Solithromycin for the Treatment of Tularemia

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Objective: Solithromycin (SOLI), a novel fluoroquinolone, is in Phase 3 clinical development for community-acquired bacterial pneumonia (CABP) and uncomplicated gonococcal infections in adults, and is being developed for both oral and intravenous (IV) use. Through an ongoing partnership with BARDA, Cempra is developing SOLI for use in pediatric populations, including for the treatment of infections by biothreat pathogens such as Francisella tularensis. In this study, the efficacy of SOLI treatment after onset of pneumonic tularemia disease was evaluated in cynomolgus macaques (CM).

Methods: CMs were challenged with an aerosolized target exposure of 1000 LD50 [1000 cfu F. tularensis (Schu S4) bacteria/animal] and monitored by telemetry for signs of infection. Sustained increase in body temperature (1.5°C for 4 hours) was used as a trigger to initiate treatments. Within 6 hours of trigger, SOLI-treated animals were administered a humanized dosage regimen designed to mimic human exposures achieved with the oral CABP regimen (800 mg loading dose, 400 mg maintenance dose). Due to species-specific differences in metabolism and clearance by the oral route but not by the IV route, SOLI was administered by IV infusion four times daily for up to 17 days. Challenge group A animals were euthanized the day following cessation of treatments and assessed for tissue pathogen load. Challenge group B animals were observed for 10 days post-treatment for signs of recovery.

Results: Six of the seven vehicle-treated control animals succumbed 5-8 days post-challenge. None of the eight SOLI-treated animals exhibited signs of tularemia after treatment, and none of the four SOLI-treated animals observed for 10 days post-treatment relapsed. All tissues and terminal blood samples collected from SOLI-treated animals were negative for viable F. tularensis bacteria. Consistent with observations of apparent microbiological cure, gross pathology findings indicated SOLI was effective in inhibiting and limiting pulmonary and systemic tularemia infection.

Conclusion: Solithromycin was curative in the NHP model for pneumonic tularemia.

### Background

- **Solithromycin (SOLI)**, a 4th generation macrolide and the 1st fluoroketolide, is in Phase 3 clinical development for community-acquired bacterial pneumonia (CABP), and is being developed for both oral (capsule and suspension) and intravenous (IV) use. In addition, Cempra is developing SOLI for the treatment (Tx) of pneumonic tularemia.

- **Francisella tularensis**, the causative agent of tularemia, is a fastidious, facultative intracellular gram-negative bacterium.

- **F. tularensis isolates** are often resistant to penicillins, cephalosporins, carbapenems, and macrolides; however, SOLI has been shown to be active against F. tularensis in vitro (MIC ≤ 0.008-4; MIC50/90 = 0.03/2), and has been shown to concentrate in macrophages and pulmonary tissues, which enhances its therapeutic potential.

- In this study, SOLI was evaluated in a Tx model of F. tularensis-infected CMs using a humanized dose regimen that mimics exposures in humans administered the oral CABP regimen (800 mg on Day 1 followed by 400 mg PO once daily Days 2-5). This regimen was found to be non-toxic to the standard-of-care comparator moxifloxacin in a Phase 3 CABP trial.

- IV dosing was chosen as the degree of metabolism with nonhuman primate (NHP) IV dosing is similar to that of humans following PO administration. Since NHPs clear SOLI more rapidly than humans, multiple daily NHP IV doses were needed to achieve similar PK profiles to those achieved in humans after once-daily PO dosing (Figure 1).

- **Aerosol Challenge**: On Study Day 0, CMs were challenged with a target dose of 1000 cfu F. tularensis (1000X LD50). SOLI dosing was started 1 hour after the challenge exposure. Infusions were given four times daily for 17 days (21 mg/kg IV on Day 1, 10 mg/kg PO once daily Days 2-5).

- **Assessments**: Challenge strain MIC analysis, cage-side clinical observations, blood culture, bacterial tissue assessment, clinical chemistry and hematology, formulation analysis, bioanalysis, population PK analysis, gross necropsy and histopathology on select tissues.

### Materials and Methods

- **Strain Source**: *F. tularensis* S4 variant (ATCC 28534).

- **Experimental Test System**: Cambodian origin CMs (Macaca fascicularis) with surgically implanted T34 telemetry telemetry and indwelling venous catheters inserted into the right femoral vein. CMs were randomly assigned to one of two aerosol challenge days, then randomized by sex and weight into vehicle or SOLI Tx groups.

### Table 1. Original Study Design

<table>
<thead>
<tr>
<th>Group</th>
<th>Study Design</th>
<th>Material</th>
<th>Route</th>
<th>Time Duration</th>
<th>Post Tx</th>
<th>Tx Duration</th>
<th>Observation Period</th>
<th>Tx</th>
<th>N (1M:1F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>SOLI (800/400)</td>
<td>IV</td>
<td>1000X LD50</td>
<td>2 (1M:1F)</td>
<td>4 (2M:2F)</td>
<td>10/11/21</td>
<td>12/3/21</td>
<td>1-8</td>
<td>8 (4M:4F)</td>
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</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Vehicle</th>
<th>Solithromycin</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presented Dose (cfu)</td>
<td>451</td>
<td>271-680</td>
<td>448</td>
</tr>
<tr>
<td>Time to Fever (h)</td>
<td>57</td>
<td>53-60</td>
<td>54</td>
</tr>
<tr>
<td>Time from Trigger to Tx (h:mm)</td>
<td>1:51</td>
<td>0:20-5:40</td>
<td>1:43</td>
</tr>
</tbody>
</table>

**Clinical Observations after Initiation of Treatment**

- **Vehicle-treated animals demonstrated signs of disease** (dry cough, hyperventilation, hunched posture, loss of appetite). Prior to euthanasia, animals progressed to a state of extreme weakness and a few of the animals demonstrated signs of respiratory distress.

- **Solithromycin-treated animals did not display signs consistent with pneumonic tularemia.**

### Survival

- **85.7%** (67%) of vehicle-treated animals were euthanized on study days 5-8. One control animal survived to Study Day 25.

- **100%** (8/8) of cynomolgus macaques treated with solithromycin survived *F. tularensis* challenge.

### Blood Culture Results

- **6 of 7** vehicle-treated animals had positive blood cultures prior to or on the day of death, indicating that the animal was infected 24-48 hr prior to death.

### Tissue Burden Results

- **All 7** vehicle-treated animals had positive cultures for lung and tracheobronchial/medesenteric lymph nodes. Five animals showed signs of hematogenous dissemination to the spleen, liver, and kidneys, of which four additionally had positive brain cultures.

- **No bacteria were detected in any of the tissues collected from 8 SOLI-treated animals, including the animal that had detectable bacteremia on Day 4.**

### Other Results

- **Solithromycin administered in an IV regimen corresponding to 800 mg on Day 1 followed by 400 mg PO once daily protected all CMs from death due to F. tularensis infection.**

- **Solithromycin inhibited and limited pulmonary and systemic infection with F. tularensis.** No bacteria were detected in any of the tissues collected from SOLI-treated animals.

- **Future studies with solithromycin are warranted to confirm the efficacy seen in this study, utilizing either a shorter Tx duration and/or an oral dose regimen, given the complications encountered with the use of indwelling catheters.**

### Conclusions

- **Solithromycin administered in an IV regimen corresponding to clinical doses of 800 mg on Day 1 followed by 400 mg PO once daily protected all CMs from death due to F. tularensis infection.**

- **Solithromycin inhibited and limited pulmonary and systemic infection with F. tularensis.** No bacteria were detected in any of the tissues collected from SOLI-treated animals.

- **Future studies with solithromycin are warranted to confirm the efficacy seen in this study, utilizing either a shorter Tx duration and/or an oral dose regimen, given the complications encountered with the use of indwelling catheters.**

### Acknowledgements

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