FDA Introductory Remarks

NDA 209006 Solithromycin Capsules
NDA 209007 Solithromycin Injection

Antimicrobial Drugs Advisory Committee Meeting
November 4, 2016

Sumati Nambiar MD MPH
Director, Division of Anti-Infective Products
Introduction

• NDAs 209006 and 209007: Solithromycin capsules and injection
• Applicant: Cempra Pharmaceuticals, Inc.
• NDAs granted priority review as the product has (Qualified Infectious Diseases Product) QIDP designation
• Proposed Indication:
  – Treatment of community acquired bacterial pneumonia (CABP) caused by *S. pneumoniae, H. influenzae, M. catarrhalis*, methicillin-susceptible *S. aureus, L. pneumophila* and *M. pneumoniae* in patients ≥ 18 years of age
• Proposed Dosing Regimens:
  – Oral only: 800 mg once on day 1, followed by 400 mg once daily on days 2-5
  – Intravenous (IV) only: 400 mg once a day for 7 days
  – IV to oral switch: Loading dose of 800 mg orally, followed by 400 mg orally once daily to complete the 7-day course
Development Program

• One Phase 2 trial and two Phase 3 trials were conducted in patients with CABP
• The Phase 2 trial was a randomized, double-blind trial comparing oral solithromycin to oral levofloxacin in 132 patients
• The co-primary efficacy outcomes were investigator-assessment of clinical response at Test of Cure (TOC) in the Intent-to-Treat (ITT) and Clinically Evaluable (CE) populations
• Clinical Success:
  – ITT population: 84.6% in the solithromycin arm and 86.5% in the levofloxacin arm
  – CE population: 83.6% in the solithromycin arm and 93.1% in the levofloxacin arm
Development Program: Phase 3 trials

- Two randomized, double-blind, noninferiority trials comparing solithromycin to moxifloxacin; pre-specified noninferiority (NI) margin of 10%.
- Study CE01-300 evaluated a 5-day oral solithromycin regimen and Study CE01-301 a 7-day IV to oral solithromycin regimen.
- The primary efficacy endpoint was Early Clinical Response (ECR) based on the symptoms of cough, dyspnea, chest pain, and sputum production 72 (60-108) hours after initiation of treatment.
- A responder for the primary endpoint should have met the following criteria:
  - improvement from baseline in at least 2 out of the 4 symptoms
  - no worsening of other symptoms
  - had not received an antibacterial drug for CABP from the first dose of study drug during the first 108 hours
  - alive through the late follow-up visit 28-35 days after the first dose of study drug
Efficacy Results: Phase 3 trials

- Both trials met the pre-specified NI margin of 10% for the primary endpoint of ECR
- Study CE01-300:
  - Responder rates were 78.2% in the solithromycin arm and 77.9% in the moxifloxacin arm; treatment difference of 0.3% (95% CI -5.5% to 6.1%)
- Study CE01-301:
  - Responder rates were 79.3% in the solithromycin arm and 79.7% in the moxifloxacin arm; treatment difference of -0.5% (95% CI -6.1% to 5.2%)
  - Numerical increase in rates of investigator-assessed clinical failure at the Short-term Follow Up (SFU) visit, 5-10 days after End of Therapy (EOT), in the solithromycin arm compared to the moxifloxacin arm
Safety Assessment

• Safety database of 920 patients at the proposed dose and duration
• Hepatotoxicity
  – In studies CE01-300 and CE01-301, incidence of ALT elevations was higher in solithromycin-treated patients compared to moxifloxacin-treated patients; this difference was more pronounced in Study CE01-301
  – No cases of Hy’s law were seen
  – ALT elevation was also seen in the COPD and NASH trials
  – One case of clinical hepatitis associated with eosinophilia was reported in the COPD trial
• Intravenous site reactions: Reported in ~31% of solithromycin recipients and in ~5% of moxifloxacin recipients
• Ketolide class adverse events:
  – No obvious signal for visual adverse effects identified so far; some reports of visual adverse reactions (blurry vision, tired eyes, black spots)
  – Patients with history of myasthenia gravis were excluded
Key Topic Areas

• Efficacy
  – In Study CE01-301, investigator assessed clinical failures were more common in the solithromycin arm at the SFU visit (5-10 days after EOT)
  – Limited clinical data are available in patients with CABP due to macrolide-resistant *S. pneumoniae*

• Safety
  – Hepatotoxicity was seen in the CABP trials; frequency of ALT elevations was higher in the solithromycin arm than in the moxifloxacin arm
  – Hepatotoxicity was also seen in the COPD trial, including a case of clinical hepatitis, as well as in the NASH trial
  – Exposure-response was seen for hepatotoxicity (AUC and ALT elevations)
  – Infusion site reactions

• Dosing Regimen
  – Proposed loading dose at the time of IV to oral switch
Outline for the Day

• Presentations by the Applicant
• Presentations by the FDA
  – Daniel Rubin, PhD: Efficacy
  – Ramya Gopinath, MD: Safety
  – Yongheng Zhang, PhD: Clinical Pharmacology
• Clarifying questions
• Lunch
• Open Public Hearing
• Questions for the committee
Question 1

• Has the Applicant provided substantial evidence of the efficacy of solithromycin for the treatment of community acquired bacterial pneumonia (CABP)?
  – If yes, please provide any recommendations for labeling.
  – If no, please discuss additional studies/analyses that are needed.
Question 2

• Has the risk of hepatotoxicity with solithromycin been adequately characterized?
  – If yes, please provide any recommendations for labeling.
  – If no, please discuss additional studies that are needed to further characterize the risk.
Question 3

• Do the efficacy results of solithromycin for the treatment of CABP, outweigh the risks including hepatotoxicity?
  – If yes, please provide any recommendations for labeling.
  – If no, please discuss additional studies/analyses that are needed.
Presentation of Clinical Efficacy

Antimicrobial Drugs Advisory Committee Meeting
November 4, 2016

Daniel Rubin, PhD
Statistical Reviewer
Division of Biometrics IV, Office of Biostatistics,
Office of Translational Sciences, CDER, FDA
Outline

• Phase 3 trial designs

• Study populations

• Efficacy results

• Efficacy conclusions
Phase 3 Trial Designs

- Randomized, active controlled, double blind, non-inferiority trials comparing solithromycin versus moxifloxacin

**Oral Study 300**
- NCT01756339
- Solithromycin 800 mg day 1
- Solithromycin 400 mg days 2-5
- N = 426

**Moxifloxacin 400 mg days 1-7**
- N = 434

**IV-to-oral Study 301**
- NCT01968733
- Solithromycin 400 mg IV days 1-7
- For IV to oral switch, 800 mg x 1, then 400 mg PO to complete 7 days
- N = 434

**Moxifloxacin 400 mg IV days 1-7**
- For IV to oral switch, 400 mg PO to complete 7 days
- N = 429

- Design principles were consistent with the current FDA draft guidance for community-acquired bacterial pneumonia (CABP) [link](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm123686.pdf)
Phase 3 Trial Designs

• Key inclusion criteria: Adults ≥18 years old, CABP diagnosed with signs, symptoms, and radiographic evidence

• Key exclusion criteria: renal failure, severe hepatic impairment, myasthenia gravis, previous hypersensitivity to macrolides, QT prolongation or QT-prolonging drugs

• Enrollment restrictions:
  – At most 25% of subjects could have a single dose of a short-acting prior antibacterial CABP treatment
  – Pneumonia Patient Outcomes Research Team (PORT) Risk Class II-IV, with Risk Class II subjects limited to 50% of Oral Study 300 and 25% of IV-to-oral Study 301
  – At most 80% of enrolled subjects could be <65 years old
  – Enrollment target of ≤75% of subjects outside North America. [Target not achieved in IV-to-oral Study 301.]
Primary Efficacy Endpoint

• Early clinical response (ECR) at the 72 (-12/+36) hour visit:
  – Improvement from baseline on ≥2 of the 4 symptoms of cough, dyspnea, chest pain, and sputum production
  – Symptoms were scored as absent, mild, moderate, or severe
  – No worsening from baseline on any of the 4 symptoms at ECR visit
  – No receipt of an alternate CABP antibiotic during the first 108 hours (4.5 days)
    [Criterion affected ≤4% of subjects in each arm of each trial.]
  – Survival through the late follow-up visit on Day 28-35
    [Criterion affected ≤2% of subjects in each arm of each trial.]

This endpoint was consistent with the FDA draft guidance and was based on recommendations from the Foundations for the National Institutes of Health
Important Secondary Endpoints and Additional Pre-specified Endpoints

• Investigator assessed clinical response at the short-term follow-up (SFU) visit on Day 12-17

• Investigator assessed clinical response at the end of therapy (EOT) visit

• Early clinical response with improvement in vital signs at the 72 (-12/+36) hour visit

• Symptom response at the Day 12-17 visit: absence of chest pain and sputum production, and absence or improvement from baseline in cough and dyspnea

• Symptom response at both the 72 (-12/+36) hour visit and the Day 12-17 visit
Statistical Analysis

• Primary efficacy analysis for each Phase 3 trial:
  – Comparison of the (solithromycin – moxifloxacin) difference in early clinical response rates with a non-inferiority margin of 10% in the intent-to-treat (ITT) population of all randomized subjects

• Protocol-defined co-primary efficacy analysis from pooled trials:
  – Comparison of the (solithromycin – moxifloxacin) difference in early clinical response rates with a non-inferiority margin of 15% in the microbiological intent-to-treat (mITT) population
  – The mITT population included patients with a baseline pathogen in sputum, pleural fluid, bronchoalveolar lavage, blood, oropharyngeal and/or nasopharyngeal swabs identified with culture, urinary antigen test, serology, and/or unapproved molecular diagnostic assays (PCR)
  – Note: The mITT-2 population was a post-hoc analysis population and included baseline pathogens identified by culture or urinary antigen tests.
Trial Conduct

- There was approximately 3% missing or indeterminate data in each arm of each trial for the primary endpoint of early clinical response.
- The total premature subject withdrawal rate was approximately 5%.
- The total premature study drug discontinuation rate was approximately 8%. The most common reason was an adverse event.
- Protocol violations largely related to baseline covariate measurements and were unlikely to have changed overall conclusions.
- An audit from the Applicant found incomplete documentation for a study site in Russia and implausible drug concentrations from a study site in Bulgaria. Together the sites enrolled 30 subjects, but results are qualitatively unchanged if excluding these sites.
Baseline Demographics – ITT Population

Oral Study 300
(N = 860 total subjects)

IV-to-Oral Study 301
(N = 863 total subjects)
Region of Enrollment – ITT Population

Oral Study 300

IV-to-Oral Study 301

- Solithromycin
- Moxifloxacin

www.fda.gov
Baseline PORT Risk Class – ITT Population

Oral Study 300

IV-to-Oral Study 301

Solithromycin
Moxifloxacin
Baseline Characteristics – ITT Population

Oral Study 300

IV-to-Oral Study 301

Prior Abx therapy
CrCl < 50 mL/min
Multilobar pneumonia
Asthma or COPD

Prior Abx therapy
CrCl < 50 mL/min
Multilobar pneumonia
Asthma or COPD

Solithromycin
Moxifloxacin
Baseline Symptoms – ITT Population

Oral Study 300

IV-to-Oral Study 301

0% 20% 40% 60% 80% 100%

Cough Dyspnea Chest pain Sputum production

Cough Dyspnea Chest pain Sputum production

Solithromycin Moxifloxacin
Baseline Pathogens – ITT Population

Oral Study 300

IV-to-Oral Study 301

- Solithromycin
- Moxifloxacin

Microbiological ITT
S. pneumoniae
H. influenzae
M. pneumoniae
L. pneumophila

S. pneumoniae
H. influenzae
M. pneumoniae
L. pneumophila
Primary efficacy analysis of Oral Study 300
– Early clinical response at 72 (-12/+36 hours)
– ITT population, 10% non-inferiority margin
– Solithromycin demonstrated non-inferiority

<table>
<thead>
<tr>
<th></th>
<th>Solithromycin (n = 426)</th>
<th>Moxifloxacin (n = 434)</th>
<th>Difference</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>333 (78.2%)</td>
<td>338 (77.9%)</td>
<td>0.3%</td>
<td>-5.5% to 6.1%</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>81 (19.0%)</td>
<td>84 (19.4%)</td>
<td>-0.3%</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>12 (2.8%)</td>
<td>12 (2.8%)</td>
<td>0.1%</td>
<td></td>
</tr>
</tbody>
</table>
Symptoms absent or improved from baseline at the early clinical response visit at 72 (-12/+36) hours in the ITT Population of Oral Study 300
Subgroup analysis of early clinical response at 72 (-12/+36) hours in the ITT population of Oral Study 300

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Solithromycin</th>
<th>Moxifloxacin</th>
<th>Difference</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior therapy</td>
<td>42/53 (79.2%)</td>
<td>32/44 (72.7%)</td>
<td>6.5%</td>
<td>-12.7% to 25.7%</td>
</tr>
<tr>
<td>No prior therapy</td>
<td>291/373 (78.0%)</td>
<td>306/390 (78.5%)</td>
<td>-0.4%</td>
<td>-6.6% to 5.7%</td>
</tr>
<tr>
<td>Microbiological ITT</td>
<td>176/235 (74.9%)</td>
<td>178/226 (78.8%)</td>
<td>-3.9%</td>
<td>-12.0% to 4.3%</td>
</tr>
<tr>
<td>Not in mITT</td>
<td>157/191 (82.2%)</td>
<td>160/208 (76.9%)</td>
<td>5.3%</td>
<td>-3.1% to 13.7%</td>
</tr>
<tr>
<td>Clinically evaluable</td>
<td>307/388 (79.1%)</td>
<td>311/390 (79.7%)</td>
<td>-0.6%</td>
<td>-6.6% to 5.3%</td>
</tr>
<tr>
<td>Not clinical evaluable</td>
<td>26/38 (68.4%)</td>
<td>27/44 (61.4%)</td>
<td>7.1%</td>
<td>-16.0% to 30.1%</td>
</tr>
<tr>
<td>PORT Risk Class II</td>
<td>168/213 (78.9%)</td>
<td>175/217 (80.6%)</td>
<td>-1.8%</td>
<td>-9.8% to 6.3%</td>
</tr>
<tr>
<td>PORT Risk Class III</td>
<td>128/168 (76.2%)</td>
<td>130/177 (73.4%)</td>
<td>2.7%</td>
<td>-7.0% to 12.5%</td>
</tr>
<tr>
<td>PORT Risk Class IV</td>
<td>37/45 (82.2%)</td>
<td>33/40 (82.5%)</td>
<td>-0.3%</td>
<td>-16.8% to 16.2%</td>
</tr>
</tbody>
</table>
Analysis of Additional Endpoints in the ITT Population of Oral Study 300

![Bar chart showing the comparison between Solithromycin and Moxifloxacin for different endpoints.](chart.png)
Estimated treatment differences and confidence intervals for additional endpoints in the ITT Population of Oral Study 300

Favors solithromycin

Favors moxifloxacin

solithromycin - moxifloxacin difference in success rates

-10% -8% -6% -4% -2% 0% 2% 4% 6% 8% 10%

ECR including vital signs
Symptom response at SFU
Sustained symptom response
Clinical response at EOT
Clinical response at SFU
Subgroup analysis of investigator assessed clinical success at SFU (Day 12-17) in the ITT population of Oral Study 300

<table>
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<tr>
<td>Prior therapy</td>
<td>42/53 (79.2%)</td>
<td>36/44 (81.8%)</td>
<td>-2.6%</td>
<td>-20.4% to 15.3%</td>
</tr>
<tr>
<td>No prior therapy</td>
<td>318/373 (85.3%)</td>
<td>340/390 (87.2%)</td>
<td>-1.9%</td>
<td>-7.1% to 3.2%</td>
</tr>
<tr>
<td>Microbiological ITT</td>
<td>197/235 (83.8%)</td>
<td>196/226 (86.7%)</td>
<td>-2.9%</td>
<td>-9.8% to 4.0%</td>
</tr>
<tr>
<td>Not in mITT</td>
<td>163/191 (85.3%)</td>
<td>180/208 (86.5%)</td>
<td>-1.2%</td>
<td>-8.5% to 6.1%</td>
</tr>
<tr>
<td>Clinically evaluable</td>
<td>342/388 (88.1%)</td>
<td>356/390 (91.3%)</td>
<td>-3.1%</td>
<td>-7.7% to 1.4%</td>
</tr>
<tr>
<td>Not clinical evaluable</td>
<td>18/38 (47.4%)</td>
<td>20/44 (45.5%)</td>
<td>1.9%</td>
<td>-21.6% to 25.5%</td>
</tr>
<tr>
<td>PORT Risk Class II</td>
<td>183/213 (85.9%)</td>
<td>193/217 (88.9%)</td>
<td>-3.0%</td>
<td>-9.8% to 3.7%</td>
</tr>
<tr>
<td>PORT Risk Class III</td>
<td>139/168 (82.7%)</td>
<td>151/177 (85.3%)</td>
<td>2.6%</td>
<td>-10.9% to 5.7%</td>
</tr>
<tr>
<td>PORT Risk Class IV</td>
<td>38/45 (84.4%)</td>
<td>32/40 (80.0%)</td>
<td>4.4%</td>
<td>-14.2% to 23.1%</td>
</tr>
</tbody>
</table>
Primary efficacy analysis of IV-to-oral Study 301

– Early clinical response at 72 (-12/+36 hours)
– ITT population, 10% non-inferiority margin
– Solithromycin demonstrated non-inferiority

<table>
<thead>
<tr>
<th></th>
<th>Solithromycin (n = 434)</th>
<th>Moxifloxacin (n = 429)</th>
<th>Difference</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>344 (79.3%)</td>
<td>342 (79.7%)</td>
<td>-0.5%</td>
<td>-6.1% to 5.2%</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>76 (17.5%)</td>
<td>78 (18.2%)</td>
<td>-0.7%</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>14 (3.2%)</td>
<td>9 (2.1%)</td>
<td>1.1%</td>
<td></td>
</tr>
</tbody>
</table>
Symptoms absent or improved from baseline at the early clinical response visit at 72 (-12/+36) hours in the ITT Population of IV-to-oral Study 301.
Subgroup analysis of early clinical response at 72 (-12/+36) hours in the ITT population of IV-to-oral Study 301

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Solithromycin</th>
<th>Moxifloxacin</th>
<th>Difference</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Prior therapy</td>
<td>82/102 (80.4%)</td>
<td>93/110 (84.5%)</td>
<td>-4.2%</td>
<td>-15.3% to 7.0%</td>
</tr>
<tr>
<td>No prior therapy</td>
<td>262/332 (78.9%)</td>
<td>249/319 (78.1%)</td>
<td>0.9%</td>
<td>-5.8% to 7.5%</td>
</tr>
<tr>
<td>Microbiological ITT</td>
<td>139/173 (80.3%)</td>
<td>121/153 (79.1%)</td>
<td>1.3%</td>
<td>-8.1% to 10.6%</td>
</tr>
<tr>
<td>Not in mITT</td>
<td>205/261 (78.5%)</td>
<td>221/276 (80.1%)</td>
<td>-1.5%</td>
<td>-8.8% to 5.7%</td>
</tr>
<tr>
<td>Clinically evaluable</td>
<td>314/391 (80.3%)</td>
<td>318/388 (82.0%)</td>
<td>-1.7%</td>
<td>-7.4% to 4.1%</td>
</tr>
<tr>
<td>Not clinical evaluable</td>
<td>30/43 (69.8%)</td>
<td>24/41 (58.5%)</td>
<td>11.2%</td>
<td>-11.5% to 34.0%</td>
</tr>
<tr>
<td>PORT Risk Class II</td>
<td>91/109 (83.5%)</td>
<td>82/107 (76.6%)</td>
<td>6.9%</td>
<td>-4.7% to 18.4%</td>
</tr>
<tr>
<td>PORT Risk Class III</td>
<td>174/215 (80.9%)</td>
<td>178/215 (82.8%)</td>
<td>-1.9%</td>
<td>-9.6% to 5.9%</td>
</tr>
<tr>
<td>PORT Risk Class IV</td>
<td>79/110 (71.8%)</td>
<td>82/107 (76.6%)</td>
<td>-4.8%</td>
<td>-17.4% to 7.7%</td>
</tr>
</tbody>
</table>
Analysis of Additional Endpoints in the ITT Population of IV-to-oral Study 301

![Chart showing the comparison between Solithromycin and Moxifloxacin for various endpoints like ECR including vital signs, Symptom response at SFU, Sustained symptom response, Clinical response at EOT, and Clinical response at SFU.](chart.png)
Estimated treatment differences and confidence intervals for additional endpoints in the ITT Population of IV-to-oral Study 301

solithromycin - moxifloxacin
difference in success rates

Favors solithromycin

Favors moxifloxacin
Subgroup analysis of investigator assessed clinical success at SFU (Day 12-17) in ITT population of IV-to-oral Study 301

<table>
<thead>
<tr>
<th>Subgroup</th>
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<th>Difference</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall ITT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical success</td>
<td>367/434 (84.6%)</td>
<td>380/429 (88.6%)</td>
<td>-4.0%</td>
<td>-8.8% to 0.8%</td>
</tr>
<tr>
<td>Clinical failure</td>
<td>54/434 (12.4%)</td>
<td>35/429 (8.2%)</td>
<td>4.3%</td>
<td>0.0% to 8.6%</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>13/434 (3.0%)</td>
<td>14/429 (3.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>87/102 (85.3%)</td>
<td>97/110 (88.2%)</td>
<td>-2.9%</td>
<td>-13.0% to 7.2%</td>
<td></td>
</tr>
<tr>
<td><strong>No prior therapy</strong></td>
<td>280/332 (84.3%)</td>
<td>283/319 (88.7%)</td>
<td>-4.4%</td>
<td>-9.9% to 1.2%</td>
</tr>
<tr>
<td><strong>Microbiological ITT</strong></td>
<td>144/173 (83.2%)</td>
<td>135/153 (88.2%)</td>
<td>-5.0%</td>
<td>-13.2% to 3.2%</td>
</tr>
<tr>
<td><strong>Not in mITT</strong></td>
<td>223/261 (85.4%)</td>
<td>245/276 (88.8%)</td>
<td>-3.3%</td>
<td>-9.4% to 2.7%</td>
</tr>
<tr>
<td><strong>Clinically evaluable</strong></td>
<td>338/391 (86.4%)</td>
<td>359/388 (92.5%)</td>
<td>-6.1%</td>
<td>-10.6% to -1.5%</td>
</tr>
<tr>
<td><strong>Not clinical evaluable</strong></td>
<td>29/43 (67.4%)</td>
<td>21/41 (51.2%)</td>
<td>16.2%</td>
<td>-6.9% to 39.3%</td>
</tr>
<tr>
<td><strong>PORT Risk Class II</strong></td>
<td>90/109 (82.6%)</td>
<td>97/107 (90.7%)</td>
<td>-8.1%</td>
<td>-18.0% to 1.8%</td>
</tr>
<tr>
<td><strong>PORT Risk Class III</strong></td>
<td>189/215 (87.9%)</td>
<td>194/215 (90.2%)</td>
<td>-2.3%</td>
<td>-8.7% to 4.0%</td>
</tr>
<tr>
<td><strong>PORT Risk Class IV</strong></td>
<td>88/110 (80.0%)</td>
<td>89/107 (83.2%)</td>
<td>-3.2%</td>
<td>-14.4% to 8.0%</td>
</tr>
</tbody>
</table>
### Reasons for clinical failure at the Day 12-17 visit in the ITT population of IV-to-oral Study 301

<table>
<thead>
<tr>
<th>Reason for end of therapy failure classification</th>
<th>Solithromycin</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical failure</td>
<td>54/434 (12.4%)</td>
<td>35/429 (8.2%)</td>
</tr>
<tr>
<td>Classified as failure at end of therapy, and failure was carried forward to the SFU visit</td>
<td>42/434 (9.7%)</td>
<td>31/429 (7.2%)</td>
</tr>
<tr>
<td>Lack of resolution or worsening of baseline signs and symptoms and required additional antibacterial medication</td>
<td>17/434 (3.9%)</td>
<td>10/429 (2.3%)</td>
</tr>
<tr>
<td>Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication</td>
<td>9/434 (2.1%)</td>
<td>9/429 (2.1%)</td>
</tr>
<tr>
<td>Study drug discontinued due to an adverse event and required additional antibacterial medication</td>
<td>15/434 (3.5%)</td>
<td>10/429 (2.3%)</td>
</tr>
<tr>
<td>Classified as failure at the SFU visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication</td>
<td>15/434 (3.5%)</td>
<td>8/429 (1.9%)</td>
</tr>
<tr>
<td>Classified as failure due to death from any cause</td>
<td>4/434 (0.9%)</td>
<td>6/429 (1.4%)</td>
</tr>
</tbody>
</table>

Subjects could be failures at both EOT and SFU, which is why numbers in separate categories do not add to the total number of clinical failures.
Co-primary efficacy analysis with weighted pooling of the Phase 3 trials in the microbiological ITT

- Early clinical response at 72 (-12/+36 hours)
- mITT population, 15% non-inferiority margin
- Solithromycin demonstrated non-inferiority

<table>
<thead>
<tr>
<th></th>
<th>Solithromycin (n = 408)</th>
<th>Moxifloxacin (n = 379)</th>
<th>Difference</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>315 (77.2%)</td>
<td>299 (78.9%)</td>
<td>-1.7%</td>
<td>-7.4% to 4.2%</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>81 (19.9%)</td>
<td>72 (19.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>12 (2.9%)</td>
<td>8 (2.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results in baseline pathogen subgroups
– Pooled mITT populations from Studies 300 and 301

<table>
<thead>
<tr>
<th>Pathogen subgroup</th>
<th>Early clinical response (72 hours)</th>
<th>Clinical response at SFU (Day 12-17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solithromycin</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td><strong>S. pneumoniae</strong></td>
<td>135/175 (77.1%)</td>
<td>149/178 (83.7%)</td>
</tr>
<tr>
<td>Macrolide resistant</td>
<td>17/24 (70.8%)</td>
<td>17/22 (77.3%)</td>
</tr>
<tr>
<td><strong>S. aureus</strong></td>
<td>31/43 (72.1%)</td>
<td>22/30 (73.3%)</td>
</tr>
<tr>
<td>Macrolide resistant</td>
<td>3/7 (42.9%)</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td><strong>H. influenzae</strong></td>
<td>78/98 (79.6%)</td>
<td>61/75 (81.3%)</td>
</tr>
<tr>
<td><strong>M. catarrhalis</strong></td>
<td>26/32 (81.2%)</td>
<td>20/26 (76.9%)</td>
</tr>
<tr>
<td><strong>L. pneumophila</strong></td>
<td>61/79 (77.2%)</td>
<td>64/80 (80.0%)</td>
</tr>
<tr>
<td><strong>M. pneumoniae</strong></td>
<td>65/76 (85.5%)</td>
<td>56/72 (77.8%)</td>
</tr>
<tr>
<td>Macrolide resistant</td>
<td>1/1 (100%)</td>
<td>2/2 (100%)</td>
</tr>
</tbody>
</table>

Macrolide resistant *S. pneumoniae*: azithromycin MIC ≥2 mcg/mL or erythromycin MIC ≥1 mcg/mL

www.fda.gov
Efficacy Conclusions

• The Phase 3 Studies 300 and 301 provided evidence that solithromycin is effective for the treatment of CABP
  – Study designs were appropriate for assessing non-inferiority
  – Overall efficacy results were similar to moxifloxacin
Presentation of Clinical Safety

Antimicrobial Drugs Advisory Committee Meeting
November 4, 2016

Ramya Gopinath, M.D.
Medical Officer
Division of Anti-Infective Products
Center for Drug Evaluation and Research, FDA
Outline

• Overview of Clinical Development Program

• Safety Overview

• Discussion of Hepatotoxicity
**Solithromycin Clinical Development Program**

<table>
<thead>
<tr>
<th>Trials</th>
<th>Solithromycin</th>
<th>Moxifloxacin/Levofloxacin</th>
<th>Phase 1 Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1 Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 Trials</td>
<td>554</td>
<td>0</td>
<td>176</td>
<td>671*</td>
</tr>
<tr>
<td><strong>Phase 2 and 3 Trials – Safety Populations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CE01-200</td>
<td>64</td>
<td>68</td>
<td>N/A</td>
<td>132</td>
</tr>
<tr>
<td>CE01-300</td>
<td>424</td>
<td>432</td>
<td>N/A</td>
<td>856</td>
</tr>
<tr>
<td>CE01-301</td>
<td>432</td>
<td>426</td>
<td>N/A</td>
<td>858</td>
</tr>
<tr>
<td><strong>Phase 2/3 Subtotal</strong></td>
<td>920</td>
<td>926</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1474</strong></td>
<td><strong>926</strong></td>
<td><strong>176</strong></td>
<td><strong>2517</strong></td>
</tr>
</tbody>
</table>

*Some subjects received both study drugs in some studies; only healthy subjects from the renal and hepatic impairment studies are included.*
# Safety Overview - Phase 3 Trials

<table>
<thead>
<tr>
<th></th>
<th>Oral Study 300</th>
<th>IV to Oral Study 301</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Soli N=424</td>
<td>Moxi N=432</td>
</tr>
<tr>
<td>Premature Withdrawal from the Study</td>
<td>18 (4.2)</td>
<td>19 (4.4)</td>
</tr>
<tr>
<td>Premature Discontinuation of Study Drug</td>
<td>28 (6.6)</td>
<td>24 (5.6)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>16 (3.8)</td>
<td>13 (3.0)</td>
</tr>
<tr>
<td>Clinical Failure</td>
<td>6 (1.4)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>6 (1.4)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>28 (6.6)</td>
<td>27 (6.3)</td>
</tr>
</tbody>
</table>

*2 patients died several months after the end of the study period and are not included here*
Deaths in the Solithromycin Arm of Phase 3 Trials

• All deaths (n=11) were characterized as Clinical Failures
• All deaths were in patients with PORT III or IV class pneumonia; 7 were in patients >65 years
• 3 deaths appeared unrelated to solithromycin
• 81 yo woman – possible solithromycin-rivaroxaban interaction; death on Day 8
• 67 yo man – underlying hepatic/cardiac disease/abnormal ECG at baseline; possible ventricular arrhythmia resulting in sudden cardiac death on Day 3
• 6 patients – potential therapeutic failures
Occurrence of Serious Adverse Events in the Pooled Phase 3 Safety Population
## Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Study 300</th>
<th>Study 301</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects with TEAEs</strong></td>
<td>Soli N=424 n (%) 36.6</td>
<td>Moxi N=432 n (%) 35.6</td>
</tr>
<tr>
<td></td>
<td>155 (36.6)</td>
<td>154 (35.6)</td>
</tr>
<tr>
<td><strong>TEAEs excluding IV infusion site reactions</strong></td>
<td>155 (36.6)</td>
<td>154 (35.6)</td>
</tr>
<tr>
<td></td>
<td>149 (34.5)</td>
<td>140 (32.9)</td>
</tr>
<tr>
<td><strong>TEAEs leading to premature drug discontinuation</strong></td>
<td>16 (3.8)</td>
<td>13 (3.0)</td>
</tr>
<tr>
<td></td>
<td>25 (5.8)</td>
<td>17 (3.8)</td>
</tr>
</tbody>
</table>
### Selected Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects in the Phase 3 Safety Populations

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>CE01-300</th>
<th>CE01-301</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Soli N=424 n (%)</td>
<td>Moxi N=432 n (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (4.2)</td>
<td>28 (6.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (3.5)</td>
<td>17 (3.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (2.4)</td>
<td>10 (2.3)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2 (0.5)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (4.5)</td>
<td>11 (2.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (2.1)</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (2.1)</td>
<td>10 (2.3)</td>
</tr>
</tbody>
</table>
Infusion Site Reactions in Study 301

Infusion-site reactions occurred in 31.3% of patients in the solithromycin arm vs. 5.2% of patients in the moxifloxacin arm.

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Soli N=432 n (%)</th>
<th>Moxi N=426 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion site erythema</td>
<td>19 (4.4)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Infusion site pain</td>
<td>45 (10.4)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>Infusion site phlebitis</td>
<td>43 (10)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Infusion site thrombosis</td>
<td>9 (2.1)</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>35 (8.1)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>
Ketolide-specific AEs

• **Exacerbation of Myasthenia Gravis (MG)** - Patients with MG were excluded from clinical trials

• **QT prolongation**
  – Patients on drugs known to prolong the QT interval were excluded from clinical trials
  – A thorough QT study was negative for QT prolongation but solithromycin-induced tachycardia was observed

• **Visual Disorders**
  – In Phase 1, there were two patients with blurry vision, and one with asthenopia (“tired eyes”)
  – In the Phase 3 trials, 1 solithromycin patient saw “black spots”

• **Syncope** – 1 patient had syncope in Phase 3; 2 in the Phase 2 study

• **Hepatotoxicity**
Hepatotoxicity

FDA Guidance and Premarketing Evaluation of DILI

Hy’s Law

Overview of Hepatotoxicity with Solithromycin

Structure-Activity Relationship

Pre-clinical Studies

Phase 1 and 2 Studies

Phase 3 Studies

Specific Populations

Non-CABP Studies

A Few Words About Telithromycin

Conclusions and Questions
FDA guidance for Premarketing Clinical Evaluation of Drug-Induced Liver Injury (DILI)*

• Drug-induced hepatocellular injury (excluding other causes) accompanied by jaundice can have a poor prognosis, with a roughly 10% rate of mortality or liver transplantation due to acute liver failure

• DILI has been one of the most frequent causes of safety-related drug marketing withdrawals for the past 50 years

• Only the most overt hepatotoxins are expected to show cases of severe DILI in 1,000-3,000 subjects

• Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies ≤1 in 10,000

Premarketing Evaluation of DILI

Challenge: To distinguish drugs likely to cause severe DILI from drugs unlikely to do so

• The type of liver injury that leads to severe DILI is predominantly hepatocellular injury (ALT/AST elevation), especially when this injury is extensive enough to reduce the liver’s functional ability to clear bilirubin or impact its synthetic function.

• The finding of a higher rate of ALT elevations in drug-treated subjects than in a control group is a sensitive, though not specific, signal of potential to cause severe DILI.

• A higher rate of more marked ALT elevations (10-15x Upper Limit of Normal [ULN]) is more specific for severe DILI, though still limited.

• The single most specific predictor for the potential of severe hepatotoxicity is…
Hy’s Law

• ALT/AST elevation $\geq 3x$ ULN + total bilirubin (TBL) elevation $>2x$ ULN, without:
  – Evidence of cholestasis
  – Any other cause of hepatic injury

• On the background of: higher incidence of hepatocellular injury caused by the drug (AST/ALT $\geq 3x$ ULN) compared with the control drug

• Such a drug is likely to cause severe DILI [resulting in liver failure or death] at a rate roughly $1/10^{th}$ the rate of Hy’s Law cases
Hy’s Law

- If the true incidence of severe injury is 1/10,000, and the rate of Hy’s Law cases is 1/1,000, about 3,000 exposed subjects (Rule of 3) would be needed to have a 95 percent probability of observing at least one Hy’s Law case in the treated population*

- No known occurrences of “false positive” Hy’s Law findings for a drug that was subsequently found NOT to cause severe DILI in a larger population

- Failure to find a Hy’s Law case does NOT imply that a drug with aminotransferase elevations is free of a risk of severe DILI (depends on the size of the exposed population, time of exposure, discontinuation rules use in protocols, true incidence rate of severe DILI).

Challenges in Predicting DILI Risk In a ‘Real World’ Post-Marketing Population

• In clinical trial databases, DILI signals may be mild-moderate & show reversible toxicity

• Drug-specific DILI clinical signatures, as well as histopathologic & liver test profiles may differ among individuals

• Risk for severe DILI caused by a drug may be more concentrated in certain patient populations; this may be detected only when the drug is used in a heterogenous real-world population

• Drug-drug interactions in the setting of wide postmarketing use of a drug in combination with possibly less monitoring may lead to increased risk of severe DILI

• The manner in which a DILI signal of mild-moderate acute hepatocellular injury detected in a small clinical study population will ‘play out’ can only be determined in adequately powered clinical studies
Hepatotoxicity

Premarketing Evaluation of DILI

Hy’s Law

Overview of Hepatotoxicity with Solithromycin

Structure-Activity Relationship

Pre-clinical

Phase 1 and 2 Studies

Phase 3 Studies

Specific Populations

Non-CABP Studies

A Few Words About Telithromycin

Conclusions and Questions
Hepatotoxicity - Solithromycin

- Despite a limited safety database in the Phase 2 and 3 trials (n=920) and the non-CABP studies (n=10), a pronounced hepatic injury signal was seen.
- A range of hepatic injury patterns - hepatocellular, cholestatic, and hypersensitivity was observed.
- There were no Hy’s Law cases.
- In 2 subjects in the Phase 3 trials, drug was stopped due to hepatic enzyme elevation.
The Structure of Solithromycin in Comparison with Telithromycin and Older Macrolides
Structure-Activity Relationship

- Quantitative structure-activity relationship (QSAR) of solithromycin was evaluated by the Division of Applied Regulatory Science at FDA; it was determined that solithromycin is 85% similar in structure to telithromycin and that hepatotoxicity would be expected with the use of solithromycin.

- Computational modeling commissioned by Cempra using DILIsym® suggested that solithromycin may have a different mechanism of hepatic injury compared with erythromycin…but other possible mechanisms of injury, such as hypersensitivity, were not evaluated in the model.

- A comparison of solithromycin with telithromycin using DILIsym® is ongoing.
Hepatotoxicity

Premarketing Evaluation of DILI
  Hy’s Law
Overview of Hepatotoxicity with Solithromycin
  Structure-Activity Relationship
  Pre-clinical
  Phase 1 and 2 Studies
  Phase 3 Studies
  Specific Populations
  Non-CABP Studies
A Few Words About Telithromycin
Conclusions and Questions
Hepatotoxicity: Nonclinical Studies

- In rats and monkeys, solithromycin is widely distributed to tissues, and with repeated dosing, accumulates in the liver at much higher concentrations than in plasma (liver concentration was 1168x plasma concentration in monkeys after 13 weeks).

- The active metabolites N-acetyl-CEM-101 and CEM-214 account for significant levels of exposure in these animals; in humans, they account for <6% exposure following oral solithromycin administration.

- Repeat-dose toxicity studies identified the liver as the primary target organ of toxicity with:
  - Biliary inflammation, centrilobular necrosis/degeneration and death observed in a 4-week oral rat study.
  - Weight loss, centrilobular hepatocellular vacuolation, Kupffer cell hyperplasia and moderate increases in AST, ALT and GGT observed in a 13-week oral monkey study.
  - Accumulation in lysosomes and phospholipidosis.

- Determination of the human equivalent dose (HED) and threshold for toxicity is difficult due to accumulation of solithromycin in the liver and macrophages.
Hepatotoxicity – Phase 1

• 41 of 550* (7.5%) healthy subjects exposed to solithromycin had ALT elevation > ULN in comparison to 2.3% of controls

• 2 (0.4%) of these healthy human volunteers discontinued solithromycin due to ALT elevation > 5x ULN
  1) 46 yo male received one dose of solithromycin 400 mg on Day 1
    **Baseline**: Normal ALT/AST
    **Day 8**: Max ALT 106 U/L (1.7x ULN) and max AST 240 U/L (5.1x ULN). Bilirubin/ALP were normal throughout. The subject was asymptomatic and AST/ALT returned to normal

*554 subjects were exposed to solithromycin in the Phase 1 studies; 550 subjects were used here per the Applicant’s analysis
Hepatotoxicity – Phase 1

2) 36 yo healthy male volunteer received three 800 mg IV doses of solithromycin on Days 1-3.

Solithromycin discontinued due to ALT elevation.
Hepatotoxicity – Phase 2

• ALT elevation > 3x ULN:
  – 1 of 59 (1.7%) patients with a post-baseline value treated with solithromycin vs. 2 of 65 (3.1%) patients treated with levofloxacin. The solithromycin patient was hepatitis C antibody positive

• AST elevation > 3x ULN:
  – 2 of 59 (3.4%) solithromycin recipients vs. 1 of 65 (1.5%) moxifloxacin recipients

• Bilirubin elevation >2x<3x ULN in 1 (1.6%) patient (Gilbert’s)
# Hepatotoxicity – Phase 3 Trials

<table>
<thead>
<tr>
<th>Hepatic enzyme</th>
<th>Degree of Elevation</th>
<th>CE01-300</th>
<th>CE01-301</th>
<th>Pooled Phase 3 Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Soli N=412 n (%)</td>
<td>Moxi N=423 n(%)</td>
<td>Soli N=418 n(%)</td>
<td>Moxi N=415 n(%)</td>
</tr>
<tr>
<td>ALT</td>
<td>&gt;ULN</td>
<td>172 (41.7)</td>
<td>141 (33.3)</td>
<td>198 (47.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;3x ULN</td>
<td>22 (5.3)</td>
<td>15 (3.5)</td>
<td>38 (9.1)</td>
</tr>
<tr>
<td></td>
<td>&gt;5x ULN</td>
<td>7 (1.7)</td>
<td>5 (1.2)</td>
<td>13 (3.1)</td>
</tr>
<tr>
<td></td>
<td>&gt;10x ULN</td>
<td>1 (0.2)</td>
<td>2 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;20x ULN</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td>Soli N=406 n(%)</td>
<td>Moxi N=416 n(%)</td>
<td>Soli N=416 n(%)</td>
<td>Moxi N=409 n(%)</td>
</tr>
<tr>
<td></td>
<td>&gt;ULN</td>
<td>130 (32)</td>
<td>112 (26.9)</td>
<td>154 (37)</td>
</tr>
<tr>
<td></td>
<td>&gt;3x ULN</td>
<td>10 (2.5)</td>
<td>8 (1.9)</td>
<td>20 (4.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;5x ULN</td>
<td>4 (1)</td>
<td>4 (1)</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;10x ULN</td>
<td>2 (0.5)</td>
<td>2 (0.5)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td></td>
<td>&gt;20x ULN</td>
<td>0</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
</tbody>
</table>
## Hepatotoxicity – Phase 3 Trials

<table>
<thead>
<tr>
<th>Hepatic enzyme</th>
<th>Degree of Elevation</th>
<th>CE01-300</th>
<th>CE01-301</th>
<th>Pooled Phase 3 Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Soli (N=412)</td>
<td>Moxi (N=422)</td>
<td>Soli (N=416)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&gt;ULN</td>
<td>15 (3.6)</td>
<td>16 (3.8)</td>
<td>21 (5.0)</td>
</tr>
<tr>
<td></td>
<td>&gt;2xULN</td>
<td>2 (0.5)</td>
<td>0</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>ALP</td>
<td>&gt;1.5xULN</td>
<td>22 (5.4)</td>
<td>17 (4)</td>
<td>21 (5)</td>
</tr>
<tr>
<td></td>
<td>&gt;3.0xULN</td>
<td>4 (0.9)</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;5.0xULN</td>
<td>3 (0.7)</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;10xULN</td>
<td>0</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>
Time to ALT and AST Elevation

- In Study 300, 73% (16/22) of patients with ALT >3x ULN experienced the maximum ALT level (MAL) between Days 1 and 5 (NB: blood was drawn on Days 1 and 4), but 27% experienced the MAL between Days 6 and 15.

- In Study 301, 50% (19/38) of patients with ALT >3x ULN experienced the MAL between Days 1 and 5, but 50% experienced it between Days 6 and 15.

- 80% of maximum AST levels in patients with AST > 3x ULN occurred between Days 1 and 5.

- Possible implications for monitoring hepatic enzymes in patients receiving treatment.
Patient CE01-300-154-0629 – 65 year old woman

Solithromycin discontinued due to ALT/AST elevation
### Hepatotoxicity - non-CABP Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Solithromycin Dose</th>
<th>Treatment Duration</th>
<th>Patients with ALT elevation &gt;3x ULN, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE01-204: COPD N=4</td>
<td>400 mg PO daily</td>
<td>28 days</td>
<td>3 (75)</td>
</tr>
<tr>
<td>CE01-205: NASH N=6</td>
<td>Originally 400 mg PO daily. Protocol amended to 200 mg PO daily, with the option of 200 mg 3x/week, then amended again to 200 mg PO daily for 1 week, then 200 mg 3x/week</td>
<td>13 weeks</td>
<td>1 (16.7)</td>
</tr>
</tbody>
</table>

*www.fda.gov*
**COPD Study/Subject 001: 69 yo Male with Cholestatic Hepatitis with Jaundice and Eosinophilia**

PMH: COPD and BPH; Medications: fluticasone-salmeterol/salbutamol inhalers and finasteride 5mg PO daily. Planned study treatment: Solithromycin 400 mg once a day for a 28-day course.

**Liver Enzyme Measurements, Eosinophil Count and INR Over Time**

<table>
<thead>
<tr>
<th>Study Day</th>
<th>ALT U/L</th>
<th>×ULN</th>
<th>AST U/L</th>
<th>×ULN</th>
<th>Total Bilirubin U/L</th>
<th>Direct Bilirubin U/L</th>
<th>ALP U/L</th>
<th>×ULN</th>
<th>EOS ×10³/µL</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>0.5</td>
<td>29</td>
<td>0.7</td>
<td>0.7</td>
<td>0.2</td>
<td>78</td>
<td>0.6</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>0.8</td>
<td>34</td>
<td>0.8</td>
<td>0.8</td>
<td>0.2</td>
<td>74</td>
<td>0.6</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>95</td>
<td>1.4</td>
<td>106</td>
<td>2.6</td>
<td>0.8</td>
<td>0.3</td>
<td>277</td>
<td>2.1</td>
<td>0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>23</td>
<td>476</td>
<td>11.9</td>
<td>368</td>
<td>9.0</td>
<td>4</td>
<td>2.2</td>
<td>1316</td>
<td>10.1</td>
<td>1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>24</td>
<td>427</td>
<td>10.7</td>
<td>322</td>
<td>7.9</td>
<td>2.9</td>
<td>1.5</td>
<td>1155</td>
<td>8.9</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>28</td>
<td>269</td>
<td>6.7</td>
<td>144</td>
<td>3.5</td>
<td>1.2</td>
<td>0.5</td>
<td>969</td>
<td>7.5</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>92</td>
<td>2.3</td>
<td>59</td>
<td>1.4</td>
<td>0.8</td>
<td></td>
<td>471</td>
<td>3.6</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>52</td>
<td>27</td>
<td>0.7</td>
<td>22</td>
<td>0.5</td>
<td>0.5</td>
<td>0.2</td>
<td>170</td>
<td>1.3</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Other investigations: Liver ultrasound normal, viral hepatitis screen negative
COPD Study/Subject 001 – Hepatic Enzyme Changes

Solithromycin discontinued due to ALT/AST/ALP/Bili elevation
Hepatotoxicity

Premarketing Evaluation of DILI
  Hy’s Law
Solithromycin Development Program
  Pre-clinical
  Phase 1 and 2 Studies
  Phase 3 Studies
  Specific Populations
  Non-CABP Studies

A Few Words About Telithromycin

Conclusions and Questions
Telithromycin

• First-in-class ketolide
• Approved by FDA in 2004 for community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS)
• Severe hepatotoxicity leading to hospitalization, death (n=4) and liver transplant (n=1) started to manifest soon after approval*
• 2006 – approved indications limited to CAP only
• Currently discontinued

http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
Telithromycin – Phase 3 Safety Populations

4937 Patients (telithromycin and comparator)

Telithromycin
3265 pts

- Controlled Trials
  2045 pts
    - 1057 CAP patients

Comparator
1672 pts

- Uncontrolled Trials
  1220 pts
    - 893 CAP patients

- Controlled Trials
  1672 pts
Telithromycin - Hepatic Data

• Nonclinical
  – Hepatotoxicity in dogs, rats, monkeys
    (Increased AST & ALT; liver necrosis in 4-week rat study; hepatocellular hypertrophy, multinucleated hepatocytes)

• Phase I
  – Clustering of hepatic AEs in elderly at 2000 mg x1 (3 of 8 subjects)
  – No clear dose-response for hepatic AEs

• Phase III Controlled CAP Trials
  – Low ALT elevation rates were observed and were similar in the telithromycin and comparator arms
  – No telithromycin-induced hepatic deaths
## ALT Elevation from Normal Baseline in the Pooled Phase 3 CAP Studies of Telithromycin*

<table>
<thead>
<tr>
<th>Extent of Elevation</th>
<th>Teli N=395, n (%)</th>
<th>All Comp N=388, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ULN</td>
<td>309 (78.2)</td>
<td>317 (81.7)</td>
</tr>
<tr>
<td>&gt;ULN ≤2x ULN</td>
<td>72 (18.2)</td>
<td>64 (16.5)</td>
</tr>
<tr>
<td>&gt;2x to ≤3x ULN</td>
<td>10 (2.5)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>&gt;3x to ≤5x ULN</td>
<td>3 (0.8)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>&gt;5x to ≤10xULN</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>&gt;15x to ≤20 x ULN</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;20x ULN</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Hepatotoxicity with Telithromycin*

- 42 cases of severe liver injury between 2004-2006

- Typical latency to onset of liver injury was rapid – median 10 days (range 2-43 days)

- Typical symptoms included abdominal pain, fatigue, weakness, jaundice, fever

- Primarily hepatocellular pattern of injury

- Abdominal pain was seen in 45% of cases; ascites in 17% of cases

- Recurrence of injury with re-exposure (n=4), suggesting hypersensitivity

Hepatotoxicity of Other Antibacterials*

• Cholestatic hepatitis/mixed cholestatic and hepatocellular injury are seen across all macrolides

• The NIH LiverTox website provides estimated incidences of these AEs per 100,000 prescriptions
  – Erythromycin: 3.6/100,000
  – Clarithromycin: 3.8/100,000

• Often occurs 1-3 weeks after starting treatment; recovery within 4-8 weeks of stopping treatment

• Asymptomatic and transient aminotransferase elevation occurs at a low rate (1-2%)

• Hypersensitivity seems less common

*https://livertox.nih.gov/
Hepatotoxicity

Premarketing Evaluation of DILI
   Hy’s Law
Solithromycin Development Program
   Pre-clinical
   Phase 1 and 2 Studies
   Phase 3 Studies
   Specific Populations
   Non-CABP Studies
A Few Words About Telithromycin
Conclusions and Questions
Conclusions – Solithromycin-related Hepatotoxicity

A pronounced hepatic injury signal is observed in a safety database of 920 patients who received a full therapeutic dose of solithromycin for 5-7 days for treatment of CABP

• Clear solithromycin exposure-ALT elevation relationship which appears to be dose- and duration-dependent

• Multiple toxicity patterns – hepatocellular, cholestatic, possible hypersensitivity
Conclusions – Solithromycin-related Hepatotoxicity

• No cases fulfilled Hy’s Law criteria, but…

• Using the “Rule of 3’s” in this limited database, the risk of serious DILI can only be capped at roughly 1:333. The likelihood of severe DILI is known to be much less than that; thus, this database is not large enough to accurately evaluate this risk.

• The additional risk of increased exposure to solithromycin through factors such as increased duration of treatment, drug-drug interactions, concomitant illnesses, and unadjusted use in renal failure needs to be considered given the robust signal observed.

• The risk of hypersensitivity – to older macrolides or solithromycin itself – and its role in severe solithromycin-related drug-induced liver injury (DILI) is unknown.
Conclusions – Solithromycin-related Hepatotoxicity

• Aminotransferase signal for hepatotoxicity seen with solithromycin in the Phase 3 trials is greater than was seen with telithromycin in Phase 3 trials; telithromycin was associated with severe hepatic injury post-marketing.

• Although exploratory computational modeling in DILIsym® may suggest that solithromycin does not have the same mechanism of hepatotoxicity as erythromycin and possibly telithromycin, the high observed incidence of hepatic injury in the relatively small Phase 3 safety database suggests the potential that solithromycin may trigger additional pathways associated with DILI, raising great concern for safety.
Presentation of Clinical Pharmacology

Antimicrobial Drugs Advisory Committee Meeting
November 4, 2016

Yongheng Zhang, PhD
Clinical Pharmacology Reviewer
Office of Clinical Pharmacology
OTS, CDER, FDA
Outline

• Pharmacokinetics highlights

• Drug interactions

• Exposure-response (E-R) relationships for efficacy and safety

• Dosing considerations
Pharmacokinetics Highlights

<table>
<thead>
<tr>
<th>ABSORPTION</th>
<th>DISTRIBUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Absolute BA~ 62% (400 mg oral/IV)</td>
<td>• Plasma protein binding (~81%)</td>
</tr>
<tr>
<td>• No food effect</td>
<td>• Volume of distribution: ~400 L</td>
</tr>
<tr>
<td>• Tmax: 2-4 hr</td>
<td>• Higher concentration in epithelial lining fluid (ELF) than in plasma</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>METABOLISM</td>
<td>EXCRETION</td>
</tr>
<tr>
<td>• CYP3A &amp; P-gp substrate &amp; inhibitor</td>
<td>• Terminal T_{1/2} ~ 8.5 hr</td>
</tr>
<tr>
<td>• Inhibits its own metabolism</td>
<td>• Fecal ~77 % (mostly metabolites)</td>
</tr>
<tr>
<td>• In plasma: parent (major) &amp; two</td>
<td>• urinary ~14 % (10% parent)</td>
</tr>
<tr>
<td>metabolites (&lt; 6 % of parent AUC)</td>
<td></td>
</tr>
</tbody>
</table>

✓ PK nonlinear due to time-dependent inhibition of CYP3A & saturation of intestinal P-gp
✓ PK highly variable
✓ Higher exposure in CABP patients than in healthy subjects
Drug Interactions

**Solithromycin**

- **Strong CYP3A/P-gp inducer** (e.g., rifampin)
- > 97% ↓ AUC & Cmax
- ~25% ↑ AUC on Day5

**CYP3A substrates** (e.g., midazolam)
- 9-fold ↑ AUC

**P-gp substrates** (e.g., digoxin)
- 30-50% ↑ AUC or Cmax

**CYP3A inhibitors** (e.g., Ketoconazole)
- ~25% ↑ AUC on Day5

**Solithromycin substrate & inhibitor**

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Outline

• Pharmacokinetics highlights

• Drug interactions

• Exposure-response (E-R) relationships for efficacy and safety

• Dosing considerations
Daily Exposure Comparison by Dosing Regimens of Two Phase 3 Trials (CE01-300 & -301)

Longer treatment & higher daily exposure in CE01-301 (IV only & IV-to-oral) vs CE01-300 (Oral only)
Exposure (AUC)-Response Relationship for Efficacy (ITT population with PK info; n=817)

- Flat exposure-response relationship identified over the exposure range observed in Phase 3 trials

**Early Clinical Response (ECR)**

- Average daily AUC\textsubscript{0-72h, free} Mean [min, max]
  - Q1: 1[0.13, 2.2] Mean: 79%
  - Q2: 2.8[2.3, 3.4] Mean: 85%
  - Q3: 4.1[3.4, 4.9] Mean: 82%
  - Q4: 6.8[5.0, 13.5] Mean: 81%

**Clinical Response at EOT**

- Average daily AUC\textsubscript{free} Mean [min, max]
  - Q1: 1.3[0.12, 2.0] Mean: 92%
  - Q2: 2.7[2.0, 3.3] Mean: 91%
  - Q3: 4.0[3.3, 4.9] Mean: 88%
  - Q4: 7.2[4.9, 16.4] Mean: 93%
AUC:MIC-Response Relationship for Efficacy
(mITT population with both MIC and PK info, n=203)

- Flat AUC:MIC-response relationship identified over the AUC:MIC range observed in Phase 3 trials
### Safety: Incidence of ALT Elevation

<table>
<thead>
<tr>
<th></th>
<th>Study CE01-300</th>
<th>Study CE01-301</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT elevation</strong>*</td>
<td>Solithromycin Oral n/N (%)</td>
<td>Moxifloxacin Oral n/N (%)</td>
</tr>
<tr>
<td>≥ 3×ULN</td>
<td>22/412 (5.3%)</td>
<td>15/423 (3.5%)</td>
</tr>
<tr>
<td>≥ 5×ULN</td>
<td>7/412 (1.7%)</td>
<td>5/423 (1.2%)</td>
</tr>
</tbody>
</table>

* ALT measured at baseline (Day -1 or 1), Days 4, 7 and 12-17.

- **Phase 1:** Dose escalation studies in phase 1 identified ALT elevation as a dose limiting factor
- **Phase 3:** Overall higher daily exposure and longer treatment in CE01-301 vs CE01-300
E-R Relationship for Probability of ALT $\geq 3 \times$ ULN

- The increase in the incidence of ALT elevation was associated with the increase in solithromycin exposure (i.e., AUC)
Outline

• Pharmacokinetics highlights

• Drug interactions

• E-R relationships on efficacy and safety

• Dosing considerations
Dosing Regimens Proposed by the Applicant

Clcr ≥ 30 mL/min

Oral-only
5 days

IV-only
7 days

IV-to-Oral
7 days

Clcr < 30 mL/min

Oral-only
5 days

IV-only
7 days

IV-to-Oral
7 days

Based on dedicated renal impairment PK study, Pop PK & PBPK model predictions

Dosing regimens studied in phase 2 & 3 trials
Dosing Considerations
(Remove oral load in IV-to-oral dosing regimen)

Clcr ≥ 30 mL/min

No oral load 800 mg

IV-to-Oral
7 days
Alternative

Oral-only
5 days

IV-only
7 days

Clcr < 30 mL/min

No oral load 400 mg

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Dosing Considerations

- Remove oral load in IV-to-oral may potentially reduce the increased risk of ALT elevation in Study CE01-301
  - The oral load resulted in the highest daily AUC on the day of switch
  - This oral load, along with the IV dose and longer treatment, may have contributed to the increased incidence of ALT elevation observed in CE01-301 (Exposure – ALT elevation relationship)
Dosing Considerations
( Remove oral load in IV-to-oral dosing regimen)

- **Efficacy not expected to be compromised**

  ✔ Patients can transition with 400 mg instead of 800 mg oral load and still maintain daily AUC at or exceeding Day 5 AUC observed in CE01-300, which was shown to be efficacious

---

![Graph showing AUC comparison between Oral and IV dosing](chart.png)
Dosing Considerations
(Remove oral load in IV-to-oral dosing regimen)

- Potentially mitigate the risk of ALT elevation in IV-to-oral
- Efficacy not expected to be compromised
- The alternative IV-to-oral dosing regimen is simpler than the original proposal, therefore, may help reduce the potential for dosing errors
Summary

• ADME & PK highlights
  ➢ no food effect, higher ELF exposure, nonlinear PK, and high PK variability

• Drug interactions
  ➢ CYP 3A & P-gp substrate/inhibitor

• E-R relationships for efficacy and safety
  ➢ Exposure – ALT elevation

• Dosing considerations
  ➢ Remove oral load in IV-to-oral dosing regimen
Thank You!