due to increasing resistance and co-resistance

SPR994 has potential to provide a new option for resistant UTI patients who do not require hospitalization

- Oral Carbapenem with ~60% Bioavailability
- MoA, Spectrum, PD and Safety as expected for a Carbapenem
- Currently In Phase 3 trial for cUTI (ADAPT-PO)

Phase 3 dosing regimen and trial design aim to directly address equivalency of an ORAL Carbapenem to IV Carbapenem
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• JMI Labs
• Meiji Seika Pharma Co., Ltd
• SPR994 Posters at ASM 2019: Poster # 602, 776, 777, 778, 779

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Back-up Slides