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6 ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

7 (AMDAC)

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12 Friday, November 4, 2016

13 8:30 a.m. to 4:26 p.m.

14

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17

18 FDA White Oak Campus

19 Building 31, The Great Room

20 White Oak Conference Center

21 Silver Spring, Maryland

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Lauren Tesh, PharmD, BCPS**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7

8 **ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS**

9 **(Voting)**

10 **Ellen M. Andrews, PhD**

11 *(Consumer Representative)*

12 Executive Director

13 CT Health Policy Project

14 New Haven, Connecticut

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1 **Lindsey R. Baden, MD**
2 *(Chairperson)*
3 Director of Clinical Research
4 Division of Infectious Diseases
5 Brigham and Women's Hospital
6 Director, Infectious Disease Service
7 Dana-Farber Cancer Institute
8 Associate Professor, Harvard Medical School
9 Boston, Massachusetts
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11 **Demetre C. Daskalakis, MD, MPH**
12 Assistant Commissioner
13 Bureau of HIV Prevention and Control
14 New York Department of Health and Mental
15 Hygiene
16 Queens, New York
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1 **Michael D. Green, MD, MPH**

2 Professor of Pediatrics and Surgery

3 Pediatrics and Surgery Division of

4 Infectious Diseases

5 University of Pittsburgh School of Medicine

6 Children's Hospital of Pittsburgh of University of

7 Pittsburgh Medical Center

8 Pittsburgh, Pennsylvania

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10 **Barbara M. Gripshover, MD**

11 Associate Professor of Medicine

12 University Hospitals Case Medical Center

13 Case Western Reserve University

14 Division of Infectious Diseases and HIV Medicine

15 Cleveland, Ohio

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1 **Jonathan R. Honegger, MD**

2 Assistant Professor of Pediatrics

3 The Ohio State University College of Medicine

4 Division of Infectious Diseases and Center for

5 Vaccines and Immunity

6 Nationwide Children's Hospital

7 Columbus, Ohio

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9 **Vincent Lo Re, MD, MSCE**

10 Assistant Professor of Medicine and Epidemiology

11 Division of Infectious Diseases

12 Department of Medicine

13 Center for Clinical Epidemiology and Biostatistics

14 Perelman School of Medicine

15 University of Pennsylvania

16 Philadelphia, Pennsylvania

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18 **Marc H. Scheetz, PharmD, MSc**

19 Associate Professor of Pharmacy Practice

20 Midwestern University Chicago College of Pharmacy

21 Downers Grove, Illinois

22

1 **ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS**
2 **(Voting) (cont.)**
3 **Peter J. Weina, MD, PhD, FACP, FIDSA**
4 Colonel, Medical Corps, USA
5 Chief, Department of Research Programs
6 Walter Reed National Military Medical Center
7 Bethesda, Maryland
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9 **TEMPORARY MEMBERS (Voting)**
10 **Thomas D. Boyer, MD**
11 Professor of Medicine, Professor of Cell Biology
12 and Anatomy, Director, Liver Research Institute
13 University of Arizona, University of Arizona
14 Health Sciences Center
15 Tucson, Arizona
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1 **William M. Lee, MD, FACP, FAASLD**
2 Professor of Internal Medicine
3 Holder of the Meredith Mosle Chair in Liver
4 Diseases
5 The University of Texas Southwestern
6 Medical Center at Dallas
7 Dallas, Texas
8
9 **J. Stephen Mikita, JD**
10 *(Patient Representative)*
11 Salt Lake City, Utah
12
13 **Michael Proschan, PhD**
14 Biostatistics Research Branch
15 National Institute of Allergy and
16 Infectious Diseases
17 Bethesda, Maryland
18
19
20
21
22

1 **ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE**
2 **(Non-Voting)**
3 **Douglas S. Levine, MD**
4 Head, Internal Medicine
5 Vice President, Global Medical Affairs
6 Shire
7 Lexington, Massachusetts
8
9 **FDA PARTICIPANTS (Non-Voting)**
10 **Edward M. Cox, MD, MPH**
11 Director
12 Office of Antimicrobial Products (OAP)
13 Office of New Drugs (OND), CDER, FDA
14
15 **Sumathi Nambiar, MD, MPH**
16 Director
17 Division of Anti-Infective Products (DAIP)
18 OAP, OND, CDER, FDA
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20 **Yuliya I. Yasinskaya, MD**
21 Cross-Discipline Team Leader
22 DAIP, OAP, OND, CDER, FDA

1 **Ramya Gopinath, MD**

2 Clinical Reviewer

3 DAIP, OAP, OND, CDER, FDA

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5 **Mark I. Avigan, MD, CM**

6 Consultative Reviewer for Hepatology

7 Office of Surveillance and Epidemiology

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9 **Daniel B. Rubin, PhD**

10 Biometrics Reviewer, Office of Biostatistics

11 Office of Translational Sciences, CDER, FDA

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1 P R O C E E D I N G S

2 (8:30 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. BADEN: If I can get everyone's
6 attention, it is now 8:30 and we should begin the
7 meeting.
8 Good morning. I'd like to first remind
9 everyone to please silence your cell phones,
10 smartphones, and any other devices if you have not
11 done so already.
12 I would like to also identify the FDA press
13 contact, Theresa Eisenman, who is there in the
14 back. If you are present -- thank you for standing
15 and waving.
16 My name is Lindsey Baden. I'm chairperson
17 of the Antimicrobial Drugs Advisory Committee. I
18 will now call this meeting of the Antimicrobial
19 Drugs Advisory Committee to order. We'll start by
20 going around the table introducing ourselves.
21 Let's start on the right with Doug Levine.
22 DR. LEVINE: My name is Dr. Doug Levine.

1 I'm the industry representative. I'm a
2 gastroenterologist at Shire pharmaceuticals.
3 DR. BOYER: I'm Dr. Thomas Boyer from the
4 University of Arizona, and I'm a hepatologist.
5 DR. SCHEETZ: I'm Marc Scheetz from
6 Midwestern University and Northwestern Medicine.
7 DR. PROSCHAN: I'm Michael Proschan. I'm a
8 statistician from the National Institute of Allergy
9 and Infectious Diseases.
10 DR. ANDREWS: I'm Ellen Andrews from the
11 Connecticut Health Policy Project, and I'm a
12 consumer representative.
13 MR. MIKITA: I'm Steve Mikita, and I'm an
14 attorney. I'm the patient representative, and I
15 have spinal muscular atrophy. Thank you.
16 DR. HONEGGER: Jonathan Honegger from Ohio
17 State University. I do pediatric infectious diss.
18 DR. WEINA: I'm Pete Weina, infectious
19 disease physician with the Walter Reed National
20 Military Medical Center.
21 DR. GRIPSHOVER: Hi. I'm Barb Gripshover.
22 I'm an infectious disease physician at Case Western

1 Reserve University in Cleveland.
2 DR. BADEN: I'm Lindsey Baden. I'm chair of
3 the committee, an infectious disease at Brigham and
4 Women's Hospital, Dana Farber Cancer Institute, in
5 Boston.
6 DR. TESH: I'm Lauren Tesh, the Designated
7 Federal Officer for AMDAC.
8 DR. GREEN: I'm Michael Green. I'm a
9 pediatric infectious disease specialist at the
10 Children's Hospital, Pittsburgh.
11 DR. DASKALAKIS: I'm Demetre Daskalakis.
12 I'm an infectious disease specialist, mainly
13 specializing in HIV medicine and prevention. And
14 I'm at the New York City Department of Health and
15 Mental Hygiene.
16 DR. LEE: I'm William Lee. I'm a
17 hepatologist at UT Southwestern in Dallas.
18 DR. LO RE: I'm Vin Lo Re. I'm an
19 infectious disease physician and clinical
20 epidemiologist at the University of Pennsylvania.
21 DR. RUBIN: Dan Rubin, statistical reviewer,
22 CDER, FDA.

1 DR. AVIGAN: Mark Avigan, Office of
2 Surveillance and Epidemiology, FDA.
3 DR. GOPINATH: I'm Ramya Gopinath, the
4 clinical reviewer for this product in DAIP.
5 DR. YASINSKAYA: Yuliya Yasinskaya, team
6 leader, DAIP.
7 DR. NAMBIAR: Sumathi Nambiar, director,
8 Division of Anti-Infective Products, CDER, FDA.
9 DR. COX: Good morning. Ed Cox, director,
10 Office of Antimicrobial Products, CDER, FDA.
11 DR. BADEN: Do remember to turn off your
12 mikes.
13 For topics such as those being discussed at
14 today's meeting, there are often a variety of
15 opinions, some of which are quite strongly held.
16 Our goal is that today's meeting will be a fair and
17 open forum for discussion of these issues, and that
18 individuals can express their views without
19 interruption. Thus, a gentle reminder, individuals
20 will be allowed to speak into the record only if
21 recognized by the chairperson. We look forward to
22 a productive meeting.

1 In the spirit of the Federal Advisory
2 Committee Act and the Government in the Sunshine
3 Act, we ask that the advisory committee members
4 take care that their conversations about the topic
5 at hand take place in the open forum of the
6 meeting.
7 We are aware that members of the media are
8 anxious to speak with the FDA about these
9 proceedings. However, FDA will refrain from
10 discussing the details of this meeting with the
11 media until its conclusion.
12 Also, the committee is reminded to please
13 refrain from discussing the meeting topics during
14 breaks or during lunch. Thank you.
15 Now I'll pass it to Dr. Lauren Tesh, who
16 will read the Conflict of Interest Statement.
17 **Conflict of Interest Statement**
18 DR. TESH: The Food and Drug Administration
19 is convening today's meeting of the Antimicrobial
20 Drugs Advisory Committee under the authority of the
21 Federal Advisory Committee Act of 1972.
22 With the exception of the industry

1 representative, all members and temporary voting
2 members of the committee are special government
3 employees or regular federal employees from other
4 agencies and are subject to federal conflict of
5 interest laws and regulations.
6 The following information on the status of
7 this committee's compliance with federal ethics and
8 conflict of interest laws covered by, but not
9 limited to, those found at 18 USC Section 208 is
10 being provided to participants in today's meeting
11 and to the public.
12 FDA has determined that members and
13 temporary voting members of this committee are in
14 compliance with federal ethics and conflict of
15 interest laws. Under 18 USC Section 208, Congress
16 has authorized FDA to grant waivers to special
17 government employees and regular federal employees
18 who have potential financial conflicts when it is
19 determined that the agency's need for a special
20 government employee's services outweighs his or her
21 potential financial conflict of interest or when
22 the interest of a regular federal employee is not

1 so substantial as to be deemed likely to affect the
2 integrity of the services which the government may
3 expect from the employee.
4 Related to the discussion of today's
5 meeting, members and temporary voting members of
6 the committee have been screened for potential
7 financial conflicts of interest of their own as
8 well as those imputed to them, including those of
9 their spouses or minor children and, for purposes
10 of 18 USC Section 208, their employers. These
11 interests may include investments, consulting,
12 expert witness testimony, contracts, grants,
13 CRADAs, teaching, speaking, writing, patents and
14 royalties, and their primary employment.
15 Today's agenda involves new drug application
16 209006 and 209007, solithromycin capsules and
17 solithromycin for injection, sponsored by Cempra
18 Pharmaceuticals, respectively, for the proposed
19 indication of treatment of community-acquired
20 bacterial pneumonia.
21 This is a particular matters meeting, during
22 which specific matters related to Cempra's NDAs

1 will be discussed.
2 Based on the agenda for today's meeting and
3 all financial interests reported by the committee
4 members and temporary voting members, no conflict
5 of interest waivers have been issued in connection
6 with this meeting.
7 To ensure transparency, we encourage all
8 standing committee members and temporary voting
9 members to disclose any public statements that they
10 have made concerning the product at issue.
11 With respect to FDA's invited industry
12 representative, we would like to disclose that
13 Dr. Douglas Levine is participating in this meeting
14 as a nonvoting industry representative, acting on
15 behalf of regulated industry. Dr. Levine's role at
16 this meeting is to represent industry in general
17 and not any particular company. Dr. Levine is
18 employed by Shire.
19 We would like to remind members and
20 temporary voting members that if the discussions
21 involve any other products or firms not already on
22 the agenda for which an FDA participant has a

1 personal or imputed financial interest, these
2 participants need to exclude themselves from such
3 involvement, and their exclusion will be noted for
4 the record.
5 FDA encourages all other participants to
6 advise the committee of any financial relationships
7 that they may have with the firms at issue. Thank
8 you.
9 DR. BADEN: We will now proceed with
10 Dr. Nambiar's introductory remarks.
11 **FDA Introductory Remarks - Sumathi Nambiar**
12 DR. NAMBIAR: Thank you, Dr. Baden, and good
13 morning, everybody. Welcome to today's meeting of
14 the Antimicrobial Drugs Advisory Committee. We are
15 here to discuss NDA 209006 and NDA 209007 for
16 solithromycin.
17 The applicant for these NDAs is Cempra
18 Pharmaceuticals. The NDAs were granted priority
19 review as the product has a qualified infectious
20 disease product designation. The proposed
21 indication is for treatment of community-acquired
22 bacterial pneumonia caused by the following

1 organisms: Streptococcus pneumoniae,
2 Haemophilus influenzae, Moraxella catarrhalis,
3 methicillin-susceptible Staph aureus,
4 Legionella pneumophila, and Mycoplasma pneumoniae.
5 And this indication is in patients 18 years of age
6 and older.
7 The proposed dosing regimens are as follows:
8 for the oral-only option, 800 milligrams once a day
9 on day 1 followed by 400 milligrams once a day on
10 days 2 to 5; for the IV-only regimen, 400
11 milligrams once a day for 7 days; and with the
12 intravenous to oral switch option, at the time of
13 oral switch is a loading dose of 800 milligrams
14 orally, followed by 400 milligrams once a day
15 orally to complete the 7-day course.
16 The development program included one phase 2
17 trial and two phase 3 trials in patients with
18 community-acquired bacterial pneumonia. The
19 phase 2 trial was a randomized, double-blind trial
20 where oral solithromycin was compared to oral
21 levofloxacin in 132 patients.
22 The co-primary efficacy outcomes were

1 investigator-assessed clinical response at the test
2 of cure visit in the intent-to-treat and clinical
3 evaluable populations. The cure rates were very
4 similar in the intent-to-treat population, and in
5 the CE population were numerically slightly lower
6 in the solithromycin arm.
7 The applicant has conducted two phase 3
8 trials, and both trials were randomized, double-
9 blind, noninferiority trials where solithromycin
10 was compared to moxifloxacin. The prespecified
11 noninferiority margin in these trials was
12 10 percent.
13 Study CE01-300 evaluated a 5-day regimen of
14 oral solithromycin, and in study CE01-301, a 7-day
15 regimen was studied with the option of switch from
16 intravenous to oral solithromycin.
17 The primary efficacy endpoint in both trials
18 was early clinical response. This was based on the
19 following four symptoms: cough, dyspnea, chest
20 pain, and sputum production. The endpoint was
21 assessed at 72 hours -- range of 60 to 108
22 hours -- after initiation of treatment.

1 For a patient to be considered a responder
2 for this primary endpoint, he or she should have
3 met the following criteria: There should be
4 improvement from baseline in at least two of the
5 four symptoms, no worsening of other symptoms,
6 patient should not have received an antibacterial
7 drug for CABP from the first dose of the study drug
8 until the first 108 hours when the ECR assessment
9 was made, and the patient should be alive through
10 the late follow-up visit. And these definitions
11 are very consistent with the draft guidance on
12 community-acquired bacterial pneumonia.
13 In both trials, the prespecified NI margin
14 of 10 percent was met for the primary endpoint of
15 early clinical response. In the oral-only study,
16 the responder rates were very similar in both arms.
17 The treatment was difference was 0.3 percent, and
18 the low bound of the 95 percent confidence interval
19 was within the prespecified 10 percent margin.
20 In CE01-301, where there's an IV to oral
21 switch, the responder rates again were very
22 similar. Treatment difference was minus 0.5

1 percent, and the low bound of the 95 percent
2 confidence interval was within the 10 percent
3 margin.
4 There was a numeric increase in the rates of
5 investigator-assessed clinical failure at the
6 short-term follow-up visit, which occurred 5 to 10
7 days after the end of therapy. This was more
8 pronounced in the solithromycin arm compared to the
9 moxifloxacin arm.
10 From a safety standpoint, 920 patients
11 comprise the safety database at the proposed dose
12 and duration. The three areas of concern are
13 hepatotoxicity, intravenous site reactions, and
14 ketolide class adverse events.
15 From a standpoint of hepatotoxicity, in both
16 studies the incidence of ALT elevation was higher
17 in solithromycin-treated patients compared to
18 moxifloxacin-treated patients. And this difference
19 was more pronounced in study CE01-301.
20 There were no cases of Hy's law seen. ALT
21 elevation was also seen in the two non-CABP trials.
22 One was a COPD trial and the other was a trial in

1 patients with NASH. There's one case of clinical
2 hepatitis associated with eosinophilia reported the
3 COPD trial.
4 Intravenous site reactions were more
5 commonly reported in solithromycin-treated
6 patients, 31 percent compared to 5 percent of
7 moxifloxacin-treated patients.
8 Two specific ketolide class adverse events
9 that are worth noting: there was no obvious signal
10 for visual adverse effects identified so far.
11 There were some reports of visual adverse
12 reactions, such as blurry vision, tired eyes, and
13 black spots; and important to note that patients
14 with a history of myasthenia gravis were excluded,
15 so one cannot assess the risk for this adverse
16 event.
17 The key topic areas of today's advisory
18 committee meeting are as follows. From the
19 efficacy standpoint, we would like some discussion
20 around the higher number of investigator-assessed
21 clinical failures seen at the short-term follow-up
22 visit. And also worth noting that there's very

1 limited clinical data in this data package in
2 patients who had CABP due to macrolide-resistant
3 Strep pneumoniae.
4 From a safety standpoint, there's a signal
5 for hepatotoxicity seen in the CABP trials, but
6 that frequency of ALT elevation was higher in the
7 solithromycin arm compared to the moxifloxacin arm.
8 Hepatotoxicity was also seen in the COPD trial,
9 including a case of clinical hepatitis, and was
10 also seen in the NASH trial. There's evidence for
11 exposure response with hepatotoxicity, and there's
12 a higher incidence of infusion site reaction.
13 We'd also like some discussion on the
14 proposed dosing regimen specifically for the
15 intravenous to oral switch, where currently there
16 is a proposed loading dose at the time of switch.
17 So the day looks as follows. We have
18 presentations by the applicant. This will be
19 followed by presentations by the FDA. Dr. Rubin
20 will present the efficacy findings, Dr. Gopinath
21 will discuss the safety findings, and Dr. Zhang
22 will present clinical pharmacology aspects of this

1 application.
2 There's time for clarifying questions after
3 both the applicant presentation and the FDA
4 presentations. Following lunch, we have time for
5 open public hearing. And this will be followed by
6 questions for the committee.
7 We have three voting questions today. The
8 first one is, has the applicant provided
9 substantial evidence of the efficacy of
10 solithromycin for the treatment of community-
11 acquired bacterial pneumonia? If yes, please
12 provide any recommendations for labeling. If no,
13 please discuss additional studies or analyses that
14 are needed.
15 The second voting question is, has the risk
16 of hepatotoxicity with solithromycin been
17 adequately characterized? If yes, please provide
18 any recommendations for labeling. If no, please
19 discuss additional studies that are needed to
20 further characterize the risk.
21 The third voting question is, do the
22 efficacy results of solithromycin for the treatment

1 of CABP outweigh the risks, including
2 hepatotoxicity? If yes, please provide any
3 recommendations for labeling. If no, please
4 discuss additional studies or analyses that are
5 needed. Thank you.
6 DR. BADEN: Thank you, Dr. Nambiar.
7 Both the Food and Drug Administration and
8 the public believe in a transparent process for
9 information-gathering and decision-making. To
10 ensure such transparency at advisory committee
11 meetings, FDA believes that it is important to
12 understand the context of an individual's
13 presentation.
14 For this reason, FDA encourages all
15 participants, including the industry's non-employee
16 presenters, to advise the committee of any
17 financial relationships that they may have with the
18 firm at issue, such as consulting fees, travel
19 expenses, honoraria, and interests in the industry,
20 including equity interests and those based upon the
21 outcome of the meeting.
22 Likewise, FDA encourages you at the

1 beginning of your presentation to advise the
2 committee if you do not have any such financial
3 relationships. If you choose not to address this
4 issue of financial relationships at the beginning
5 of your presentation, it will not preclude you from
6 speaking.
7 We will now proceed with applicant
8 presentations. Dr. Fernandes?
9 **Applicant Presentation - Prabhavathi Fernandes**
10 DR. FERNANDES: Good morning. I am Prabha
11 Fernandes, founder, president, and CEO of Cempra
12 Pharmaceuticals. For more than four decades, I
13 have focused on anti-infectives, first in clinical
14 microbiology and then infectious diseases, and then
15 in pharmaceutical discovery and development,
16 including clarithromycin.
17 I have worked on solithromycin since its
18 acquisition in 2006, so I'd like to thank the FDA
19 and the advisory committee for your time today to
20 discuss this molecule. Let's talk about the
21 development of solithromycin.
22 We have extensive experience with this

1 molecule and the macrolide class as a whole.
2 Solithromycin was selected from a library of
3 potential macrolides acquired in 2006. We
4 identified the different chemical structure of
5 solithromycin, suggesting it would have a better
6 efficacy with a better safety profile relative to
7 telithromycin.
8 From 2006 to 2009, extensive nonclinical
9 studies were conducted to understand the mechanism
10 of action for telithromycin toxicities, as it was
11 important to differentiate solithromycin from this
12 earlier macrolide.
13 Our first phase 3 study testing the oral
14 formulation was complete in December of 2014, and
15 the IV to oral was completed in 2015. This was the
16 first time an oral antibiotic was studied in CABP
17 using the new FDA guidance.
18 Currently we also have ongoing studies in
19 other indications, including gonorrhea, pediatric
20 CABP, and are exploring longer-term dosing using
21 smaller trials in COPD and NASH.
22 Pediatric phase 1 trials were completed

1 using the intravenous formulation, oral capsules,
2 and the suspension formulations, and has begun
3 enrollment in a global pivotal phase 2/3 CABP
4 pediatric trial with all these dosing formulations.
5 We also plan to study solithromycin for
6 additional exploratory studies for unmet needs,
7 such as infections in pregnancy. Toxicology and
8 preclinical work for this has been completed
9 successfully.
10 Here is the proposed indication.
11 Solithromycin has been developed for the treatment
12 of adult community-acquired bacterial pneumonia
13 caused by susceptible isolates of the bacteria
14 shown here.
15 Solithromycin can be administered both
16 orally and parenterally. Notably, treatment can
17 also be switched from intravenous to oral dosing to
18 treat patients in the hospital and outpatient
19 setting. Having the flexibility of oral and IV
20 dosing allows dosing of moderate to severe CABP.
21 This is especially important because macrolides are
22 administered primarily in the outpatient setting.

1 Solithromycin comes in a capsule containing
2 200 milligrams of drug, and solithromycin for
3 injection is a vial that contains 400 milligrams of
4 drug powder. A suspension formulation is also
5 being tested for our pediatric program.
6 Solithromycin is a fourth generation
7 macrolide antibiotic and the first member of the
8 fluoroketolide subclass. All the macrolides have a
9 similar basic structure of a macrolactone ring and
10 N-dimethyl sugar, including the ketolides that give
11 certain common macrolide properties.
12 The third generation macrolides have a keto
13 group instead of a sugar, hence called ketolides,
14 and a side chain. The one approved member of this
15 generation is telithromycin, and this compound has
16 a pyridine in its side chain.
17 Telithromycin was developed because of the
18 rising macrolide resistance in the late 1990s.
19 After approval for simple respiratory tract
20 infections and CABP, serious adverse events were
21 noted, and label changes were made to allow its use
22 only in CABP, a serious infection.

1 The problem of macrolide resistance is
2 higher now, and the need for a new macrolide is
3 even greater, than in the 1990s. Solithromycin
4 also has fluorine at the 2 position and a side
5 chain that is chemically different, more stable and
6 with better pharmacokinetics than that of
7 telithromycin. In fact, as you will hear later
8 today, solithromycin is more closely related to
9 clarithromycin in some of its biological
10 properties.
11 Solithromycin is different chemically and
12 biologically from telithromycin, as it does not
13 contain a pyridine moiety. This moiety has been
14 shown to block certain nicotinic acid acetylcholine
15 receptors that could be responsible for the side
16 effects associated with telithromycin.
17 Also, the imidazole site change from
18 telithromycin is replaced with a 1,2,3-triazole,
19 which improves the stability in the molecule.
20 Lastly, the fluorine was added to improve activity
21 against resistant strains as well as to improve
22 pharmacokinetics.

1 Let me show you the side effects associated
2 with telithromycin that were unlike those of older
3 macrolides. The side effects of concern found with
4 telithromycin are visual disturbances, exacerbation
5 of myasthenia gravis, syncope or loss of
6 consciousness, and liver toxicity.
7 Having been in drug development for more
8 than 30 years, I realized that the side chain has a
9 pyridine structure, which is used by central
10 nervous system chemists to block the nicotinic acid
11 acetylcholine receptor. As we will show you, these
12 side effects are not mechanistically associated
13 with solithromycin due to its different structure.
14 Here is the telithromycin structure with
15 this pyridine side chain. And this is the
16 nicotinic acid structure. They look very similar.
17 Nicotinic acid receptors are homo- and heteromeric
18 diverse receptors that are expressed in the central
19 and peripheral nervous system, where they control
20 multiple critical body functions. Compounds with
21 the pyridine moiety are known to interact with
22 these receptors, as they are analogues of nicotine.

1 That is why you see some telithromycin unique side
2 effects that are different from the other
3 macrolides.
4 Inhibition of the receptors in the eye
5 results in visual disturbances, which were seen
6 even in the clinical trials of telithromycin.
7 Inhibition of pre- and postsynaptic neuromuscular
8 junction receptors can cause the myasthenia gravis
9 exacerbation seen with telithromycin.
10 Macrolides are too large to pass the
11 blood/brain barrier. However, the side chain
12 metabolite of telithromycin is cleaved and the
13 putative pyridine/imidazole metabolite is small
14 enough to pass the blood/brain barrier, where it
15 inhibits the nicotinic acid receptors and could
16 cause loss of consciousness.
17 Let me now turn to the discussion of hepatic
18 toxicity in telithromycin.
19 The hypothesis for the severe hepatic
20 toxicity of telithromycin is based on the newly
21 described autonomic regulation of the innate
22 immunity that has been called inflammatory reflex

1 by Dr. Kevin Tracey.
2 The vagus nerve releases acetylcholine,
3 which interacts with alpha-7 nicotinic acid
4 receptors on target cells, including macrophages.
5 This alpha-7 nicotinic acid receptor is exactly the
6 same as in the eye. Agents that cause
7 inflammation, such as microbes, alcohol, Tylenol,
8 can cause macrophages to release cytokines like
9 TNF-alpha, resulting in inflammation and cell death
10 of hepatocytes.
11 In a negative feedback inhibition loop,
12 acetylcholine released by the vagus nerve interacts
13 with the alpha-7 acetylcholine receptors, resulting
14 in suppression of the cytokine release by
15 macrophages.
16 Our hypothesis, demonstrated by data showing
17 that telithromycin inhibits the alpha-7 nicotinic
18 acid receptor, is that it can interrupt
19 acetylcholine-mediated feedback inhibition of
20 inflammation, contributing to the rare and severe
21 episodes of DILI. Since an inciting inflammatory
22 factor must be actively occurring concomitant to

1 the alpha-7 blockade by telithromycin, it would be
2 a rare event.
3 Now for the brief description of our
4 toxicology studies.
5 In 4-week toxicology, solithromycin had the
6 same NOAEL as clarithromycin and telithromycin at
7 100 milligrams per kilogram per day at the liver.
8 In 13-week daily oral dosing, the liver NOAEL of
9 solithromycin were shown to be less toxic than that
10 of telithromycin and clarithromycin.
11 Intravenous solithromycin was well tolerated
12 in dogs and monkeys in 4-week daily dosing.
13 Solithromycin has been demonstrated to be safe in
14 segment 1, 2, and 3 developmental toxicology and
15 nonclinical animal work to allow phase 1 studies in
16 pregnancy.
17 Solithromycin has been shown to be safe for
18 newborn nursing rats. As we will show you in our
19 presentation, solithromycin showed a positive
20 benefit-risk profile. Today we'll focus on data
21 from our two phase 3 studies. IV and oral
22 solithromycin monotherapy showed efficacy

1 comparable to that of approved potent
2 fluoroquinolone, with an acceptable safety profile
3 in adult patients with CABP.
4 With this information in mind, here is the
5 agenda for today's presentation. Dr. Julio Ramirez
6 will touch on the background of CABP and discuss
7 the unmet medical need in the field. I will return
8 to discuss our microbiological data. Then Dr.
9 David Oldach, chief medical officer at Cempra, will
10 address the phase 3 clinical study design.
11 Dr. Anita Das, the lead statistician on the
12 solithromycin program, will follow to show the
13 efficacy results. Dr. Oldach will then return to
14 discuss the safety data, followed by Dr. Paul
15 Watkins of the University of North Carolina at
16 Chapel Hill, who will discuss the liver safety.
17 Lastly, Dr. Steve Vacalis will conclude by
18 providing a primary care perspective.
19 We also have with us today additional
20 experts who are available to take your questions.
21 All external presenters have been compensated for
22 their time and travel to today's meetings.

1 It is my pleasure to invite Dr. Ramirez to
2 the podium. Thank you very much.
3 **Applicant Presentation - Julio Ramirez**
4 DR. RAMIREZ: Thank you very much. I'm
5 Julio Ramirez, chief, infectious diseases at
6 University of Louisville. Today I'm going to
7 address the unmet need for the treatment of
8 community-acquired pneumonia.
9 I will review the epidemiology of pneumonia,
10 then I'll give a historical review of the treatment
11 guidelines, and lastly discuss the treatment
12 options that we have today.
13 According to the CDC, pneumonia is the
14 eighth leading cause of death in the U.S. and the
15 number one cause of death due to infectious
16 diseases. Therefore, research on developing drugs
17 for this disease is essential.
18 We used the University of Louisville
19 pneumonia study to calculate the incidence of CABP
20 in the United States. We started with the adult
21 population in Louisville. During the first year of
22 the study, were approximately 94 [sic] patients

1 were hospitalized. We identified close to 4,000
2 patients with community-acquired pneumonia who were
3 hospitalized in the city of Louisville. The annual
4 incidence of hospitalization due to CABP is
5 664 patients per 100,000 population.
6 Applying this incidence to the entire adult
7 population of the United States, we estimate that
8 there are approximately 1.6 million patients are
9 hospitalized with community-acquired pneumonia each
10 year.
11 Again, from our University of Louisville
12 study, we see a clear impact of age on
13 hospitalizations. You can see here elderly
14 patients are extremely high risk for
15 hospitalization due to pneumonia.
16 In our study, we were able to characterize
17 the impact of comorbidities for adults with CABP.
18 From a baseline value of 664 patients per 100,000,
19 these comorbidities significantly increase the risk
20 for hospitalization due to pneumonia. For example,
21 a patient with diabetes will have three times the
22 risk of developing pneumonia, and this risk will

1 increase 16-fold for a patient with COPD.
2 Let's move to my second point, the treatment
3 of CABP according to national guidance. I was one
4 of the original members of the initial committee of
5 the American Thoracic Society that published the
6 2001 guidelines. Considering the most common
7 typical and atypical pathogens likely to cause
8 pneumonia, listed here, the guidelines recommend
9 empiric therapy for ambulatory patients with
10 macrolides or quinolones.
11 According to the 2001 guidelines, patients
12 should be treated with a macrolide, preserving
13 quinolone for a patient with risk factors for
14 community-acquired pneumonia due to macrolide-
15 resistant pneumococcus. For hospitalized patients
16 not in the ICU, two regimens were suggested, either
17 a beta-lactam plus a macrolide or a quinolone.
18 Once patients reach clinical stability, it
19 was suggested to switch the patient to oral
20 antibiotics. A patient with beta-lactam plus
21 macrolides could be switched to an oral macrolide,
22 and a patient with a quinolone could be switched to

1 an oral quinolone.
2 At that time, we were aware of the presence
3 of a streptococcal pneumonia resistant to
4 macrolides, and this subject was a primary
5 discussion of the committee. Let me briefly review
6 our discussion to explain our guideline
7 recommendations at that time.
8 Macrolide antibiotics attached to ribosomal
9 subunits kill the pneumococcus by inhibited protein
10 synthesis. Some pneumococci acquire the mefA gene,
11 and this gene allows the pneumococcus to develop a
12 pump to remove macrolides from the cells. Some of
13 the pneumococci acquire the ermB gene that allows
14 the pneumococci to alter the target site where the
15 macrolide is supposed to attach.
16 Pneumococci with a pump are considered to
17 have low-level resistance to macrolides.
18 Pneumococci that change the target site are
19 considered to have high-level resistance to
20 macrolides. That's the biology.
21 Now, historically, at the time of
22 erythromycin in the 70s, we didn't have any

1 pneumococci resistant to macrolides. If we imagine
2 all streptococcal pneumonia in the United States,
3 0.5 micrograms of macrolides were able to kill all
4 pneumococci.
5 However, by the year 2000, when we were
6 writing the national guidelines, that picture had
7 changed dramatically. Resistance to macrolides
8 grew to approximately 10 percent of pneumococci in
9 the United States, some with low-level resistance
10 and some with high-level resistance. We recognized
11 that resistant pneumococci were present primarily
12 in patients with underlying conditions. That was
13 the picture in 2000.
14 The problem of macrolide resistance,
15 however, has continued to grow over the years.
16 According to the CDC, the rate of resistance
17 reached 35 percent by the year 2006. Here I'm
18 showing new surveillance data from 2014. They
19 suggest a level of streptococcal pneumonia
20 resistant to macrolides potentially as high as
21 50 percent across the U.S., with high-level
22 resistance of about 33 percent.

1 This is another way to look at macrolide
2 resistance. Here is a schematic representation of
3 a streptococcal pneumonia in the U.S. in 2014
4 showing almost 50 percent of the population with
5 some level of resistance to macrolides.
6 The question for the treating physician is
7 the following: At what level of antibiotic
8 resistance should a particular antibiotic not be
9 used for empiric therapy? This question was
10 addressed in the IDSA/ATS Guidelines for Management
11 of Community-acquired Pneumonia, published in 2007.
12 The 2007 guidelines recommended an alternative
13 agent to macrolides when more than 25 percent of
14 pneumococci develop high-level resistance to
15 macrolides.
16 Now let's review our current treatment
17 options based on the guidelines published in 2007.
18 Macrolides were suggested for outpatient
19 therapy, as well as inpatient therapy with one
20 important caveat. Where the prevalence of high-
21 level macrolide resistance is too high, it is not
22 recommended.

1 Since high-level resistance to macrolides
2 already have surpassed 25 percent, here is my
3 interpretation of our current options for treatment
4 of pneumonia. Due to high-level resistance rates,
5 we lost macrolides for outpatient therapy, and we
6 have lost macrolides as an option for switching
7 patients from IV to oral antibiotics.
8 So what about beta-lactams and quinolones,
9 the other potential first line treatment options?
10 Before, macrolides were considered first line
11 antibiotics due to their activity against typical
12 and atypical pathogens. Beta-lactams covered
13 typical pathogens, but they failed to cover
14 atypical pathogens. And quinolones covered both.
15 But quinolones are associated with
16 collateral damage, killing of enteric and negative
17 bacteria and other colonic organisms associated
18 with development of C. diff colitis. Now we have
19 data showing an association between quinolone use
20 and selection of multi-drug-resistant gram-negative
21 organisms.
22 This year, the FDA make a safety

1 announcement indicating that quinolones may be
2 associated with disabling and potentially permanent
3 serious side effects. These side effects may
4 involve tendons, muscles, joints, nerves, and the
5 central nervous system.
6 Stewardship efforts are needed in the field
7 of community-acquired pneumonia. Recently
8 published guidelines by the IDSA and the Society
9 for Clinical Immunology of America address ways to
10 improve antibiotic stewardship.
11 Some of these methods, based on the strong
12 evidence that apply to the field of community-
13 acquired pneumonia, are: intervention to reduce
14 the use of antibiotics with high risk for C. diff,
15 interventions to reduce antibiotic therapy to the
16 shortest effective duration, and promotion of IV to
17 oral switch options.
18 This all leaves us with a huge gap in our
19 current CABP treatment options. I really feel that
20 we need to restore macrolides as a treatment option
21 for our patients with CABP. Macrolides were the
22 most widely prescribed antibiotics for CABP due to

1 their well-understood benefit and well-
2 characterized safety profile.
3 We need an antibiotic with a targeted
4 spectrum of activity, such as a macrolide. And we
5 need an option to prevent the overuse of broad-
6 spectrum antibiotics associated with the
7 development of C. diff colitis. From a clinical
8 perspective, I strongly believe that restoration of
9 macrolide therapy will be a valuable addition to
10 our current treatment options.
11 Thank you. I will now return the podium to
12 Dr. Fernandes.
13 **Applicant Presentation - Prabhavathi Fernandes**
14 DR. FERNANDES: Thank you, Dr. Ramirez.
15 I will now present the microbiology and
16 pharmacokinetic data pertaining to solithromycin.
17 Let me first start with the mechanism of
18 action of solithromycin. The solithromycin
19 mechanism of action is improved over the other
20 macrolides as it has additional interaction sites
21 on the bacterial ribosome. Solithromycin has a
22 total of three, while older macrolides have one and

1 telithromycin has two binding sites.
2 Solithromycin, like other macrolides,
3 inhibits protein synthesis by binding in the
4 peptide tunnel of the ribosome. This is the first
5 interacting site by the N-dimethyl group that
6 solithromycin shares with all other macrolides.
7 Additionally, solithromycin interacts with
8 the second site by the long site chain, which is
9 similar to the other ketolides. A third site of
10 interaction is the fluorine at position C2.
11 These three interacting sites confer with
12 very tight binding, which could be the reason
13 solithromycin is mostly bactericidal, contrasting
14 the other macrolides, that are bacteriostatic.
15 These additional interactions also likely account
16 for the low resistance rates and improved activity
17 against macrolide-resistant isolates, including
18 telithromycin-resistant strains of Strep
19 pneumoniae.
20 Let's look at the antibacterial activity of
21 solithromycin in the global surveillance program.
22 As you can see here, solithromycin is active

1 against a broad range of respiratory pathogens,
2 including strains resistant to beta-lactams,
3 fluoroquinolones, and other macrolides.
4 Solithromycin is 16-fold more potent against
5 azithromycin-susceptible pneumococci, and has an
6 MIC-90 of 0.12 micrograms per mL. All strains in
7 surveillance studies have an MIC of less than or
8 equal to 1 microgram per mL, including those
9 isolated in Asia.
10 Among Staph aureus, MRSA are mostly
11 susceptible to solithromycin, unlike azithromycin.
12 MRSA are uncommon in CABP, and unlike azithromycin,
13 about 60 percent of MRSA are also susceptible to
14 solithromycin.
15 Solithromycin had comparable activity to
16 azithromycin against Haemophilus influenzae and
17 Moraxella catarrhalis. And as you will see,
18 solithromycin was effective in treating CABP when
19 these pathogens were involved.
20 Macrolides are added to the treatment of
21 CABP to cover atypical pathogens. Mycoplasma
22 pneumoniae had increased virulence in recent years,

1 and is also known to cause serious disease, even in
2 adults. Azithromycin-resistant Mycoplasma is
3 increasing, and solithromycin is very active
4 against these resistant strains. Solithromycin is
5 also very active against the atypical pathogen
6 Legionella, which is also known to cause severe
7 CABP.
8 Now turning to the intracellular penetration
9 of solithromycin.
10 In vitro, solithromycin is more potent than
11 azithromycin against intracellular phagocytized
12 Legionella pneumophila, with activity in
13 phagolysosomes. It is active in all compartments
14 of the cell.
15 Let's discuss the activity on resistant
16 strains.
17 As you can see here, solithromycin is active
18 against penicillin-resistant pneumococci. It is
19 also effective against macrolide-resistant
20 pneumococci, specifically against erm, mef, and
21 erm/mef combinations, as well as strains with
22 ribosomal mutations. Solithromycin is also active

1 against quinolone-resistant strains.
2 As you can see here on the right,
3 azithromycin is not active against the majority of
4 these strains, and solithromycin is active at less
5 than or equal to 1 microgram per mL against all of
6 these strains.
7 Solithromycin had a low rate of spontaneous
8 mutation in single-step mutational analysis, as is
9 known for the older macrolides. The frequency of
10 spontaneous mutation was less than 10 to the
11 minus 9. Solithromycin had a low occurrence of
12 decreased susceptibility in initial experiments
13 conducted to determine multi-step resistance
14 development.
15 We challenged resistance development by
16 conducting further multi-step experiments using
17 strains that were already resistant to the older
18 macrolides carrying ermB and mef resistance.
19 Multi-step transfers at sub-MIC experiments showed
20 that the organism was still susceptible to
21 therapeutic levels of solithromycin, as seen here.
22 Increasing the MICs above 1 microgram per mL could

1 occur with the additional transfers but is a very
2 rare event, with mutations at multiple sites on the
3 50S ribosome.
4 Solithromycin appears to have a low
5 potential to cause C. difficile associated
6 diarrhea. In an intestinal microflora study, oral
7 solithromycin had little effect on Bacteroides
8 species, the major and protective constituent of
9 the intestinal microbiota. No C. difficile strains
10 or toxin were identified.
11 Now let me move to the phase 1
12 pharmacokinetic results.
13 Based on PK/PD modeling of phase 1 single
14 and multi-dose data and a mouse pneumonia data
15 where AUC over MIC was shown to be the critical
16 factor, target attainment was calculated, and the
17 dosing regimen for our CABP trials were selected.
18 A loading dose of 800 milligrams was selected, with
19 a maintenance dose of 400 milligrams.
20 The right half of this slide shows in red
21 day 5 plasma levels with the 800/400 milligram dose
22 regimen, and in blue is the 400 milligrams daily

1 only, showing that by day 5, the plasma levels are
2 the same with and without the loading dose.
3 However, the 800 milligram loading dose achieves
4 near steady state plasma levels from the first day
5 onwards.
6 For intravenous solithromycin, the
7 pharmacokinetics are very similar to oral dosing.
8 However, no loading dose is necessary, as high
9 levels are reached with IV administration of
10 400 milligrams on day 1, as shown here by the green
11 line. The 800 milligram oral dose is presented in
12 red for comparison.
13 Now let us discuss the intravenous to oral
14 switch.
15 If the patient is switched to oral dosing,
16 a loading dose was studied in order to ensure
17 maintenance of sufficient blood levels based on
18 phase 1 plasma level data. As shown on the left
19 side in the phase 3 intravenous to oral trial, we
20 have noted higher blood levels than anticipated
21 from the phase 1 trials.
22 As learned from the phase 3 trial and in

1 agreement with the FDA, the oral loading dose
2 following IV therapy may not be necessary to get
3 sufficient exposure, as shown on the right side of
4 the slide.
5 Since our first indication was CABP, we ran
6 phase 1 studies to determine the solithromycin
7 concentrations in the lung, in the alveolar
8 macrophages, and in the epithelial lining fluid, or
9 ELF. Solithromycin achieves high plasma levels.
10 The ELF levels is 10 times and the macrophage
11 levels are 200 times the plasma levels.
12 Next, let's look at the PK/PD target
13 attainment of solithromycin.
14 The proposed solithromycin clinical, oral,
15 and IV dosing regimens are expected to provide high
16 probabilities of PK/PD target attainment for both
17 ELF total drug AUC over MIC, the most relevant
18 target for the indication of CABP, and the plasma
19 free drug AUC over MIC.
20 Shown here in light blue for the ELF total
21 drug AUC/MIC ratio associated with a 1 log CFU
22 reduction from baseline, percent probabilities of

1 PK/PD target attainment approached or exceeded
2 90 percent up to an MIC value of 4 micrograms per
3 mL across dosing regimens.
4 Shown here in dark blue for an MIC value of
5 0.12 microgram per mL, which is the MIC 90 for
6 Strep pneumoniae based upon global surveillance
7 data, the percent probabilities of PK/PD target
8 attainment was greater than or equal to 94 and
9 greater than or equal to 99 percent for the oral
10 and intravenous-to-oral dosing regimens,
11 respectively.
12 Finally, I will discuss the clinical PK
13 data. The bioavailability of solithromycin is not
14 influenced by food. No dose adjustment is needed
15 for mild to severe hepatic impairment or in mild to
16 moderate renal impairment. However, dose
17 adjustments are recommended for severe renal
18 impairment with creatinine clearance of less than
19 30 milliliters per minute, as plasma levels could
20 be increased twofold in these patients.
21 The drug-drug interaction profile for
22 solithromycin shown here is typical of a macrolide.

1 In vitro studies identified CYP3A4 and *P-gp as
2 mechanisms, as both a substrate and an inhibitor,
3 through which drug-drug interactions could occur.
4 Clinical studies were conducted to confirm these
5 mechanisms and provide quantitative guidance to
6 solithromycin exposure or co-medication exposure.
7 In summary, solithromycin is active against
8 typical and atypical pathogens, including
9 macrolide-resistant strains. It is more potent
10 than the other macrolides against intracellular
11 pathogens. Solithromycin has a low potential to
12 cause C. difficile-associated diarrhea. It was
13 shown to have a low rate of spontaneous mutations
14 and a higher barrier to resistance.
15 The PK/PD data shows more than 90 percent
16 target attainment, based on both total drug ELF and
17 free drug plasma levels. The oral formulation has
18 good bioavailability to allow for an IV to oral
19 switch regimen. Thank you. Dr. Oldach will now
20 present the study designs for our phase 3 trials.
21 **Applicant Presentation - David Oldach**
22 DR. OLDACH: Thank you, Dr. Fernandes.

1 Good morning. My name is David Oldach. I'm
2 the chief medical officer at Cempra, with oversight
3 responsibilities for our clinical development
4 program. Before we get into the results, we will
5 first touch on the study design for our two phase 3
6 studies as well as to discuss dosing.
7 Our phase 3 program consisted of two pivotal
8 trials with similar designs. In study 300,
9 patients were treated with oral solithromycin for 5
10 days, and in study 301, patients were given IV
11 solithromycin, with an option to switch to oral
12 capsules, for a total treatment duration of 7 days.
13 Both trials were randomized, double-blind, active-
14 controlled, multi-center, global noninferiority
15 studies.
16 Moxifloxacin was used as the active control
17 because it is a potent fluoroquinolone in wide use
18 for treatment of CABP. It is an accepted single-
19 agent therapy with convenient IV to oral
20 transition. The same assessments, outcome
21 measures, and testimony points were used in both
22 trials.

1 Randomization was stratified by geographic
2 region, by history of asthma and/or COPD, and by
3 PORT risk class. The PORT class, or Pneumonia
4 Outcomes Research Team class, is a severity index
5 for pneumonia. In study 300, enrollment of PORT II
6 severity CABP was limited to no more than
7 50 percent of patients. In study 301, PORT II
8 enrollment was limited to no more than 25 percent,
9 with the added requirement that at least 25 percent
10 of patients be of PORT IV severity.
11 Here's the schematic for the design of the
12 oral study. In this trial, we compared 5 days of
13 solithromycin therapy to 7 days of treatment with
14 moxifloxacin. The 5-day course of solithromycin
15 was in alignment with current efforts to reduce
16 overall antibiotic use, including duration of
17 therapy, as reasonably acceptable -- as clinically
18 reasonable. The moxifloxacin duration was in
19 accordance with its label. 426 patients were
20 randomized to solithromycin and 434 to
21 moxifloxacin.
22 The primary endpoint of early clinical

1 response was assessed at day 4. Blinded placebo
2 was given to solithromycin patients on days 6 and
3 7. Short-term and long-term follow-up were also
4 assessed after the end of treatment.
5 In study 301, given the greater severity of
6 disease, all patients received 7 days of therapy.
7 434 patients were randomized to solithromycin and
8 429 to moxifloxacin. All patients received IV
9 study drug on day 1 and all could have received up
10 to 7 once-daily IV doses.
11 Patients randomized to solithromycin
12 received 400 milligrams on day 1 followed by 400
13 milligrams IV daily until predefined oral switch
14 criteria were met, at which time investigators had
15 the option to switch to oral therapy. Patients
16 randomized to moxifloxacin received 400 milligrams
17 IV daily, and a switch to oral dosing continued
18 with 400 milligrams daily for the remainder of the
19 treatment period.
20 Enrollment criteria were similar between
21 studies. All patients needed to have at least
22 three of the cardinal symptoms of CABP listed here.

1 They additionally had to have fever, hypothermia,
2 or pulmonary signs on physical examination.
3 The diagnosis of CABP had to be
4 radiographically confirmed. Administration of a
5 single dose of a short half-life antibiotic during
6 the evaluation period prior to enrollment was
7 permitted, but this was limited to no more than
8 25 percent of patients.
9 Exclusion criteria included severe COPD or
10 bronchiectasis, mean QTcF greater than 450
11 milliseconds at screening, AST or ALT greater than
12 threefold the upper limit of normal, total
13 bilirubin greater than twofold the upper limit of
14 normal, and diagnoses of HIV infection, organ
15 transplant, active cancer, or myasthenia gravis.
16 In accordance with FDA guidance, early
17 clinical response, or ECR, was selected as the
18 primary endpoint for both studies. This was the
19 first prospective use of early clinical response as
20 a primary endpoint in a registrational trial of an
21 antibiotic for CABP. As already shown in the
22 schematics, ECR was determined at day 4 after the

1 first dose of study drug.

2 A patient was defined as a responder if the
3 following four criteria were met. There had to be
4 an improvement in at least two of the four cardinal
5 CABP symptoms present at baseline. There could be
6 no worsening of any symptom. The patient could not
7 have received another antibiotic for the treatment
8 of CABP. In addition, any patient death prior to
9 the late follow-up visit was defined as failure for
10 the early clinical response.

11 Shown here are the methods used to establish
12 microbiological diagnoses, including culture,
13 antigen detection, serology, and PCR diagnostics.
14 Investigators in our trials went to great effort to
15 identify pathogens, resulting in a diagnosis in
16 nearly 50 percent patients. These results together
17 define the microbiological ITT, or mITT,
18 population. Thank you. Dr. Das will now present
19 the efficacy data.

20 **Applicant Presentation - Anita Das**

21 DR. DAS: Thank you, Dr. Oldach.

22 My name is Anita Das, and I'm the lead

1 statistician on the solithromycin program. I've
2 been involved in the development of antibiotics for
3 over 10 years, including working with the FNIH
4 Biomarkers Consortium on the development of
5 endpoints for CABP trials.
6 First, I will present the statistical
7 aspects from the two pivotal trials.
8 Study 300 had co-primary endpoints, which
9 was in alignment with the 2009 FDA draft CABP
10 guidance, and discussions at the 2011 ADAC meeting.
11 One of the co-primary efficacy endpoints in study
12 300 was early clinical response in the intent-to-
13 treat, or ITT, population. The other co-primary
14 endpoint was early clinical response in the mITT
15 population in data pooled across the two phase 3
16 studies.
17 Study 301 had one primary endpoint, early
18 clinical response in the ITT population, which was
19 aligned with the FDA guidance of 2014. Early
20 clinical response in the mITT population for the
21 pooled studies was a secondary endpoint for this
22 study.

1 To determine the sample size for the two
2 studies, based on data from the phase 2 study it
3 was assumed that 73 percent of patients in the ITT
4 population would be early clinical responders.
5 Using a noninferiority margin of 10 percent, as
6 noted in the 2009 FDA guidance, a one-sided alpha
7 of 0.025, and 90 percent power, the total sample
8 size for each study was determined to be 860
9 patients.
10 Assuming the same percentage of patients
11 with a response, and using a 15 percent
12 noninferiority margin in the pooled mITT
13 population, as noted in the 2009 FDA guidance,
14 there was more than 90 percent power to show
15 noninferiority with a microbiologic diagnosis as
16 low as 25 percent of the ITT population in each
17 study.
18 A key secondary endpoint in both studies was
19 the investigator's assessment of clinical response
20 at the short-term follow-up, or SFU, visit. Three
21 symptom-based endpoints at SFU were also
22 determined. Symptom response of the cardinal CABP

1 symptoms was defined as the absence of chest pain
2 and sputum production, and the absence of or
3 improvement from baseline in cough and dyspnea.
4 Sustained early clinical response required
5 the patient to be an early clinical responder,
6 maintain the response at the SFU visit, and be
7 absent of chest pain and sputum production.
8 Resolution of the four cardinal CABP symptoms was
9 defined as absence of all symptoms.
10 We also examined the percentage of patients
11 showing an improvement in the CABP symptoms at
12 day 4, the end of treatment, or EOT, visit, and the
13 SFU visit.
14 Now I will show the results from the oral
15 study, study 300.
16 The demographic characteristics were
17 comparable between treatment groups. Slightly more
18 than half of the patients were male, with a mean
19 age of 59 years in the solithromycin group and 57
20 years in the moxifloxacin group. More than
21 30 percent of patients in each group were greater
22 than or equal to 65 years of age. About 22 percent

1 of the study population was enrolled in the United
2 States.
3 Also, the baseline disease characteristics
4 were similar in the two treatment groups.
5 Approximately 15 percent of patients in each group
6 had a history of asthma and/or COPD. Each
7 treatment group was evenly divided between patients
8 in the PORT II and PORT III/IV risk classes.
9 A slightly lower percentage in the
10 solithromycin group met SIRS criteria and the
11 modified ATS severity criteria. Twelve percent
12 and 10 percent of solithromycin and moxifloxacin
13 patients received an antibiotic in the 7 days prior
14 to randomization.
15 This stacked bar graph shows that the
16 distribution of severity of the four CABP symptoms
17 were similar at baseline between the treatment
18 groups. The majority of patients had moderate to
19 severe symptoms, as indicated by the green and red
20 bars.
21 Approximately 50 percent of randomized
22 patients in both treatment groups had a confirmed

1 pathogen at baseline. The most common baseline
2 pathogen was Streptococcus pneumoniae. Atypical
3 pathogens were also commonly identified. The
4 distribution of pathogens was balanced between
5 treatment groups, with the exception of Haemophilus
6 influenzae, seen in 19 percent of solithromycin
7 patients versus 13 percent of moxifloxacin
8 patients.
9 Ninety-five percent of patients completed
10 the study in both treatment arms. The primary
11 reason for discontinuation from study was
12 withdrawal of consent.
13 I will now show you the co-primary endpoint
14 results.
15 In study 300, oral solithromycin was
16 noninferior to moxifloxacin for the co-primary
17 endpoint or early clinical response in the ITT
18 population. About 78 percent of patients in both
19 the solithromycin and moxifloxacin groups were
20 responders. The treatment difference of
21 solithromycin minus moxifloxacin was 0.3, with the
22 lower bound of the 95 percent confidence interval

1 for the treatment difference greater than the
2 prespecified noninferiority margin of 10 percent.
3 Solithromycin was also noninferior to
4 moxifloxacin in the analysis of early clinical
5 response in the pooled mITT population from studies
6 300 and 301. Seventy-seven percent of patients
7 were responders for solithromycin versus 79 percent
8 for moxifloxacin. The lower bound of the 95
9 percent confidence interval for the treatment
10 difference of solithromycin and moxifloxacin was
11 greater than the prespecified noninferiority margin
12 of 15 percent.
13 Since both co-primary endpoints met the
14 noninferiority assessment, oral solithromycin was
15 shown to be noninferior to oral moxifloxacin in
16 study 300.
17 Let's now look at outcomes at SFU.
18 Endpoints at the SFU visit showed comparable
19 results in the solithromycin and moxifloxacin
20 groups. The percentage of patients assessed as
21 clinical success by the investigator at SFU was
22 85 percent or higher in both treatment groups.

1 Seventy-four percent of solithromycin and
2 76 percent of moxifloxacin patients were responders
3 based on the symptom response endpoint, which was
4 defined similarly to early clinical response.
5 Sustained early clinical response was
6 64 percent in both treatment groups, and resolution
7 of the cardinal symptoms of CABP was also similar
8 in both treatment groups. In both treatment
9 groups, CABP symptoms showed improvement at day 4,
10 EOT, and SFU. The percent improvement in each
11 symptom was similar between the solithromycin and
12 moxifloxacin groups.
13 Now I will present the results for the IV to
14 oral study, study 301.
15 Baseline demographics were balanced between
16 the two treatment groups. About half of the
17 patients were male, with the mean age of
18 approximately 61 years. More than 40 percent of
19 patients were 65 years of age or older. A total of
20 11 percent of patients were enrolled in the U.S.,
21 with the majority of patients enrolled in Eastern
22 Europe.

1 The treatment groups had similar CABP
2 disease characteristics at baseline. Twenty-
3 two percent of patients in each group had a history
4 of asthma and/or COPD. By design, approximately
5 75 percent of patients in each treatment group were
6 PORT risk class III or IV, with the remaining
7 patients categorized as PORT risk class II.
8 The majority of patients met the SIRS
9 criteria, while only about 5 percent met the
10 modified ATS severity criteria. About 25 percent
11 of patients in both treatment groups received
12 antibiotics in the 7 days prior to randomization.
13 Also in study 301, the severity distribution
14 of the cardinal symptoms of CABP at baseline was
15 similar between the treatment groups. The symptoms
16 were mostly moderate to severe, except for chest
17 pain, where the severity was evenly divided between
18 moderate and severe and mild or none.
19 Approximately 40 percent of ITT population
20 had a pathogen identified at baseline. The
21 distribution of pathogens was balanced between
22 treatment groups. As in study 300, the most common

1 baseline pathogen was Streptococcus pneumoniae.
2 Ninety-four percent of patients in the
3 solithromycin group completed the study, and
4 95 percent in the moxifloxacin group. Slightly
5 more patients in the solithromycin group withdrew
6 from the study due to withdrawn consent and adverse
7 events.
8 Let's now look at the primary endpoint
9 result.
10 IV to oral solithromycin was found to be
11 noninferior to moxifloxacin for early clinical
12 response. A total of 79 percent of patients in
13 both treatment groups were a responder. The lower
14 bound of the 95 percent confidence interval for the
15 treatment difference was greater than the
16 prespecified noninferiority margin of 10 percent.
17 As in study 300, solithromycin achieved a
18 high investigator success rate of 85 percent in the
19 ITT population. Eighty-nine percent of
20 moxifloxacin patients were a clinical success.
21 Symptom-based endpoints at the SFU visit
22 also showed similar results in both treatment

1 groups. Eighty percent of solithromycin patients
2 and 77 percent of moxifloxacin patients were
3 considered responders at the SFU visit based on the
4 symptom response by major CABP symptoms. Sustained
5 early clinical response was 68 percent in both
6 treatment groups, and resolution of the four
7 cardinal symptoms of CABP was also similar in both
8 treatment groups.
9 Additional data supporting the efficacy of
10 solithromycin is provided here. The percentage of
11 patients showing improvement in each of the
12 symptoms of CABP were high and comparable between
13 the treatment groups at each time point, day 4, end
14 of therapy, and SFU. These analyses, based on the
15 symptoms of CABP, demonstrate comparable efficacy
16 for solithromycin and moxifloxacin at the SFU time
17 point.
18 Now I will present several analyses that
19 were done in the pooled data so as to provide a
20 more robust data set. These include the subgroup
21 analyses and the by-pathogen early clinical
22 response rate and the by-pathogen investigator's

1 clinical success rate at the SFU visit.
2 A consistent effect was observed for early
3 clinical response in demographic subpopulations in
4 the ITT population. Of note, the responder rate in
5 North America was 73 percent in the solithromycin
6 group and 66 percent in the moxifloxacin group.
7 Subpopulation analyses were also conducted
8 for characteristics related to baseline disease
9 severity. Treatment differences were consistent in
10 analyses of patients classified as PORT II or PORT
11 III/IV. Responder rates in the prior antibiotic
12 subgroups were also similar between treatment
13 groups, and were slightly higher in those patients
14 who received a prior antibiotic.
15 About 20 patients in each treatment group
16 were bacteremic at baseline. In this subgroup,
17 65 percent of patients in the solithromycin group
18 and 67 percent of patients in the moxifloxacin
19 group were responders.
20 Let's now look at the pathogen-specific
21 results in the mITT population.
22 Early clinical response rates were also

1 similar for solithromycin- and moxifloxacin-treated
2 patients for each target pathogen. Comparable
3 clinical success rates for each target pathogen
4 were also seen at the SFU visit in the mITT
5 population. With the exception of Staphylococcus
6 aureus, the clinical success rate in the
7 solithromycin group was 80 percent or greater for
8 each target pathogen.
9 In conclusion, data from these two large
10 phase 3 studies demonstrate that solithromycin is
11 effective in the treatment of adults with CABP
12 using both oral and IV regimens. Solithromycin
13 demonstrated noninferiority to moxifloxacin for the
14 primary outcome of early clinical response, high
15 success rates at the SFU visit based on
16 investigator assessment of clinical response, and
17 similar response rates to moxifloxacin for all
18 symptom-based endpoints at SFU.
19 Early clinical response findings were
20 consistently observed across demographic,
21 geographic region, and disease severity
22 subpopulations by pathogen. Early clinical

1 response rates and investigator-assessed clinical
2 success rates for target CABP pathogens were also
3 comparable to those observed for moxifloxacin.
4 Thank you. Dr. Oldach will now present the
5 safety data.
6 **Applicant Presentation - David Oldach**
7 DR. OLDACH: Thank you, Dr. Das.
8 I'll now review pooled data from our two
9 phase 3 studies, which demonstrate that both IV and
10 oral solithromycin have an acceptable safety
11 profile for patients with CABP.
12 Over 2,000 patients and healthy adults
13 have been exposed to at least a single dose of
14 solithromycin. This includes 1474 patients from
15 our phase 1, 2, and 3 CABP development program.
16 Today we'll focus most of our discussion on the
17 safety data in the 856 patients from our phase 3
18 CABP studies.
19 Here you see adverse events from the pooled
20 phase 3 studies. The overall incidence of adverse
21 events was higher in the solithromycin group at
22 44.2 percent compared to moxifloxacin at

1 35.2 percent. The difference was mostly
2 attributable to a higher incidence of infusion site
3 events which, when excluded, show overall AE rates
4 of 35.5 and 34.3 percent. Infusion-related adverse
5 events, including pain and phlebitis, have been
6 commonly observed with other IV macrolide
7 antibiotics.
8 The occurrence of serious adverse events, or
9 SAEs, was comparable across studies. Most were
10 related to the underlying pneumonia or attributed
11 to comorbid conditions. Mortality rates were low
12 for both studies in both treatment arms. Let's
13 walk through each of these categories in more
14 detail.
15 Outside of infusion site events, the
16 incidence of specific adverse events was comparable
17 between solithromycin and moxifloxacin. The most
18 common AEs were diarrhea, headache, nausea, and
19 dizziness, most of mild severity.
20 In the phase 3 program, three moxifloxacin
21 patients were identified with C. difficile-
22 associated diarrhea. In contrast, no C. difficile-

1 associated diarrhea was identified in any
2 solithromycin patient across the greater than 2,000
3 patient and subject global development program.
4 The incidence of infusion-related adverse
5 events was higher for solithromycin. This was not
6 unexpected. The infusion solution has an acidic pH
7 and this is a macrolide antibiotic. There were no
8 infusion-related serious adverse events. Overall,
9 among patients who experienced infusion site
10 events, drug was discontinued due to these adverse
11 events in only 10 patients.
12 Among the 135 patients experiencing an
13 infusion AE, most events were mild or moderate in
14 severity, resolved rapidly, and rarely led to
15 treatment discontinuation. Infusion-related events
16 considered severe occurred in 8 solithromycin
17 patients. Symptoms in 7 of these patients resolved
18 on the same or next day. One patient developed
19 phlebitis, which resolved by the SFU visit. No IV-
20 related reaction of any severity resulted in long-
21 term sequelae.
22 Adverse events leading to discontinuation of

1 study drug were reported in less than 5 percent of
2 patients in either arm. With the exception of
3 infusion site events and worsening pneumonia, most
4 preferred terms were reported in only a single
5 solithromycin or moxifloxacin patient.
6 Therefore, in this table, AEs leading to
7 discontinuation are presented by system, organ, and
8 class. Infusion site reactions emerge as the most
9 common AE associated with discontinuation of
10 solithromycin.
11 The overall incidence of serious adverse
12 events was 6.8 percent in the solithromycin group
13 and 5.8 percent with moxifloxacin. In this table,
14 all events reported in two or more solithromycin
15 patients are presented.
16 The most common events beyond pneumonia were
17 pleural effusion and associated empyema,
18 respiratory failure, and acute myocardial
19 infarction. Most SAEs were related to the
20 underlying disease or to other underlying medical
21 conditions that were exacerbated by the pneumonia
22 episode.

1 Moving to the deaths observed in our phase 3
2 studies, 11 deaths occurred in solithromycin
3 patients and 13 deaths occurred in moxifloxacin
4 patients across the phase 3 studies. Most deaths
5 in each treatment group were attributable to
6 underlying respiratory or cardiac diseases in
7 patients presenting with multiple comorbidities and
8 risk factors.
9 Now let's discuss adverse events of special
10 interest.
11 We reviewed cardiac, liver, vision, hearing,
12 and infusion-related AEs using MedDRA's SMQ, or
13 Standardized MedDRA Query, of the AE database. Our
14 interest in cardiac diseases relates to both older
15 macrolides and quinolones, given their known effect
16 on QT.
17 We examined hearing disorders, as they had
18 been well-described with older macrolides. Our
19 interest in liver-related adverse events, loss of
20 consciousness, vision disorders, and myasthenia
21 gravis is derived from observations with
22 telithromycin.

1 Here you can see the individual MedDRA query
2 results in our phase 3 program. Point estimates to
3 the left over the vertical line connote lower risk
4 with solithromycin. There are no notable
5 differences between solithromycin and moxifloxacin
6 in the rates of these adverse events.
7 Cardiac disorders, including cardiac
8 failure, QT prolongation, and tachyarrhythmias all
9 occurred with low frequency. Hypotonic or
10 hyporesponsive episodes, which are related to loss
11 of consciousness, fainting, or syncope were rare
12 events.
13 With regard to liver-related adverse events,
14 hepatobiliary AEs were comparable between the two
15 arms. Most solithromycin liver-related AEs were
16 asymptomatic elevations of ALT or AST.
17 The vision disorders AE rate of 0.12 percent
18 refers to a single solithromycin patient with
19 floaters. For solithromycin, the hearing
20 impairment AE rate of 0.12 percent refers to a
21 single patient with otitis media. No patients on
22 solithromycin reported tinnitus or hearing

1 dysfunction.
2 Telithromycin is known to impair visual
3 accommodation, and we have discovered that this is
4 due to inhibition of nicotinic acetylcholine
5 receptors in the ciliary ganglia of the eye.
6 In contrast, impairment to visual
7 accommodation is not a feature of solithromycin.
8 Here you can see all eye or vision AEs among all
9 solithromycin patients in the integrated study
10 database. Nine events were reported by seven
11 patients throughout our phase 1 through phase 3
12 program with over 1400 patients. No patient in the
13 phase 2/3 CABP trials reported blurred vision.
14 This profile further differentiates solithromycin
15 from telithromycin.
16 It has been suggested that cases of syncope
17 or fall or hypotonia may indicate a telithromycin-
18 like effect of loss of consciousness. Syncope,
19 fall, or hypotonia were rare events across the
20 solithromycin program, and when observed, all
21 occurred well after completion of solithromycin
22 dosing. In the case of hypotonia, this was a

1 miscoded event. Solithromycin is not associated
2 with syncope or loss of consciousness.
3 Overall, cardiovascular-related adverse
4 events were reported in fewer solithromycin that
5 moxifloxacin patients, with 3 percent in the
6 solithromycin group and 4.7 percent with
7 moxifloxacin. Here are the cardiovascular events
8 that occurred in at least two patients in either
9 group. Events occurring in only one patient are
10 listed in your briefing books.
11 We performed a thorough QT study in healthy
12 volunteers. Solithromycin was administered as a
13 rapid single-dose infusion of 800 milligrams,
14 achieving a supratherapeutic mean concentration of
15 6 micrograms per mL. Here you can see plotted the
16 QTcF double delta -- that is, the placebo-adjusted
17 change from baseline in QTcF for solithromycin and
18 moxifloxacin.
19 The upper bounds of the 90 percent
20 confidence interval around the mean solithromycin
21 QTcF values, in blue, were less than 5 milliseconds
22 at each prespecified time point, unlike

1 moxifloxacin. This was the negative thorough QT
2 study, and it can be concluded that solithromycin
3 does not prolong QT.
4 In the thorough QT study with
5 supratherapeutic solithromycin exposure following
6 IV infusion, there was an increase in mean heart
7 rates. In contrast, among patients with pneumonia,
8 the central tendency is for heart rate to decline
9 with solithromycin therapy. Here you can see mean
10 heart rates over time from baseline through day 5
11 in both the oral and IV to oral trials. The curves
12 for solithromycin and moxifloxacin are nearly
13 superimposable.
14 Now let's discuss hepatic safety.
15 It is well-known that macrolides may cause
16 transient and asymptomatic elevation in serum
17 aminotransferase levels. All patients in the
18 phase 3 program had hepatic safety parameters
19 measured at baseline, day 4, day 7, and day 14.
20 These were all monitored at a central laboratory.
21 This table presents the rates of
22 transaminase elevation to specific thresholds and

1 the rates of elevation of both transaminase and
2 bilirubin. A few important observations can be
3 made.
4 ALT elevation greater than threefold the
5 upper limit of normal occurred more frequently with
6 solithromycin. These ALT elevations were typically
7 asymptomatic, not associated with bilirubin
8 elevation or hepatic dysfunction, and they resolved
9 rapidly.
10 ALT elevations greater than tenfold the
11 upper limit of normal was a rare observation. The
12 observation of both transaminase elevation and
13 bilirubin elevation was a rare event with both
14 drugs. We'll discuss the solithromycin patients
15 meeting these criteria in a moment.
16 Here are the rates of transaminase elevation
17 in solithromycin patients broken out by study. ALT
18 elevation occurred more frequently in the IV to
19 oral trial, consistent with the finding that ALT
20 elevation is an exposure-related phenomenon with
21 solithromycin.
22 Hy's law is used as a predictive tool to

1 identify drugs with high risk for drug-induced
2 liver injury. Laboratory criteria include elevated
3 transaminase and bilirubin values, which are not
4 attributable to cholestasis. To meet criteria as a
5 Hy's law case, the abnormality should not be
6 attributable to alternative clinical explanation.
7 An independent hepatic safety advisory board
8 reviewed all potential cases and determined that no
9 Hy's law cases were observed.
10 Let's review the eDISH plot. This eDISH
11 plot presents all treatment-emergent maximal ALT or
12 AST values versus maximal bilirubin levels in
13 patients across our development program. The
14 vertical line falls on AST or ALT threefold the
15 upper limit of normal, while the horizontal line
16 falls on total bilirubin twofold the upper limit of
17 normal.
18 Patients in the upper right quadrant meet
19 laboratory criteria for Hy's law, provided that
20 alkaline phosphatase level is less than twofold the
21 upper limit of normal. As you can see, two
22 solithromycin CABP patients and one moxifloxacin

1 CABP patient met Hy's law limited liability
2 criteria. None of these was a Hy's law case.
3 Now, when we add into this plot data from
4 our NASH and COPD trials with their longer-term
5 dosing, one additional patient falls into the right
6 upper quadrant of possible Hy's law patients. This
7 patient was also not a Hy's law case. We'll
8 discuss these patients in more detail in a moment.
9 You'll note that our eDISH plot differs from
10 the eDISH plot in FDA's briefing book. FDA
11 presents five solithromycin patients in the upper
12 right quadrant, which is the quadrant of potential
13 concern, while we present three solithromycin and
14 one moxifloxacin, as I have just shown.
15 The FDA plot includes AST -- ALT but not
16 AST, and included baseline laboratory values, which
17 were obtained prior to study drug exposure in their
18 analysis set. FDA in this way identified
19 solithromycin patients with elevated bilirubin at
20 baseline that qualified them for inclusion in the
21 right upper quadrant of their eDISH plot.
22 Each of these additional patients was

1 treated successfully with solithromycin and had a
2 decline in bilirubin on study drug. None of these
3 patients met Hy's law criteria on solithromycin.
4 Let's look more closely at the solithromycin
5 patients identified in Cempra's eDISH analysis.
6 The first potential Hy's law case from the
7 CABP program was a 58-year-old female in the
8 solithromycin group who developed shock liver in
9 the context of multi-system organ failure due to
10 sepsis prior to her death on day 13.
11 The second potential case, also in the
12 solithromycin group, was a 34-year-old female with
13 ALT elevation at day 12 to 3.8-fold the upper limit
14 of normal with normal bilirubin. In follow-up at
15 day 26, transaminases were normal but bilirubin,
16 mostly indirect, was 2.4-fold the upper limit of
17 normal. Gilbert's syndrome likely contributed to
18 the bilirubin elevation, and these elevations did
19 not occur concurrently. Neither of these was a
20 Hy's law case.
21 Now let's discuss the patient from our
22 longer-term dosing, COPD pilot study. In

1 exploratory studies, Cempra is evaluating the
2 safety of longer-term dosing strategies. In a COPD
3 pilot study evaluating the anti-inflammatory
4 effects of solithromycin, patients received daily
5 solithromycin or placebo for 28 days.
6 One patient in this study developed an
7 episode of cholestatic hepatitis. This 69-year-old
8 with a history of COPD and prostatic hypertrophy
9 received 400 milligrams of daily oral solithromycin
10 for 23 days. Concomitant medications included
11 multi-dose inhalers and finasteride.
12 At baseline on day 8, all hepatic safety
13 tests were in the normal range. On day 15, ALT,
14 AST, and alkaline phosphatase were elevated, with
15 normal bilirubin. Dosing continued. On day 23,
16 further increase of ALT and alkaline phosphatase
17 with elevation of total bilirubin to 4 milligrams
18 per deciliter led to study drug discontinuation.
19 These parameters identified this event as an
20 episode of cholestatic hepatitis.
21 Within 5 days of discontinuing study drug,
22 bilirubin had normalized and ALT and AST improved

1 markedly, with steady improvement thereafter. The
2 absence of fever or rash, the rapid resolution of
3 biochemical and clinical abnormalities, and the
4 transient nature of the eosinophilia all point away
5 from this being a case of hypersensitivity.
6 This patient's case was reviewed by the
7 hepatic safety advisory board and was not
8 considered a Hy's law case. Importantly, this
9 event occurred with longer-term solithromycin
10 dosing at 400 milligrams daily, a regimen that will
11 not be developed or recommended by Cempra.
12 To summarize the safety data, both IV and
13 oral solithromycin demonstrated an acceptable
14 safety profile for patients with CABP. ALT
15 elevations were observed and were typically
16 asymptomatic and without bilirubin elevation. No
17 Hy's law cases were observed.
18 There were no cases of C. difficile-
19 associated diarrhea in solithromycin patients.
20 This supports the hypothesis that solithromycin has
21 a potential role in a antibiotic stewardship
22 efforts, which are targeting this complication of

1 currently available therapies.
2 Infusion-related adverse events were obvious
3 with solithromycin and were typically limited to
4 mild or moderate severity. Solithromycin has a
5 negative thorough QT study, and no vision or
6 hearing adverse event signal.
7 Now, looking to ongoing safety evaluations,
8 Cempra is committed to continuous evaluation of
9 solithromycin safety to assist healthcare providers
10 and regulators through extensive monitoring of
11 safety outcomes. We will be tracking and reporting
12 safety data from multiple ongoing studies conducted
13 by Cempra and by our partner, Toyama in Japan, as
14 listed here.
15 Our hepatic safety advisory board, led by
16 Professor Watkins, will meet on a regular and ad
17 hoc basis, as needed, to review potential liver
18 injury events as they are reported to Cempra, in
19 the medical literature, or through the MedWatch
20 system.
21 We will conduct enhanced pharmacovigilance
22 activities with the goal of creating a broader net

1 to prospectively identify rare or idiosyncratic
2 hepatic events. We are presently in discussion
3 with three comprehensive healthcare systems. Under
4 consideration are programs through the Veterans
5 Administration, Harvard Pilgrim, and Kaiser, which
6 cover millions of U.S. lives.
7 We are developing algorithms to identify
8 appropriate ICD-10 hepatic events in patients
9 treated for CABP. These systems employ electronic
10 medical records with centralized data warehouses to
11 capture events that can provide information on a
12 weekly basis.
13 We expect to be able to access preexisting
14 risk factors and prescribed medications in these
15 analyses. And we will ensure these events will be
16 adjudicated by our hepatic safety advisory board.
17 Now at this time Dr. Paul Watkins will share
18 his view of the hepatic safety profile of
19 solithromycin and other macrolide antibiotics.
20 **Applicant Presentation - Paul Watkins**
21 DR. WATKINS: Good morning. I'm Paul
22 Watkins, professor and hepatologist at the

1 University of North Carolina in Chapel Hill. I'm a
2 consultant compensated by Cempra for my time.
3 I'm also the chair of the steering committee
4 of the Drug-Induced Liver Injury Network that has
5 created a registry of people who have experienced
6 liver injury due to marketed drugs in the United
7 States. And I'd like to show the committee the
8 major drugs that have been determined to cause
9 drug-induced liver industry in that registry.
10 On the left, you can see the top ten
11 therapeutic classes of drugs implicated in liver
12 injuries in the DILIN registry. N equals the
13 number of people in each category. And it is clear
14 that antimicrobials are by far the leading cause of
15 liver injury due to drugs.
16 On the right, you can see the top ten single
17 drugs causing liver injury in the registry. The
18 top culprit is Augmentin, followed by other common
19 antibiotics, including Bactrim, the macrolide
20 azithromycin, and the fluoroquinolones
21 ciprofloxacin and levofloxacin. In fact, the vast
22 majority of antibiotics in use in the U.S. have

1 been implicated in causing clinically important
2 liver injury.
3 In FDA briefing document, Dr. Avigan has
4 written a thoughtful and thorough assessment of the
5 liver safety concerns with solithromycin. To
6 summarize, this pretty much boils down to two
7 issues.
8 The first is the incidence of serum ALT
9 elevations, which is greater with solithromycin
10 than was observed in clinical trials of other
11 currently approved macrolide antibiotics. These
12 elevations have been well characterized clinically
13 as being asymptomatic and transient. As I will
14 show you, these elevations have been
15 mechanistically characterized at an unprecedented
16 level for an NDA submission.
17 The second issue is the shadow of Ketek,
18 which produced very rare, severe, and idiosyncratic
19 reactions, which were not predicted in its original
20 NDA clinical trial database or observed in the more
21 than 20,000 patients treated with Ketek prior to
22 FDA approval.

1 Let's first discuss the ALT elevations.
2 As noted on the first slide, I also direct
3 the UNC Institute for Drug Safety Sciences, which
4 is largely focused on defining mechanisms
5 underlying drug-induced liver injury. As part of
6 this effort, I chair the scientific advisory
7 committee for the DILIsym initiative, which is a 5-
8 year-old public-partnership that has involved
9 scientists and academia, and from 15 of the top 20
10 pharmaceutical companies, and FDA support of two
11 post-doctoral students on the project. The
12 initiative is developing software designed to
13 understand and predict liver safety liabilities in
14 new drug candidates.
15 The DILIsym initiative has shown that three
16 properties account for dose-dependent elevations in
17 serum ALT in greater than 90 percent of the drugs
18 that have been modeled to date. These properties
19 are oxidative stress and mitochondrial dysfunction
20 that can each be measured in cultured cells, and
21 bile acid transporter inhibition measured in
22 express transport proteins.

1 The relevant exposures of the liver to the
2 drug can be estimated by PBPK modeling, and this
3 information, together with the measured drug
4 properties, are entered into the model, which
5 includes a simulated population that has been
6 created by varying the key variables in the model
7 to include highly susceptible individuals for each
8 of the three mechanisms, along with variation in
9 liver exposure.
10 If requested, I would be happy to describe
11 this modeling process further and also share with
12 the committee data confirming the high success rate
13 of this modeling approach with all the drugs that
14 have been modeled in this way to date, much of
15 which has already appeared in peer-reviewed
16 journals.
17 To handle proprietary projects such as was
18 conducted for Cempra, DILIsym Services was created,
19 and I'm part owner in that company.
20 I am now going to show you the results of
21 DILIsym modeling for solithromycin, erythromycin,
22 clarithromycin, and telithromycin.

1 Here are the results predicted in the
2 simulated population versus the actual clinical
3 trial data. And I'd like to point out that the
4 simulated results are actual predictions, not
5 fitted to the clinical data.
6 As you can see, the incidence of elevations
7 in serum ALT greater than three times the upper
8 limit of normal, predicted by DILIsym in both
9 solithromycin studies, is reasonably close to what
10 was actually observed in the two clinical studies.
11 The prediction becomes much closer when only
12 patients with normal serum liver chemistries at
13 study entry are included. And these are the
14 observed values in parentheses.
15 DILIsym modeling to date obtained for two
16 other common macrolide antibiotics -- oops, I guess
17 it comes in at the end. All right -- the two
18 macrolide antibiotics, erythromycin and
19 clarithromycin, also revealed an incidence of serum
20 ALT elevations reasonably close to the range
21 reported from the clinical studies.
22 Interestingly, no elevations in serum ALT

1 were predicted when the data obtained from
2 telithromycin were entered into the model. And in
3 fact, the incidence of elevations in serum ALT
4 greater than three times the upper limit of normal
5 was reported to be near zero in the clinical
6 trials. That's as reported in the FDA briefing
7 document prepared for the 2006 ADCOM for Ketek. I
8 see that the values with normal serum ALT at
9 baseline have just been added to the figure.
10 In fact, getting back to Ketek, there were
11 no serious liver injuries or Hy's law cases
12 predicted in the simulated population for Ketek or
13 any of the drugs that are listed here. But as
14 noted by Dr. Avigan, the DILIsym model has not yet
15 incorporated adaptive immune mechanisms likely to
16 be involved in rare idiosyncratic liver injuries
17 due to macrolide antibiotics.
18 There are, in fact, no tests or modeling
19 currently capable of reliably predicting with any
20 drug the kind of very rare and idiosyncratic liver
21 injuries that occurred with Ketek. Even the
22 greater than 20,000 patients in clinical trials of

1 Ketek did not predict this liability, which was
2 only detected once hundreds of thousands of
3 patients were treated with the drug.
4 The last point to make clear on this slide
5 is that for macrolide antibiotics, the incidence of
6 serum ALT elevations does not predict the potential
7 for serious idiosyncratic DILI.
8 I also want to point out that the
9 predominant mechanism accounting for ALT elevations
10 with solithromycin was interference with
11 mitochondrial respiration. This resulted from the
12 drug inhibition of enzymes involved in the electron
13 transport chain. And there's no reason to believe
14 this involves damage to mitochondria, and the
15 transient nature of the ALT elevation supports
16 this.
17 A second point is that the liver effects of
18 solithromycin measured for DILIsym modeling are
19 quite different from those of telithromycin, which
20 has no detectable effect on mitochondrial
21 respiration.
22 I'll also note that the predominant

1 mechanism for erythromycin is an inhibition of bile
2 acid transporters. And solithromycin's effects on
3 the liver are most similar to those of
4 clarithromycin, which is a relatively safe
5 antibiotic for the liver. These observations
6 further support the conclusion that serum ALT
7 profile of solithromycin should not be considered a
8 predictor of telithromycin like DILI.
9 So in summary, serum ALT elevations
10 associated with solithromycin treatment have been
11 well characterized clinically and mechanistically.
12 Within the macrolide class, the incidence of serum
13 ALT elevations have not predicted serious safety
14 liabilities. And the mechanism underlying the
15 elevations with solithromycin is consistent with
16 the transient nature of the elevations observed.
17 In terms of the shadow of Ketek, I have
18 shown that the effects of solithromycin and
19 telithromycin on liver cells measured for the
20 DILIsym modeling are quite different. I also
21 believe that it's a biologically plausible
22 hypothesis that the anticholinergic effects

1 attributed to telithromycin's pyridine moiety acts
2 to enhance liver inflammation and may contribute to
3 its idiosyncratic liver injury potential.
4 Finally, the risk of extremely rare and
5 idiosyncratic liver injuries, such as have been
6 linked to telithromycin, cannot be currently
7 predicted, and it would likely require tens of
8 thousands of treated patients to detect. It would
9 therefore seem to me that an active
10 pharmacovigilance program such as proposed by the
11 sponsor is a reasonable way forward.
12 Thank you. Dr. Steve Vacalis will now
13 present his clinical perspective.
14 **Applicant Presentation - Steve Vacalis**
15 DR. VACALIS: Thank you, Dr. Watkins.
16 Good morning. I'm Steve Vacalis. Today I
17 have the privilege to give you a real-world primary
18 care perspective on community-acquired bacterial
19 pneumonia.
20 As a board-certified family medicine
21 physician in North Carolina, I've practiced
22 traditional inpatient and outpatient medicine for

1 nearly 20 years. I've helped start the hospital's
2 program at our community hospital, and continue to
3 treat a variety of patients with and without
4 pneumonia on an outpatient basis for the last
5 6 years.
6 Primary care physicians like myself will
7 diagnose and treat the lion's share of CABP
8 patients. Roughly 4 and a half million patients
9 with pneumonia are diagnosed in the primary care
10 clinics and urgent care centers each year. More
11 than 80 percent are treated as outpatients only.
12 Most of these patients will be treated empirically,
13 based on the cardinal symptoms of CABP alone.
14 But what is leading to this increased number
15 of pneumonia cases nationally? Here is what we do
16 know. Susceptibility rates have decreased across
17 most antibiotics for Strep pneumoniae since 2010.
18 The macrolides specifically have been shown to be
19 less effective, with national resistance levels
20 near 50 percent for pneumococcus. And in my state
21 of North Carolina, resistance is over 53 percent.
22 Because of this, I no longer prescribe macrolide

1 monotherapy since I'm concerned that my patients
2 will fail based on these resistance rates.
3 Since the national resistance to macrolides
4 is so high, the IDSA/ATS Special Consideration
5 Guideline is now the only viable option remaining
6 for patients in my practice setting. This option,
7 however, leads to the overuse of fluoroquinolones,
8 increasing the risk of serious disabling and
9 potentially permanent side effects, as outlined by
10 the FDA this past summer with its boxed warning.
11 My practice treated six patients with
12 pneumonia last month. Two came from the hospital
13 and one was sent to the hospital for additional
14 care. All six patients received a fluoroquinolone
15 either to start or by the end of their treatment.
16 This speaks to and stresses the fact that
17 macrolides failures exist and are avoided in
18 regions with resistance levels greater than
19 25 percent.
20 My practice and other clinicians are in need
21 of new antibiotic therapies. Ideally, it should
22 have a manageable potential side effect profile,

1 and should address stewardship needs. The approval
2 of solithromycin would potentially restore the
3 macrolide monotherapy option suggested in the
4 guidelines and could decrease the overuse of
5 fluoroquinolones for most patients with CABP.
6 Our main goal when treating patients with
7 pneumonia is to decrease their need for
8 hospitalization and IV medications, or if they're
9 already in hospital, to reduce their hospital stay.
10 We want to ensure that we prescribe the right drug
11 for the right bug, while being mindful of the
12 guidelines. Basically, we strive to eliminate
13 clinical failures.
14 A failure is defined as giving a second
15 course of the same antibiotic; starting a second
16 and different antibiotic during therapy; being seen
17 in an urgent care or in an emergency room while on
18 an antibiotic because of worsening symptoms;
19 getting admitted to hospital; or even death.
20 Personally, I'm excited to know that
21 solithromycin will provide efficacy comparable to a
22 fluoroquinolone with an acceptable safety profile.

1 Having an IV to oral switch option will potentially
2 minimize hospital stays and expedite hospital to
3 outpatient transition. This IV to oral option is
4 simple for both the treating physician and the
5 patient.
6 The fact that no episodes of C. difficile-
7 associated diarrhea were observed with
8 solithromycin is encouraging. This GI condition
9 can be difficult to treat, potentially spread to
10 other patients, and increase the time in hospital.
11 Solithromycin coverage of typical and
12 atypical pathogens of CABP, both against
13 susceptible as well as macrolide-resistant strains,
14 makes it even more attractive to providers. This
15 would streamline empiric decision-making.
16 Solithromycin is demonstrated to be
17 noninferior to moxifloxacin, a very potent
18 antibiotic. In regards to safety, solithromycin
19 was found to be well tolerated overall. Infusion
20 site reactions were observed with solithromycin,
21 and I believe we will be able to manage these
22 efficiently when they occur.

1 I am encouraged that the liver enzyme
2 elevations observed were asymptomatic and
3 transient. I also think Cempra's post-approval
4 plan to monitor for potential rare safety events is
5 important and comforting.
6 So what does this all mean for our patients
7 and the providers that treat them? The data
8 suggests a positive benefit-risk for solithromycin.
9 If approved, it will provide clinicians with a new
10 clinical option within the macrolide class that has
11 activity against many pathogens with an acceptable
12 safety profile.
13 Proper use of solithromycin for CABP alone
14 will address critical antibiotic stewardship needs.
15 It will reduce the need for combination therapy,
16 limit use of fluoroquinolones, and provide a short
17 course of therapy, remembering that over 80 percent
18 of the community-acquired bacterial pneumonia
19 patients will be treated in the outpatient setting,
20 position solithromycin perfectly for my practice
21 and my patients.
22 Thank you. Dr. Fernandes will now return to

1 take your questions.

2 **Clarifying Questions to the Presenters**

3 DR. BADEN: I would like to thank

4 Dr. Fernandes and her colleagues for a very

5 thorough and extensive presentation of a lot of

6 data to facilitate our discussion and understanding

7 of the potential of this product.

8 I'd like to open to clarifying questions.

9 Please remember to state your name for the record

10 before you speak. If you can please direct your

11 questions to a specific presenter. And for members

12 of the panel, if you can get mine or Lauren's

13 attention, we will keep a list to go around and ask

14 as many questions as we can. We must stop at

15 approximately 10:35, so we have about 10, 15

16 minutes for questions. And then we'll take a

17 break. I'm sorry -- yes, 10:35 is the break. So

18 we have 20 minutes for questions.

19 So Vincent, Dr. Lo Re?

20 DR. LO RE: Yes. Hi. Vincent Lo Re,

21 University of Pennsylvania. I have two questions.

22 The first question was, on slide CO-53, you

1 mentioned that the daily AUC over time, with and
2 without the oral dosing, seems to be no different
3 with the loading versus not. And I'm just
4 wondering why the loading dose was ultimately
5 recommended. That was question one.
6 Then question two was, in the study 301, we
7 were told in the introduction that the rate of
8 investigator-associated failures at the SFU visit
9 seemed to be higher for solithromycin versus
10 moxifloxacin by an amount that seemed to meet
11 statistical significance. And I didn't hear any
12 comment about that, and I just wanted to get some
13 sense of what the thought was from the sponsor.
14 DR. FERNANDES: Thank you. Dr. Bhavnani
15 from ICPD?
16 DR. BHAVNANI: Hi. Sujata Bhavnani from
17 ICPD, Schenectady, New York.
18 The decision to use an oral load in the IV
19 to oral dosing regimen was made earlier in the
20 development program. And these were based on
21 analyses that we did with a phase 1 model, phase 1
22 population PK model, preclinical PK/PD targets for

1 efficacy in simulation. These data showed us that
2 with an oral load, we would obtain optimal PK/PD
3 target attainment for patients with higher MIC
4 values.
5 Subsequently, after we used the phase 3 PK
6 data, refined the population PK model, we found
7 that the AUCs were higher, 15 to 20 percent, in
8 phase 3 patients. Thus, the oral load was no
9 longer needed, and we had the head room to switch
10 to an oral regimen without the use of the oral
11 loading regimen.
12 DR. FERNANDES: The second question, I would
13 like Dr. Oldach to address? Dr. Das.
14 DR. DAS: Dr. Anita Das. Let me make two
15 comments on your question. So first, the analysis
16 that was done by us and by FDA differed a little
17 bit in how the indeterminate responses or missing
18 data were handled.
19 We counted all missing data -- which was
20 low, about 3 percent -- we counted missing data as
21 failures; whereas in the analysis done by the FDA,
22 they looked at failure versus not failure. So

1 those missing datas would not have been counted as
2 a failure. And that accounted for a difference in
3 us saying statistically significant versus not.
4 But to also address the question, when we
5 looked at the difference -- because there is a
6 numerical difference -- there are several issues
7 that don't affect efficacy that affected the
8 outcome rates in this study. One of them is a drug
9 supply issue.
10 There were five solithromycin patients where
11 we had an interruption in drug supply, and they
12 received a non-study antibiotic and were this
13 counted as failures. And secondly, the infusion
14 pain reactions -- there were about 2.3 percent
15 received another antibiotic, and thus were counted
16 as failures.
17 So in summary, we don't believe that any of
18 the numerical differences are a reflection of
19 efficacy. And if you look at the symptom-based
20 endpoints, all of the different symptom-based
21 endpoints, you'll see high and comparable results
22 for solithromycin and moxifloxacin at the SFU

1 visit.
2 DR. BADEN: Thank you, Dr. Das.
3 DR. BADEN: If members of the panel have a
4 follow-on question to the question just asked,
5 please let me know so we can build on any themes
6 rather than be more staccato.
7 Dr. Boyer?
8 DR. BOYER: Thanks for the presentation on
9 liver toxicity. This is not the first drug that
10 causes elevated liver tests, and it's difficult to
11 know the significance of that.
12 My question is, in the case of particular
13 concern, the 69-year-old gentleman who had COPD and
14 became jaundiced. I must admit I object to the
15 Hy's law. And knowing Hy Zimmerman, he'd probably
16 object, too. But all it means is they're more
17 likely to get into trouble with their liver
18 disease. But people who don't meet that law, so to
19 speak, may also get into trouble.
20 This patient clearly became jaundiced, and
21 the implication stated in the presentation is there
22 was no sign of a hypersensitivity reaction. In

1 point of fact, the patient did develop
2 eosinophilia, and to my assessment, this is a clear
3 case of drug-induced liver injury.
4 So I'd like some more comment from the
5 sponsor about this and the rationale behind not
6 labeling this a case of severe drug-induced liver
7 injury.
8 DR. FERNANDES: Dr. Oldach?
9 DR. OLDACH: David Oldach. We're in
10 complete agreement that this episode of liver
11 injury was attributable to study drug. There's no
12 question about that. We don't know whether this
13 was hypersensitivity-induced or a physiologic
14 response of mild mitochondrial stress carried out
15 23 days.
16 We've come to understand mechanistically the
17 way in which solithromycin affects hepatocytes.
18 And what we've learned, and what we've learned with
19 our phase 1 study and with the longer-term dosing,
20 COPD and NASH trials, is that we have to manage
21 drug exposure.
22 So for CABP, a 5- to 7-day dosing regimen is

1 not predicted to produce comparable events. And
2 when they do occur, we expect that they will
3 respond or recover quickly. The COPD trial, giving
4 400 milligrams a day in a carefully controlled
5 study, which provided important data to you and to
6 us, indicates that 400 milligrams a day is too
7 much. We are in complete agreement about that.
8 The modeling predicts that the dose that
9 we're doing currently on our NASH study is an
10 appropriate dose, but we will continue to accrue
11 data for that circumstance as well.
12 So in summary, we agree that the COPD
13 patient with cholestatic hepatitis had a drug-
14 induced liver entry. There's no question. But we
15 think this is due to dose and duration, something
16 which we were actively exploring in our trials.
17 Thank you.
18 DR. FERNANDES: Thank you, Dr. Oldach.
19 DR. BOYER: Just to follow-up, I don't think
20 that's an accurate statement of what we see here.
21 There's clearly a hypersensitivity reaction with
22 eosinophilia, number one. Number two, these kinds

1 of reactions are not predictable, not dose-related,
2 and are idiosyncratic and can occur in 1 in 10,000
3 to 1 to 100,000 cases.
4 So I just don't know that we can discount
5 this as something that's dose-related. I don't
6 think that appears this way at all. This seems to
7 be an idiosyncratic drug reaction that's not
8 predictable.
9 DR. BADEN: Dr. Lee, did you have a follow-
10 up question on the same theme?
11 DR. LEE: Yes. On the same theme, I think.
12 Again, I think the point of short-duration
13 treatment is that there may be incidents of ALT
14 elevations, for example, a week or two afterward.
15 So the first question I had was, could we have a
16 look at the exact time that the ALTs were measured
17 and specifically how many values were obtained
18 post-treatment?
19 DR. FERNANDES: Dr. Oldach?
20 DR. OLDACH: David Oldach. ALTs were
21 measured at baseline; at day 4; at the end of
22 treatment, which was typically a day 7 visit; and

1 then at the short-term follow-up visit, which was
2 5 to 10 days after the end of treatment, so
3 typically around day 14.
4 Additional ALTs or liver function tests
5 would be measured had there been an abnormality
6 that required further follow-up. But there was no
7 scheduled evaluation after day 14.
8 DR. LEE: Okay. So there wasn't a day 30,
9 for example?
10 DR. OLDACH: There was a day 30 visit, but
11 it did not include laboratory testing unless there
12 was follow-up of an adverse event or an
13 abnormality.
14 DR. LEE: All right.
15 DR. OLDACH: I think, again, the issue is,
16 if you could keep people to just using it for
17 5 days -- 7 days, whichever -- that's fine. But I
18 think what Dr. Boyer was implying was that these
19 longer uses get you into a different realm of an
20 immune-based reaction, which might cause an ALT in
21 the 5-day exposure. But again, the ALT might not
22 appear until day 12, after you've stopped looking.

1 But again, if the drug were maintained for
2 a longer period of time -- now, again, it's not
3 supposed to be maintained for a longer period of
4 time. But again, this was the issue with
5 bromfenac, is that it was always used for short-
6 term use. And then in practice, once it was
7 approved, it was used for much longer periods of
8 time, and that's when the trouble came.
9 So I think it's clinical trial versus what's
10 going to be practiced in the community that may be
11 important.
12 DR. FERNANDES: We are trying to determine
13 the dose for longer treatment. That was the
14 purpose of those studies. What would be the
15 appropriate dose if it were to be used for a longer
16 period of time? Because macrolides have been used
17 in the past for TB and malaria and other things.
18 So that was why we were doing the study.
19 And we've dialed back on the dose, and we're
20 continuing to see what is the safe dose. But in
21 CABP, for 5 to 7 days at most, it seems safe and
22 gives you the benefit.

1 DR. BADEN: Dr. Lee, just to make sure I
2 understand your point, if the therapy is stopped at
3 day 7, is a day 14 ALT reasonable, or do you have
4 ongoing concern that hepatic injury may not
5 manifest for another week or two?
6 DR. LEE: I'm not sure. But I think
7 certainly with Augmentin, for example, there's
8 clear injury that evolves, I would say, probably
9 after day 14 in some instances. So maybe a day 21
10 or a 30 would capture all of those events.
11 DR. BADEN: Dr. Green, you had a follow-on
12 question?
13 DR. GREEN: Yes. Thank you. Michael Green.
14 It's really two questions.
15 The first is -- and this I'd give to
16 Dr. Watkins; maybe he could answer this
17 question -- with the telithromycin hepatotoxicity
18 events, do we know what the duration of therapy was
19 for those patients, since we're now trying to
20 differentiate between longer- and shorter-course
21 therapy? And I have a second question after I
22 have the answer to that.

1 DR. FERNANDES: So I'll start that off, and
2 perhaps Dr. Watkins can take anything additional on
3 that. Firstly, telithromycin was approved for a
4 few simple infections as well as CABP, and it
5 ranged anywhere from 7 to 14 days. So it could be
6 used for 5 days, for instance, for bronchitis,
7 pharyngitis, sinusitis, and other indications in
8 the upper respiratory tract, as well as for cab.
9 DR. GREEN: But I'm looking at specifically
10 if anybody's done the analysis on those that
11 experienced severe liver disease. Were they
12 getting on-label or did they get, as we're worried
13 about, the potential use of prolonged exposure?
14 Just to sort of separate whether it's prolonged
15 exposure versus the idiosyncratic reaction
16 occurring with a short course exposure.
17 DR. FERNANDES: Yes. I believe it was
18 small. It was the regular recommended thing. But
19 maybe Dr. Watkins --
20 DR. WATKINS: Paul Watkins, University of
21 North Carolina, Chapel Hill. As I mentioned, the
22 risk really only became evident postmarketing, and

1 there were 40, about 40 cases that were published
2 in the journal Hepatology that characterized that
3 liver injury as rapid onset, actually, within the
4 first, certainly, 10 days of treatment with
5 telithromycin.
6 They didn't report a one-month event there.
7 It was within -- I don't know what the treatment
8 indication was, but it was a rapid onset event.
9 DR. GREEN: Then my follow-on question to
10 you is, and we heard your statement, but given that
11 the model that you talked about completely failed
12 to identify the liver injury, or failed to
13 appreciate the liver injury from telithromycin, and
14 given that a large clinical program didn't identify
15 it in any of their cases, how comfortable can we
16 really be that if this drug comes to market and is
17 widely used, that we're not going to see a similar
18 event?
19 I know what you said, but I just really have
20 some concern because I don't think we completely
21 understood that mechanism. The model didn't
22 predict it, and a large number of patients studied

1 under trial didn't identify it.
2 DR. WATKINS: Well, that's correct. You
3 can't exclude the possibility that there's going to
4 be a 1 in 100,000 event rate until the drug goes
5 out in the real world. The main concern has been
6 the imbalance in ALT elevations, which has a
7 mechanism that I believe is reassuring, and the
8 legacy of Ketek. But in fact, the effects of the
9 drug on the liver are quite different from
10 solithromycin.
11 So at the time of approval of any drug, you
12 can't exclude rarity of syncratic events. And you
13 certainly can't explain it here.
14 DR. BADEN: Dr. Watkins, before you sit,
15 continue to follow on on this theme.
16 So if I understand you correctly, the
17 imbalance or increase observed, ALT greater than 3x
18 in the solithromycin group, is not a concern?
19 DR. WATKINS: What is happening is the drug
20 is influencing mitochondrial respiration by
21 inhibiting the enzymes in the electron transport
22 chain. That is an inhibition that goes away when

1 the drug goes away.
2 It does impair the generation of ATP in the
3 liver cell. So some liver cells are compromised
4 and are releasing ALT. So in that sense, it would
5 be nice if the drug didn't do that. However, it is
6 a mechanism that the liver rapidly adapts to, and
7 the data suggests that's through mitogenesis,
8 actually, making more mitochondria, just like your
9 muscles make more mitochondria in an exercise
10 routine.
11 DR. BADEN: So you see it as not a concern?
12 DR. WATKINS: No. I wouldn't -- I wouldn't
13 simplify it that much. I mean, more of the DILIsym
14 modeling for companies is to determine a dose level
15 that will have no ALT elevations. We would
16 obviously prefer a drug that has not ALT
17 elevations.
18 However, that was nearly the case with
19 telithromycin, and yet it had this very rare
20 idiosyncratic event that nothing can predict right
21 now.
22 DR. BADEN: So that was a follow-on. Now, I

1 also get to ask questions in the roster.
2 So on an efficiency issue, you note that
3 solithromycin is active against macrolide-resistant
4 pneumococcus, and that appears to be a key target
5 population.
6 In the 24 individuals who were macrolide-
7 resistant, if I got the numbers correctly from the
8 different presentations, do you know the nature of
9 the resistance in those organisms and whether or
10 not the mechanisms of resistance may impact the
11 activity of this agent?
12 DR. FERNANDES: I don't. Dr. Oldach?
13 DR. OLDACH: David Oldach. We did assess
14 the mechanisms of resistance for these pathogens,
15 and they're presented here in this slide. You can
16 see the majority were ermB, ermB or the combination
17 of ermB with mef. The erm mutation typically
18 confers high-level resistance, and most of these
19 pathogens were successfully treated.
20 DR. BADEN: Thank you, Doctor.
21 DR. BADEN: Dr. Scheetz?
22 DR. SCHEETZ: Thank you. Marc Scheetz. I

1 have two questions surrounding PK, probably for
2 different people.
3 My first is a clarification on whether or
4 not an oral loading dose is being suggested after
5 an IV to oral switch. And surrounding that, I was
6 wondering if they could possibly address -- is the
7 only thing that's currently well-modeled the serum
8 pharmacokinetics?
9 Or what do we know about the
10 intercompartmental transfer -- basically, the
11 transfer from the blood to the two areas that we're
12 really concerned about, one being the lung, that
13 might be epithelial lining fluid and alveolar
14 macrophages, and the second being the liver?
15 So I'm interested in really what the PK
16 looks like if an oral loading dose is being
17 suggested, and what that might mean relative to
18 first pass effect, so on and so forth. And then I
19 have a follow-up question about PBPK that I can ask
20 after this.
21 DR. FERNANDES: Okay. Somebody from ICPD?
22 DR. BHAVNANI: Sujata Bhavnani. Just to

1 address the issue of the oral load once again, we
2 did do modeling with ELF, effect site exposures and
3 plasma exposures. And we did look at target
4 attainment with and without that oral load.
5 Let me just -- so in this slide, what you
6 can see in blue are the IV to oral dosing regimens
7 with the oral load, which switched that were done
8 on day 2 to day 7; and in orange, without the oral
9 load, so transitioning to 400 milligrams.
10 You can see that probabilities of target
11 attainment, using effect site exposures, ELF, were
12 high well beyond the observed MIC distribution for
13 pneumococcus. So I believe that was your first
14 question.
15 DR. SCHEETZ: And just relevant to that, so
16 a load is being suggested or not being suggested?
17 DR. BHAVNANI: Just to clarify again,
18 earlier we thought the load was necessary. But
19 after the modeling that was done based on the phase
20 3 data, we see that both regimens, both IV to oral
21 regimens with and without the load, would be
22 effective.

1 So there are incremental benefits, of
2 course, of transitioning without that load. And I
3 think the sponsor agrees with that recommendation
4 from the agency.
5 DR. FERNANDES: Thank you, Dr. Bhavnani.
6 DR. SCHEETZ: And then if I can just ask a
7 follow-up question.
8 We've talked a little bit about the PBPK
9 model, and I was just wondering if Dr. Watkins can
10 expound upon that a little bit. Are there
11 empirical data that are being input into the model?
12 Have mechanistic studies been done with
13 solithromycin, or rather are these kind of putative
14 interactions that are population model-based?
15 Really, how good is the model?
16 DR. FERNANDES: Dr. Watkins?
17 DR. WATKINS: I was hoping you'd ask that
18 question. The slide before this one, please. As
19 you can see, I haven't practiced this a lot here.
20 Anyway, what the model is is what's called a
21 quantitative system pharmacology model. It will be
22 the next slide, not this one. There. If you can

1 put this up. It's basically reducing processes
2 that are relevant to toxicity to differential
3 equations. So this is done by engineers and
4 mathematicians with science input.
5 The endpoint is really death of liver cells
6 releasing their contents, which contains ALT/AST
7 and the biomarkers you see down on the right. And
8 then a secondary innate immune response. And if
9 you have then the next slide, the model has been
10 made -- no. You can go to the next slide. Sorry
11 for this. The initial slide you showed would be
12 good, the actual profile.
13 What's been done, the model's been built
14 with what is called exemplar compounds. So
15 companies have come with compounds that had ALT
16 elevations or other issues, safety issues, in
17 clinical trials. And the model was built around
18 that.
19 What I'm showing you on this slide, if you
20 bring it up, are the actual drugs that have been
21 put into the model without modifying the model or
22 fitting the model to the results. And it's just

1 very simple. It's good and bad.
2 So you can see the drugs in the two columns.
3 The ones that don't have names are proprietary
4 compounds. And you can see the only two that
5 didn't model, given good -- and I'll explain
6 that -- was really a compound A and telithromycin
7 because even in the most sensitive patient, we did
8 not predict ALT elevations for that drug.
9 Now, what determines good and bad, if you go
10 to the next slide -- there. You can put that up,
11 sure. Oh, sorry, slide up -- are the actual
12 criteria. So there's actually criteria for good
13 and bad, and actually ranges within that.
14 So did it predict the frequency of ALT
15 elevations? Did it predict the dose-response? Did
16 it predict the injury severity based on ALT? Did
17 it predict the injury timing, et cetera? These are
18 all things that are in the model and assessed by a
19 panel of people -- in other words, whether it's a
20 good performance or not.
21 And telithromycin is one of the two drugs to
22 date that did not get a good rating. We really

1 felt we couldn't model that. Did that answer your
2 question?
3 DR. SCHEETZ: I think somewhat. I'm still a
4 little confused on whether or not there are
5 actually empiric data linked to a direct mechanism
6 that we know for sure is associated -- or is linked
7 to liver injury.
8 DR. WATKINS: So the three mechanisms that I
9 spoke to, there are other mechanisms that were put
10 into the model but turned out not to be predictive.
11 DR. SCHEETZ: So does the model just predict
12 those, or do we actually know that that's linked,
13 that the mechanism hasn't been identified for
14 solithromycin?
15 DR. WATKINS: The mechanism has been
16 identified by assaying the drug for those three
17 properties. And by putting it in the model, if it
18 predicts, the assumption is that that's the correct
19 mechanism.
20 DR. BADEN: I will take chair's prerogative,
21 and we will complete this episode of further
22 inquiry.

1 We'll take a 15-minute break. Panel
2 members, please remember there should be no
3 discussion of the meeting topics during the break
4 amongst yourselves or with any member of the
5 audience. We'll resume at 10:50, and we'll have
6 time for more discussions later in the morning.
7 (Whereupon, at 10:37 a.m., a brief recess
8 was taken.)
9 DR. BADEN: It's 10:51. We shall call the
10 meeting back to order, and we shall now proceed
11 with the agency's presentations.
12 **FDA Presentation - Daniel Rubin**
13 DR. RUBIN: Thank you for the opportunity to
14 present on the efficacy of solithromycin for the
15 treatment of community-acquired bacterial
16 pneumonia.
17 I'll discuss the phase 3 trial designs, the
18 study populations, the efficacy results, and my
19 efficacy conclusions.
20 The phase 3 trials were randomized, active-
21 controlled, double-blind, noninferiority trials
22 that compared solithromycin to moxifloxacin.

1 Study 300 and study 301, respectively, evaluated a
2 five-day oral therapy regimen and a seven-day
3 intravenous oral therapy regimen, with the dosing
4 displayed on this slide.
5 Each trial enrolled approximately 430
6 subjects per arm. The design principles were
7 generally consistent with those specified in the
8 current FDA draft guidance document for developing
9 antibacterial drugs to treat community-acquired
10 bacterial pneumonia.
11 The key inclusion criteria were that adults
12 at least 18 years old were to have community-
13 acquired bacterial pneumonia diagnosed with signs,
14 symptoms, and radiographic evidence. The key
15 exclusion criteria were renal failure, severe
16 hepatic impairment, myasthenia gravis, previous
17 hypersensitivity to macrolides, and QT prolongation
18 or QT-prolonging drugs.
19 The trials restricted enrollment in several
20 ways to increase the sensitivity for detecting
21 possible efficacy differences. At most, 25 percent
22 of subjects could have had a single dose of a

1 short-acting prior antibacterial CAP therapy.
2 Subjects were to be in PORT risk class 2, 3 or 4,
3 with PORT 2 subjects comprising, at most, a half of
4 the oral trial and, at most, a quarter of the IV-
5 to-oral trial.
6 At most, 80 percent of subjects were to be
7 younger than 65 years. The trials also had a
8 target enrollment of, at most, 75 percent of
9 subjects outside of North America, although the
10 target was not achieved in the IV-to-oral study.
11 The primary efficacy endpoint was early
12 clinical response. This was defined after 72
13 hours, or three days, with a visit window from 60
14 hours to four and a half days.
15 To be considered a responder, subjects were
16 to have improvement from baseline on at least two
17 of the four symptoms of cough, dyspnea, chest pain,
18 and sputum production.
19 Symptoms were scored as absent, mild,
20 moderate, or severe. There was also to be no
21 worsening from baseline on any of the four
22 symptoms. There was to be no receipt of alternate

1 therapy through the end of the visit window,
2 although this criterion affected relatively few
3 subjects.
4 Finally, to be classified as a responder,
5 subjects had to survive through a late follow-up
6 visit, although this criterion again affected few
7 subjects.
8 This primary endpoint was consistent with
9 the FDA draft guidance and was based on
10 recommendations from the Biomarkers Consortium of
11 the Foundations for the National Institutes of
12 Health for forming a well defined and reliable
13 outcome that measures patient benefit and for which
14 a large antibacterial treatment effect could be
15 justified in a noninferiority trial.
16 Important secondary endpoints or additional
17 prespecified endpoints included investigator
18 assessment of clinical response at the short-term
19 follow-up, or SFU, visit 12 to 17 days after
20 baseline. This was 5 to 10 days after the end of
21 therapy and was essentially the overall judgment of
22 whether the patient had been cured.

1 Also, investigator-assessed clinical
2 response at the end of therapy. In addition, early
3 clinical response with programmatically defined
4 important in vital signs. Further, symptom
5 response at the day 12 to 17 SFU visit, which
6 required absence of chest pain and sputum
7 production and absence or improvement from baseline
8 in cough and dyspnea. And, finally, symptom
9 response at the 72-hour visit that was sustained
10 through the day 12 to 17 visit.
11 The primary statistical analysis of each
12 phase 3 trial was to be a comparison of the
13 difference in early clinical response rates between
14 solithromycin and moxifloxacin, with a
15 noninferiority margin of 10 percent. This was to
16 be conducted in the intent-to-treat population of
17 all randomized subjects.
18 A co-primary analysis was also to be
19 conducted using a weighted pooling of the phase 3
20 trials. This was to be a comparison of the
21 difference in early clinical response rates using a
22 larger noninferiority margin of 15 percent, but in

1 the microbiological intent-to-treat population of
2 subjects with microbiologically identified
3 bacterial pneumonia at baseline.
4 By co-primary, it was understood that to
5 meet win criteria for each trial, solithromycin
6 would need to demonstrate noninferiority both with
7 the 10 percent margin in the ITT analysis and with
8 the 15 percent margin in the pooled of MITT
9 analysis.
10 The rationale for this co-primary analysis
11 was that there may have been greater sensitivity to
12 detect efficacy differences between antibacterial
13 drugs in subjects known to have bacterial disease.
14 Here, baseline pathogens could be identified
15 from blood specimens, respiratory specimens,
16 urinary antigen tests, or serology. Note that an
17 MITT-2 population was a separate analysis
18 population with greater reliance on traditional
19 cultures. However, this was defined by the
20 applicant at FDA request after unblinded results
21 were known for the oral trial. So it was not a
22 prespecified analysis population and it won't be a

1 focus of this presentation.
2 In terms of trial conduct, you will see on
3 the following slides that there was minimal missing
4 or indeterminate data for the primary endpoint.
5 This was in the 3 percent range and results were
6 insensitive to how missing data were handled.
7 The total premature subject withdrawal rate
8 in the phase 3 trials was approximately 5 percent.
9 The total premature study drug discontinuation rate
10 was approximately 8 percent, with the most common
11 reason being an adverse event.
12 Protocol violations mainly related to
13 baseline covariate measurements, which were
14 unlikely to have changed the overall conclusions.
15 Finally, an audit from the applicant
16 identified two study sites with imperfect
17 documentation. But the results I'll present are
18 qualitatively unchanged when excluding subjects
19 from these study sites.
20 The next several slides present the baseline
21 characteristics of subjects in the phase 3 trials.
22 In general, you'll see that baseline factors were

1 relatively well balanced between the solithromycin
2 group and the moxifloxacin control group.
3 In terms of demographics, you can see from
4 this slide of the approximately 860 total subjects
5 in each trial, the studies included both males and
6 females with pneumonia, subjects were predominantly
7 white, and the trials enrolled a fair proportion of
8 subjects greater than 65 years old.
9 The majority of enrolled subjects were from
10 Europe. Subjects from the United States comprised
11 approximately a fifth of subjects in the oral trial
12 and approximately a tenth of subjects in the
13 intravenous-to-oral trial.
14 One difference between the trial designs
15 related to PORT scores. In the oral trial, one-
16 half of subjects were in PORT risk class 2. In the
17 intravenous-to-oral trial, only one-quarter of
18 subjects were in risk class 2.
19 This slide shows several other baseline
20 factors. Prior therapy was used by only about a
21 tenth of subjects in the oral trial, but by about
22 one-quarter of subjects in the intravenous-to-oral

1 trial. Also, although the trials attempted to
2 exclude subjects with estimated creatinine
3 clearance below 30 milliliters per minute, a
4 nontrivial number of subjects were in these trials
5 with a clearance below 50 milliliters per minute.
6 This slide shows that the baseline symptoms
7 of cough, dyspnea, chest pain, and sputum
8 production that were used for the primary efficacy
9 endpoint were generally present at baseline.
10 In terms of baseline pathogens, over half of
11 randomized subjects in the oral trial and slightly
12 under 40 percent of randomized subjects in the
13 intravenous-to-oral trial were in the
14 microbiological intent-to-treat population. The
15 most common pathogen was strep pneumo, which
16 infected around one-fifth of randomized subjects.
17 I will now discuss the efficacy results for
18 the oral trial, which was study 300. In the
19 primary efficacy analysis, the early clinical
20 response rates were nearly identical between
21 solithromycin and moxifloxacin, with both groups
22 having about a 78 percent response rate.

1 The confidence interval for the difference
2 in response rates went from negative 5.5 percent to
3 6.1 percent. Because the prespecified
4 noninferiority margin was 10 percent and the lower
5 confidence limit ruled out a loss of efficacy of
6 more than 5.5 percent, the statistical conclusion
7 was that solithromycin demonstrated noninferiority
8 in this trial.
9 The endpoint was a composite based on four
10 symptoms, and this slide shows the rates at which
11 cough, dyspnea, chest pain, and sputum production
12 were absent or improved from baseline at the early
13 clinical response visit. The results were similar
14 between solithromycin and moxifloxacin for each of
15 the four symptoms.
16 This is a busy slide, but it shows subgroup
17 results for the early clinical response endpoint.
18 In a noninferiority trial, it's important to assess
19 results in subgroups that may have greater
20 sensitivity for detecting efficacy differences
21 between antibacterial drugs.
22 You can see that results for solithromycin

1 were either favorable or similar to the overall
2 results in several of these groups, such as
3 subjects without prior therapy, highlighted here in
4 red, with about 78 percent response in each groups;
5 and, subjects with microbiologically confirmed
6 pneumonia, which I'll discuss in more detail later
7 in the presentation; clinically evaluable subjects
8 who sufficiently complied with the protocol; and,
9 subjects with high PORT scores.
10 This slide shows success rates in the two
11 groups for additional efficacy endpoints, including
12 investigator-assessed clinical response at the end
13 of therapy visit and the SFU visit 12 to 17 days
14 after baseline in this oral trial.
15 For these additional efficacy endpoints, you
16 can see from the estimated treatment effects and
17 confidence intervals that the differences in
18 success rates between solithromycin and
19 moxifloxacin appeared to be contained within 10
20 percent in either direction.
21 For reference, this slide shows subgroup
22 analyses for the endpoint of investigator-assessed

1 overall clinical response at the SFU visit 12 to 17
2 days after baseline. Response rates for this
3 endpoint generally appeared acceptable for
4 solithromycin in subgroups enriched for detecting
5 efficacy differences, such as subjects without
6 prior antibacterial therapy, shown in red.
7 I will next discuss the efficacy results in
8 the intravenous-to-oral trial, which was study 301.
9 As in the first trial, for the primary endpoint of
10 early clinical response, you see almost identical
11 success rates of about 79 percent in the
12 solithromycin group and the moxifloxacin control
13 group. The confidence interval for the difference
14 in success rates went from negative 6.1 percent to
15 5.2 percent. Thus, solithromycin again met the
16 noninferiority margin of 10 percent.
17 The symptom components of the primary
18 endpoint had similar rates of absence or
19 improvement between the solithromycin and
20 moxifloxacin groups at the 72-hour visit.
21 Here are the subgroup results for the early
22 clinical response endpoint in the intravenous-to-

1 oral trial. As in the previous trial, the results
2 often appeared similar to the overall results in
3 subgroups where you might expect to have a better
4 chance of determine efficacy differences, such as
5 subjects without prior antibacterial therapy, shown
6 in red.
7 This slide shows success rates in the two
8 groups for additional efficacy endpoints. One
9 difference between the intravenous-to-oral trial
10 and the previously discussed oral trial related to
11 results for the secondary endpoint of clinical
12 response as SFU, which was the investigator-
13 assessed clinical response at the short-term
14 follow-up visit 12 to 17 days after baseline.
15 In this trial, there was a stronger trend
16 disfavoring solithromycin. As I'll show in the
17 next slide, there were 54 clinical failures in the
18 solithromycin group compared to 35 clinical
19 failures in the moxifloxacin group. And the
20 difference in failure rates hovered around the
21 level of nominal statistical significance.
22 Now, one thing to keep in mind is that when

1 multiple analyses are conducted across trials,
2 endpoints and subgroups, it's not surprising that
3 chance can lead to some analyses looking
4 unfavorable. So we didn't want to over-interpret
5 these results, but we did attempt to look into them
6 in more detail.
7 The numerically lower clinical response rate
8 did not appear to be due to subjects in the
9 solithromycin group having worse symptoms at this
10 SFU visit. For instance, you can see from this
11 slide that the rates of symptom response at this
12 day 12 to 17 SFU visit actually favored
13 solithromycin, where symptom response was defined
14 as absence of chest pain and sputum production and
15 absence or improvement from baseline in cough and
16 dyspnea.
17 One question the review team had about these
18 investigator-assessed clinical response results was
19 whether the overall results, shown in red in the
20 top rows, were less favorable in this intravenous
21 trial than the oral trial because there was some
22 kind of falloff in the efficacy of solithromycin

1 for subjects with more severe disease.
2 Here are subgroup results for this endpoint
3 in this intravenous-to-oral trial, which may shed
4 some light on this issue. The difference between
5 solithromycin and moxifloxacin did reach the level
6 of nominally statistically significant inferiority
7 in the subgroup of clinically evaluable subjects
8 that had sufficient outcome data capture and
9 sufficiently complied with protocol provisions,
10 shown in red. However, if there was an efficacy
11 falloff with severity, you might expect the very
12 worst results to be seen in subjects with the
13 highest PORT scores. That didn't appear to be
14 happening.
15 You can see that the difference in success
16 rates between solithromycin and moxifloxacin was
17 less favorable in PORT risk class 2 subjects than
18 PORT risk class 4 subjects.
19 I mentioned that the clinical response
20 results didn't seem to be due to solithromycin
21 leading to any worse symptoms at the day 12 to 17
22 visit. This slide shows that it was not possible

1 to determine the precise reasons for investigator-
2 assessed clinical failure from the information
3 collected on case report forms, because
4 investigators marked very general categories for
5 this endpoint, such as whether, in their overall
6 impression, the patient required additional
7 therapy.
8 In my final slides, I'll discuss results for
9 the co-primary efficacy analysis in the
10 microbiological intent-to-treat population of
11 subjects with a baseline bacterial pathogen. This
12 analysis was based on a weighted pooling of
13 subjects from the combined phase 3 trials.
14 Early clinical response rates were again
15 similar between solithromycin and moxifloxacin.
16 The lower confidence limit for the difference in
17 success rates was negative 7.4 percent, and, thus,
18 solithromycin met the 15 percent noninferiority
19 margin that had been specified for this analysis.
20 Here are results in subgroups from the
21 pooled trials defined by baseline pathogens. The
22 table shows both early clinical response at 72

1 hours and investigator-assessed clinical response
2 at the SFU visit on day 12 to 17. There was a lot
3 of noise about these success rates because the
4 subgroups had small sample sizes. So the
5 differences between solithromycin and moxifloxacin
6 bounced around.
7 Numerically, the solithromycin group had
8 lower rates of response for subjects with strep
9 pneumo. There were limited numbers of subjects
10 with macrolide-resistant pneumonia, using the
11 definitions below the table.
12 From these macrolide-resistant sample sizes,
13 it's difficult to gauge the performance of
14 solithromycin, but the moxifloxacin comparator
15 seemed to perform adequately. And it's unknown
16 what the falloff in clinical efficacy would have
17 been had these subjects been treated with a
18 different macrolide, like clarithromycin.
19 To summarize my efficacy conclusions, the
20 phase 3 trials, in my view, did provide
21 statistically reliable evidence that solithromycin
22 is effective for the treatment of community-

1 acquired bacterial pneumonia.

2 The study designs appeared appropriate for

3 assessing noninferiority, and the overall efficacy

4 results appeared similar to those of the

5 moxifloxacin comparator. Thank you.

6 **FDA Presentation - Ramya Gopinath**

7 DR. GOPINATH: Good morning, everyone. My

8 name is Ramya Gopinath. I'm very happy to be here

9 to share with you our analysis of the safety data.

10 In my presentation this morning, I'll just

11 reiterate what you've already heard about the

12 overview of the clinical development program. I'll

13 then go on to give you a general safety overview of

14 this program. And the majority of my talk will be

15 devoted to a discussion of hepatotoxicity, which we

16 thought was a significant safety signal in this

17 submission.

18 Just really quickly, you've seen this data a

19 few times before. So I won't spend too much time

20 on it. Essentially, in the phase 1 trials, there

21 were a total of 554 patients who received different

22 doses and durations of solithromycin.

1 In the phase 2 and 3 trials, there were a
2 total of 920 patients who received the dose and
3 duration of solithromycin that's proposed for the
4 treatment of CABP.
5 As you can see, in CE01-301, there were just
6 432 patients who actually received the IV-to-oral
7 formulation.
8 This is a safety overview and, again, some
9 of this data you've seen before. There were
10 reasonably equivalent rates of premature withdrawal
11 from the study, but if you can see -- I'm going to
12 use my pointer here a little bit. So I apologize
13 if you're having trouble in the back.
14 As you can see, in study 301, there is a
15 slightly higher rate of withdrawal, as well as drug
16 discontinuation. As has been noted before, most of
17 these were because of adverse events and clinical
18 failures.
19 Serious adverse events were fairly
20 equivalent among all the treatment arms, and deaths
21 also occurred at an equivalent rate, more or less,
22 among all the treatment arms.

1 A little closer look at the deaths in the
2 solithromycin arm. In the protocol, all deaths
3 were characterized as clinical failures. All
4 deaths in the solithromycin arm of the pooled
5 population were in patients with PORT 3 or 4 class
6 pneumonia, and seven of them were in patients who
7 were greater than 65 years of age. In our
8 analysis, we felt that three of the deaths were
9 clearly unrelated to solithromycin.
10 The two patients that I have listed on the
11 slide are patients in whom there potentially could
12 have been an interaction, drug-drug or some effect
13 on the cardiac system, but complete details are
14 lacking there. In six of the patients, we thought
15 that they were at least potential therapeutic
16 failures.
17 This provides you a quick overview of the
18 serious adverse events in the pooled phase 3 study
19 population. Sometimes it's easier to see it in
20 aggregate. I'll remind you that a serious adverse
21 event is characterized as one that resulted in
22 death, a life-threatening experience,

1 hospitalization or prolongation of hospitalization,
2 incapacity in any way, and any condition that
3 required medical or surgical treatment to avoid one
4 of the previously listed serious adverse events.
5 The important points on this slide are,
6 again, that if you notice that most of the SAEs
7 occurred in a few of the system organ classes, here
8 on the Y-axis, and this is the number of patients
9 on the X-axis, with the numbers along each
10 histogram indicative of the number of patients who
11 experienced that.
12 Here, the important point is that most of
13 them occurred in the respiratory, thoracic, and
14 mediastinal disorder SOC, as well as in the
15 infections and infestations and the cardiac
16 disorders.
17 When we looked at these cases more closely,
18 many of them were reflective of the underlying
19 disease, that is, pneumonia, and its potential
20 complications, so empyema, respiratory failure, et
21 cetera.
22 I would like to draw your attention to the

1 fact that hepatobiliary disorders, there are very
2 small numbers of patients represented here. And I
3 would like to make the point that in this protocol,
4 any elevation of a hepatic enzyme or any other
5 abnormality that was not accompanied by a clinical
6 manifestation was not counted as an adverse event.
7 So that's an important point to keep in mind as we
8 move forward.
9 This is a quick overview of the treatment-
10 emergent adverse events. Again, this is broken
11 down by study and along here is just the categories
12 that we're looking at. You can see that basically
13 in three of the treatment arms, the incidence of
14 TEAEs was approximately 35 percent. But you can
15 see that in the solithromycin arm of study 301,
16 which is the intravenous-to-oral study, there was a
17 much higher incidence of TEAEs.
18 Now, this was mostly reflected in the fact
19 that these patients had infusion-related events,
20 because if we subtracted the infusion-related
21 events from the overall rate, you can see that it
22 really evens out.

1 Again, there is an imbalance over here in
2 terms of the TEAEs leading to study drug
3 discontinuation, and most of those were caused by
4 infusion-related events that led to discontinuation
5 in ten patients.
6 These are, again, selected treatment-
7 emergent adverse events that occurred in greater
8 than or equal to 2 percent of subjects in these
9 phase 3 trials. You've seen this data before. I
10 won't spend much time on it, except to point out
11 that, again, most of these were what one might
12 expect for an antibacterial.
13 I will just point out that abdominal pain
14 occurred more commonly with the oral form and there
15 was a slight imbalance in occurrence of dizziness.
16 Infusion site reactions, again, we've heard
17 about. The important point here is that they
18 occurred much more commonly -- there was a very
19 marked imbalance in their occurrence in the
20 solithromycin arm, with 31 percent of patients
21 having it as opposed to about 5 percent in the moxi
22 arm.

1 I'll just make the point that most of these
2 or almost all of them were mild or moderate in
3 severity, but they did lead to study drug
4 discontinuation in ten patients.
5 We were, of course, interested in looking at
6 the ketolide-specific adverse events. As you've
7 already heard, patients with myasthenia gravis were
8 actually excluded from clinical trials. And so we
9 really don't have any information about what
10 potential impact solithromycin would have on this
11 group of patients.
12 As has already been noted, a thorough QT
13 study was actually negative for solithromycin and
14 patients who had baseline prolongation of QT
15 interval and those who were on drugs that were
16 known to prolong QT interval were excluded from
17 these clinical trials.
18 Of note, there were two patients in the
19 solithromycin arm who did seem to have QT
20 prolongation on therapy, but there were multiple
21 other confounding factors. And so the effect of
22 the drug was not clear.

1 Visual disorders, as you've heard also, was
2 really not much of an issue. Syncope also occurred
3 in very few patients. But hepatotoxicity, in our
4 analysis, was a very significant signal and I will
5 spend the rest of my talk emphasizing and outlining
6 the analysis that we did of this.
7 This is how the rest of the talk is going to
8 be broken down. I thought it would be useful to
9 provide everybody a little bit of a framework in
10 which to consider these adverse events. How do we
11 assess the premarketing evaluation of the potential
12 for drug-induced liver injury, which I will
13 subsequently refer to as DILI? What is meant by
14 Hy's law and why is detection of that important in
15 a premarket evaluation?
16 I'll also then move on to an overview of the
17 hepatotoxicity seen, a few words about the
18 structure-activity relationship, and then the
19 signals that were seen at various stages in the
20 development program.
21 I'll start with a few words about what the
22 FDA guidance for premarketing clinical evaluation

1 of DILI actually says, and you can see that the
2 reference is provided at the bottom of the slide.
3 The overarching concern here is that drug-
4 induced hepatocellular injury, when all other
5 causes are eliminated and which is accompanied by
6 jaundice, can have a poor prognosis, with a roughly
7 10 percent rate of mortality or liver
8 transplantation due to acute liver failure.
9 DILI has been one of the most frequent
10 causes of safety-related drug marketing withdrawals
11 for the past 50 years. And we've heard a little
12 bit about that already. I'll address it again a
13 little bit later in my presentation.
14 However, it's important to remember that
15 numbers matter and only the most overt hepatotoxins
16 are expected to show cases of severe DILI in one to
17 3000 subjects. More commonly, most of the drugs
18 that have been withdrawn from the market for
19 hepatotoxicity have caused death or transplantation
20 at frequencies of less than or equal to one in
21 10,000.
22 The challenge for us at the FDA is to

1 distinguish drugs that are likely to cause severe
2 DILI from drugs that are unlikely to do so. The
3 type of liver injury that leads to severe DILI is a
4 predominantly hepatocellular pattern, as
5 characterized by elevation in AST and ALT. This is
6 particularly the case when the injury is extensive
7 enough to reduce the liver's functional ability to
8 clear bilirubin or to impact its synthetic
9 function.
10 The finding of a higher rate of ALT
11 elevation, therefore, in drug-treated subjects
12 compared to a control is a sensitive, although not
13 totally specific signal of the potential to cause
14 DILI.
15 It follows then that a higher rate of more
16 marked ALT elevations may be more specific for
17 severe DILI, although the ability to predict these
18 occurrences is still limited.
19 The single most specific predictor for the
20 potential of severe hepatotoxicity is encapsulated
21 in Hy's law. Hy's law, as you've heard before, is
22 an AST or ALT elevation greater than three times

1 the upper limit of normal in combination with a
2 total bilirubin rise greater than two times upper
3 limit of normal, and, importantly, without any
4 evidence of cholestasis or any other cause of
5 hepatic injury.
6 This is critical because the liver has a lot
7 of redundant capacity. So by the time you actually
8 get a rise in bilirubin, that is a marker of fairly
9 significant hepatocellular injury.
10 This signal is often seen in a development
11 program on the background of a higher incidence of
12 hepatocellular injury that is caused by the drug
13 compared with the control drug.
14 A drug that manifests these findings is
15 likely to cause severe DILI, which is defined as
16 resulting in liver failure or death at a rate
17 that's roughly one-tenth the rate of the Hy's law
18 cases. In other words, if the true incidence, as I
19 showed you previously, of severe injury is
20 approximately one in 10,000 and the rate of Hy's
21 law cases is approximately one in 1000, then 3000
22 exposed patient would be needed to have a 95

1 percent probability of observing at least one Hy's
2 law case in the treated population.
3 This has been described previously, as well
4 as in the literature, and is known as the Rule of
5 3.
6 It is important to remember that no known
7 occurrences of false positive Hy's law findings for
8 a drug have been noted. That is, if there is a
9 signal of Hy's law, that drug almost has always
10 caused severe injury in the postmarketing setting
11 when greater numbers of patients are exposed to the
12 drug. But very importantly, failure to find a Hy's
13 law case does not imply that a drug with
14 aminotransferase elevations is free of the risk of
15 severe DILI.
16 Some of the variables that could impact this
17 are, very importantly, the size of the exposed
18 population, the duration of exposure to the drug,
19 the discontinuation rules that are used in the
20 clinical protocols, and, finally, the true
21 incidence rate of severe DILI itself.
22 What are the challenges? This is the

1 framework that we work with and that we use to
2 monitor, coupled with the facts that have already
3 been observed with many drugs. But how does this
4 translate into a real world postmarketing
5 population?
6 In clinical trial databases, DILI signals
7 may be mild to moderate and show reversible
8 toxicity. Drug-specific DILI clinical signatures,
9 as well as histopathologic and liver test profiles
10 may differ among individuals for reasons that are
11 not completely understood, and I will demonstrate
12 that to you when I talk about some of the specific
13 patients that were seen in the clinical development
14 program.
15 The risk for severe DILI caused by a drug
16 may be more concentrated in certain populations,
17 and this signal may then not be detected until the
18 drug is used in a heterogeneous, real world
19 population, because in the population enrolled in
20 clinical trials, most of these concerning
21 conditions would be controlled for.
22 Additionally, drug-drug interactions in the

1 setting of wide postmarketing use of a drug, in
2 combination with potentially less careful
3 monitoring of potential side effects or drug-drug
4 interactions, when used in a clinical setting, may
5 lead to increased risk of severe DILI.
6 Finally, the manner in which this signal
7 that's detected in a small premarketing population
8 will actually play out when the drug is used in a
9 larger population can only really be determined
10 through the use of adequately powered clinical
11 studies.
12 Let's pivot to the consideration of all of
13 these principles to the development program of
14 solithromycin. I'll give you a brief overview of
15 what we saw in the program and just a few words
16 about the structure-activity relationship, as that
17 has already been covered in a lot of detail.
18 Remember that the safety database in the
19 phase 2 and 3 trials, in which patients received a
20 dose and duration of solithromycin that's intended
21 for CABP, comprised 920 patients. The following
22 data that I will show you are actually mostly from

1 the phase 3 trials and that brings the total down
2 to 856 patients exposed to solithromycin.
3 There were also very important safety
4 information that have come out of the non-CABP
5 studies of solithromycin, with a very small N, just
6 ten patients, but it really serves to inform the
7 discussion about the hepatic safety.
8 In all of these numbering less than 1000
9 patients, a pronounced hepatic injury signal was
10 seen. It's important to remember and realize that
11 a range of hepatic injury patterns was actually
12 seen. So there is a very clear signature of
13 hepatocellular injury, which I will show you in the
14 following slides.
15 There was also, in common with other
16 macrolides, a cholestatic signature, but there were
17 also concerns about hypersensitivity, which I will
18 also discuss in the coming slides.
19 There were no Hy's law cases, but there were
20 a couple of patients who did fulfill the laboratory
21 criteria. But because of other factors, they were
22 judged not to fulfill the complete criteria for

1 Hy's law. In two subjects in the phase 3 trials,
2 drug was actually stopped due to hepatic enzyme
3 elevation.
4 Just a step back. Again, I'm not going to
5 spend a lot of time on this slide, just to point
6 out that the structure of solithromycin, here in
7 the bottom left, differs with the addition of the
8 fluorine, as well as the loss of the pyridine
9 moiety that is seen on the side chain of
10 telithromycin.
11 We requested an internal consult from the
12 Division of Applied Regulatory Science at FDA for
13 an assessment of the quantitative structure-
14 activity relationship of solithromycin. They
15 determined that solithromycin is 85 percent similar
16 in structure to telithromycin, as can be seen from
17 the diagram, and that hepatotoxicity would be
18 expected with the use of solithromycin.
19 Cempra, as we've heard, has commissioned
20 computational modeling of hepatic injury using the
21 DILIsym program and this suggested, as we have
22 heard this morning, that solithromycin may have a

1 different mechanism of hepatic injury compared with
2 erythromycin. However, it's very important to
3 understand that in this model, other possible
4 mechanisms of injury, such as hypersensitivity or
5 an immunoallergic contribution, were not evaluated
6 at all.
7 A comparison of solithromycin with
8 telithromycin we understand is ongoing and we have
9 received some preliminary information about this.
10 Let me then go right into the actual
11 development program of solithromycin itself, and
12 I'll begin with a consideration of the non-clinical
13 studies.
14 In rats and monkeys, solithromycin is widely
15 distributed to tissues and with repeated dosing, it
16 accumulates in the liver at much higher
17 concentrations than in plasma. And according to
18 the applicant's information, the liver
19 concentration in a 13-week monkey study was more
20 than 1000 times the plasma concentration. And this
21 is a very important point to keep in mind, as well.
22 There is a very differential concentration of

1 solithromycin.

2 The active metabolites account for a

3 significant level of exposure in animals, but in

4 humans they seem to be less significant, accounting

5 for less than 6 percent exposure following oral

6 solithromycin administration.

7 Repeat dose toxicity studies, again,

8 identified the liver as the primary target organ of

9 toxicity. As you can see, in the oral rat study,

10 there was biliary inflammation, centrilobular

11 necrosis, and even death observed. In a 13-week

12 oral monkey study, there was weight loss, there was

13 centrilobular evacuation, Kupffer cell hyperplasia,

14 and moderate increases in hepatic enzymes.

15 Accumulation within lysosomes was seen and

16 phospholipidosis was observed, which is common to

17 all macrolides.

18 The very important part of this phase of the

19 study was that the determination of the human

20 equivalent dose and the threshold of toxicity is

21 very difficult to determine because of the

22 accumulation of solithromycin in the liver and in

1 macrophages.
2 As I showed you, in the monkeys, it is
3 impossible to know how the plasma concentration
4 really translates into the concentration in the
5 target organ, i.e., the liver.
6 In phase 1 studies, 7.5 percent of healthy
7 subjects exposed to solithromycin had an ALT
8 elevation greater than the upper limit of normal in
9 comparison to 2.3 percent of controls. The
10 controls comprised people who received placebo,
11 intravenous normal saline, even digoxin in some of
12 the studies. Of these, two were of great concern,
13 because these were healthy human volunteers in whom
14 the use of solithromycin was actually stopped due
15 to ALT elevations greater than five times upper
16 limit of normal, and I'll describe these two
17 patients and their course.
18 Number one was a 46-year-old male who
19 received just a single dose of 400 milligrams of
20 solithromycin orally on day one. As you recall, he
21 was a healthy patient -- was a healthy subject, I
22 should say -- and had a normal ALT and AST at

1 baseline.

2 After receiving just a single dose of

3 solithromycin, on day eight, his AST was five times

4 upper limit of normal. Bilirubin and ALT remained

5 normal throughout. Of note, this subject was

6 asymptomatic and his AST and ALT returned to

7 normal.

8 The second patient is a 36-year-old, healthy

9 male volunteer enrolled in another one of the

10 phase 1 trials who received three 800 milligram

11 intravenous doses of solithromycin on days one to

12 three. This figure shows you the course of his

13 liver enzymes.

14 Just to orient you, here along the Y-axis

15 are the liver test values. Along the X-axis are

16 the study days. The enzymes are depicted in

17 different colors.

18 The dates up here show you where the

19 administration of solithromycin began and where it

20 stopped. You can see the important point here is

21 that when the elevation of ALT was noted here,

22 solithromycin was stopped. But the very important

1 point to take away from this figure is the fact
2 that the AST and ALT levels depicted in the red and
3 the blue continued to rise for a day or two even
4 after the drug was stopped, and then they began to
5 decline and eventually returned to normal.
6 In phase 2, again, you'll recall that there
7 were fewer patients exposed, 64 patients exposed to
8 solithromycin, and there were really no very clear
9 signals seen.
10 We'll skip right on to phase 3. Now, this
11 is a very busy slide and I'm going to use my
12 pointer up here to walk you through it.
13 On the leftmost column is the ALT and AST.
14 Along the top are the individual clinical trials,
15 as well as the pooled population, and the different
16 treatment arms are seen here.
17 If we look at the top row here and walk
18 along it, you can see that there is a very clear
19 imbalance between the occurrence of ALT elevation
20 to anywhere above the upper limit of normal in the
21 solithromycin arm of both studies and in the pooled
22 population.

1 If we look at the degrees of enzyme
2 elevation that are generally thought to be more
3 significant, walking along the second line, you can
4 see that this imbalance persists and is
5 particularly marked in the IV-to-oral study, where
6 almost three times the number of patients in the
7 solithromycin arm experienced ALT elevation greater
8 than three times upper limit of normal. This
9 imbalance was seen in the pooled population, as
10 well. When we look at the greater than five times,
11 the same trends are observed.
12 The bottom half of this table depicts the
13 AST values and you can see that the same trends
14 apply, with a definite imbalance in terms of the
15 occurrence of significant AST elevation in the
16 solithromycin arm compared to moxifloxacin.
17 This next table is exactly the same
18 analysis, but this time using bilirubin and ALP, or
19 alkaline phosphatase. If you look here, you see
20 that a total of four patients in the pooled
21 solithromycin arm had a bilirubin elevation greater
22 than two times upper limit of normal, and it was

1 greater than that that occurred in the moxifloxacin
2 arm.
3 In the bottom half, you can see that there
4 is, in common with other macrolides, a cholestatic
5 picture. But I would like you to take away from
6 these couple of slides the fact that the AST and
7 ALT signature in the elevations that were seen
8 signifying hepatocellular injury were much more
9 marked in the clinical development program than the
10 signature of cholestasis.
11 This goes back to a couple of the comments
12 that were made in the discussion following the
13 sponsor's presentation. When we look at the time
14 to ALT and AST elevation -- in other words, what
15 relationship did these elevations have to the
16 actual administration of the drug -- we see some
17 interesting things.
18 In study 300, 73 percent of patients with a
19 significant ALT elevation experienced the maximum
20 level, MAL, between days one and five. Now, you
21 recall that according to the protocol, blood work
22 was only done on day one and day four. So we don't

1 really have a good idea what happened in between.
2 The next time point was at the end of therapy at
3 day seven.
4 However, you can see that almost 30 percent
5 or almost a third of patients experienced the
6 maximum ALT level between days six and 15. Recall
7 that in study 300 patients received oral
8 solithromycin and the duration of the course was
9 five days. So, clearly, there's almost a third of
10 these patients who had ALT elevations who
11 experienced the maximum much beyond the actual time
12 of exposure to the drug itself.
13 In study 301, this imbalance becomes even
14 more evident, with a full 50 percent of patients
15 experiencing the maximum ALT level between days six
16 and 15. Now, you recall that in study 301 the
17 treatment duration was seven days, IV-to-oral
18 solithromycin.
19 AST seemed to peak much earlier on. So
20 80 percent peaked in the early time period when the
21 patient was actually on treatment. Importantly,
22 these data raise possible implications for the

1 monitoring of hepatic enzymes in patients receiving
2 treatment. In other words, it seems to be unclear
3 who is going to develop the rise in liver enzymes,
4 when they're going to develop it, and what type of
5 monitoring would actually pick these up. Even if
6 they were picked up, what would the potential
7 course for somebody who was found to have an
8 elevation be subsequently?
9 I'd like to illustrate this fact by
10 considering this 65-year-old woman who was enrolled
11 in the oral study, study 300. She was 65 and had
12 hypertension and a couple of other medical
13 conditions at baseline.
14 She was on a variety of medications,
15 including valsartan and hydrochlorothiazide, and
16 she was treated with solithromycin orally for five
17 days. This figure, again, is similar to what I
18 showed you before, with the liver test values along
19 the Y-axis and the study days along the X-axis.
20 The dates depicted here are when the treatment with
21 solithromycin began and when it ended and depicted
22 also with this green line here.

1 You can see that in this 65-year-old woman
2 who started with normal enzymes on treatment, she
3 had a very significant elevation of both AST and
4 ALT, with a much smaller signature of cholestasis,
5 signified by ALP, on oral solithromycin. The
6 maximum point here is more than 20 times upper
7 limit of normal.
8 The study treatment was actually
9 discontinued after five days. And you'll recall
10 that in the oral study, the last two days of
11 treatment were actually placebo. So this patient
12 did not receive placebo.
13 Pivoting now to the safety information that
14 comes out of the non-CABP trials, as I mentioned
15 before, the number of patients in these trials is
16 small, only ten patients, but there's very
17 important safety information that has come out of
18 that.
19 The top of this table looks at CE01-204,
20 which is a COPD trial that was based in the UK, and
21 it enrolled four patients. The planned treatment
22 was 400 milligrams PO daily of solithromycin, with

1 a planned duration of 28 days.
2 You can see that of these four patients,
3 fully three, so 75 percent of this, albeit, very
4 small population actually had very significant
5 hepatic enzyme elevation, and I will come back to
6 that in my description of these patients.
7 CE01-205 is a small study that looks at
8 solithromycin for the reduction of inflammation in
9 non-alcoholic steatohepatitis, NASH, and
10 encompasses thus far six patients. When the
11 protocol was originally submitted, it was to use
12 400 milligrams PO daily of solithromycin for a
13 total duration of 13 weeks.
14 However, after considering some of the
15 safety information that came out of the COPD trial,
16 the protocol for the NASH trial was amended to 200
17 milligrams of solithromycin daily, with the option
18 of reducing it even further to 200 milligrams three
19 times a week in the event of hepatic enzyme
20 elevation.
21 More recently, the protocol has been amended
22 once again to -- the dose of solithromycin has been

1 amended to now 200 milligrams PO daily for one week
2 and then 200 milligrams three times a week for the
3 rest of the 13 weeks.
4 In this population, there was one patient
5 who had significant enzyme elevation with an ALT
6 greater than three times upper limit or normal. In
7 this patient, solithromycin treatment was actually
8 stopped for 16 days until his enzymes returned to
9 normal and then was restarted at a lower dose of
10 three times a week.
11 Let's look more closely at the subject in
12 the COPD trial who had cholestatic hepatitis with
13 jaundice and eosinophilia. As you've heard, this
14 is a 69-year-old male who had COPD and a prostatic
15 hypertrophy and was on a couple of medications,
16 including finasteride.
17 The planned study treatment, again, was 400
18 milligrams of solithromycin once a day for a 28-day
19 course. The table is a busy one, so again I'll
20 walk you through it. On the left-hand side are the
21 study days. Across the top are the hepatic
22 enzymes, and then eosinophil count, as well as the

1 INR as a measure of hepatic synthetic function.
2 Under each enzyme is the actual value, as
3 well as the fold increase above upper limit of
4 normal. You can see that on day one, this patient
5 with COPD on the medications, including
6 finasteride, had a completely normal liver enzyme
7 profile. This pattern was still evident at day
8 eight. By day 15, his enzymes had started to rise
9 and there was evidence of cholestasis here.
10 The investigators elected to continue
11 solithromycin in this patient and by day 23, a very
12 significant elevation of all the hepatic enzymes
13 was seen. Most significantly, he had the
14 development of eosinophilia.
15 A week earlier he had a normal eosinophil
16 count and then had a much higher, 1600 count of
17 eosinophils. At that time, the patient, as you can
18 see, he had a total bilirubin count of four or a
19 value of four and he was clinically jaundiced and
20 pruritic.
21 It was judged that he was not sick enough to
22 be actually admitted to hospital, but both

1 finasteride and solithromycin were discontinued
2 immediately on day 23. Of note, finasteride has,
3 of course, been in use for some years and is not
4 noted to cause significant liver injury.
5 As you can see, over the next few days his
6 liver enzymes, after the solithromycin was
7 discontinued, continued to drop and by day 52,
8 several weeks after exposure to the drug, his liver
9 enzymes actually came back to normal.
10 Of note, during the investigation of this
11 patient, an ultrasound was done, which was normal,
12 and a viral hepatitis screen was also done and that
13 was negative, as well.
14 On the next slide, this just shows you a
15 different way of looking at the same data. Again,
16 graphically you can see that solithromycin was
17 discontinued here at day 23 because of the very
18 significant enzyme elevations seen. Over time,
19 here, there is not only an elevation of alkaline
20 phosphatase, but a very significant elevation of
21 both AST and ALT. So a very mixed picture, in
22 combination with eosinophilia and the rise in

1 bilirubin that you see here.
2 The other two patients -- I've mentioned the
3 fact that three patients in the COPD trial had very
4 significant elevations of hepatic enzymes. I
5 should mention that of the other two patients, one
6 was noted to have significant elevation in her
7 liver enzymes, that is, ALT at day 26 when she was
8 almost finished with her regimen. At that point,
9 solithromycin was discontinued and when the patient
10 came back on day 31 -- so after five days off
11 solithromycin -- she had an even higher ALT
12 elevation at that time. Clearly, there was ongoing
13 injury even after the solithromycin had been
14 discontinued.
15 The third patient in the COPD trial was a
16 man who had enzyme elevation noted on day 15.
17 Again, it was elected to continue therapy and by
18 the next time point when enzymes were measured, the
19 liver enzymes were actually trending down and came
20 back to normal while he was still on therapy.
21 Even though the study was so small, it
22 provides us a very nice microcosm of multiple

1 patterns of behavior of liver enzymes and multiple
2 potential patterns of injury in different people.
3 Going on, of course, as you've heard, no
4 discussion of solithromycin, a ketolide, can take
5 place without reference to telithromycin, the first
6 in class ketolide. So I'll say a few words about
7 this.
8 Telithromycin was the first in class
9 ketolide and was approved in 2004 by the FDA for
10 community-acquired pneumonia, acute exacerbation of
11 chronic bronchitis, and acute bacterial sinusitis.
12 Within several months after its approval, reports
13 started to come in of severe hepatotoxicity, which
14 eventually led to hospitalization, eventual death
15 in four patients, and liver transplantation in one
16 patient.
17 I should mention that these reports were
18 primarily on the basis of voluntary reporting into
19 the adverse event reporting system and, therefore,
20 are very likely to have underestimated the amount
21 of liver injury that potentially did occur with
22 telithromycin.

1 In 2006, the approved indications for this
2 drug were reduced and were limited to CAP only.
3 However, over the subsequent years, because of the
4 signature of severe liver injury seen, the use of
5 telithromycin fell out of disfavor and it is
6 currently discontinued.
7 Just a reminder about the numbers here. As
8 you can see, about 5000 patients were enrolled in
9 the phase 3 safety population. Of those, there
10 were about 3000 who were actually exposed to
11 telithromycin and in about 2000 of those patients,
12 they were enrolled in controlled trials and of the
13 controlled trials, there were approximately 1000
14 patients who were enrolled in the controlled CAP
15 trial.
16 You will see that the safety database with
17 telithromycin in the original NDA submission was
18 not really vastly different from what we are seeing
19 in the solithromycin development program.
20 The nonclinical data looks quite similar to
21 what was seen in solithromycin, with increased
22 liver enzymes, liver necrosis in the four-week rat

1 study, hepatocellular hypertrophy. In phase 1,
2 there was a clustering of hepatic AEs that were
3 seen in elderly patients, three of eight, who were
4 exposed to a fairly high dose, a single high dose
5 of telithromycin. But importantly, in the phase 3
6 controlled CAP trials, a low ALT elevation rate was
7 observed with telithromycin and, importantly, this
8 was actually similar between telithromycin and the
9 comparator arm and there were no telithromycin-
10 induced hepatic deaths.
11 This table is taken from the original review
12 of telithromycin for the original NDA submission
13 and this depicts ALT elevation from a normal
14 baseline in the pooled phase 3 CAP studies of
15 telithromycin. You can see that when we look at
16 the significant elevations, there is really
17 virtually no difference between telithromycin and
18 the comparator.
19 However, as encapsulated later in a paper in
20 Hepatology in 2008, 42 cases of severe liver injury
21 that were known and that were judged to be
22 potentially related to telithromycin were collected

1 in this paper. These occurred within a two-year
2 period from the approval of telithromycin to 2006.
3 The typical latency in these cases was often rapid,
4 with a median of ten days, but a range of two to 43
5 days, so clearly not all uniform.
6 Typical symptoms here included abdominal
7 pain, which occurred in a high proportion of
8 patients, fatigue, weakness, jaundice, and fever.
9 There was a primarily hepatocellular pattern of
10 injury seen and often very severe. As I said,
11 abdominal pain was seen in almost a majority, and
12 ascites, interestingly, in almost 20 percent of
13 patients.
14 Recurrence of injury with re-exposure was
15 seen in four known patients. These were patients
16 who had been exposed to telithromycin earlier and
17 then were re-exposed, and hypersensitivity was
18 thought to be a mechanism of their injury.
19 When we look at the hepatotoxicity of other
20 antibacterials, we've heard some of that already in
21 the sponsor's presentation, but clearly cholestatic
22 hepatitis and even a mixed picture are seen across

1 all macrolides.
2 If you look in the NIH Livertox website,
3 this provides estimated incidences of these AEs per
4 100,000 prescriptions, and you can see that they
5 occur less than four per 100,000. Of note,
6 although I didn't put it on this slide, the number
7 for telithromycin was 5.5.
8 These types of injuries often occur one to
9 three weeks after starting treatment and the
10 recovery usually is within four to eight weeks of
11 stopping.
12 According to the Livertox website, there was
13 an asymptomatic and transient aminotransferase
14 elevation that occurred at a low rate of 1 to 2
15 percent. Now, this contrasts with the rate of 7
16 percent that we saw with solithromycin in the
17 combined treatment arm. And hypersensitivity seems
18 less common here.
19 Finally, some conclusions. A pronounced
20 hepatic injury signal is observed in a safety
21 database of 920 patients who received a full
22 therapeutic dose of solithromycin for five to seven

1 days for the treatment of CABP. I should mention,
2 one thing I forgot to mention in an earlier slide
3 was that if you look at the elevations, the table
4 that I showed you had the elevations from all
5 baselines, but if you look at the elevation of ALT
6 from a normal baseline, which would be compared to
7 the telithromycin data that I showed you earlier,
8 there is a clear imbalance.
9 We have done this analysis internally and
10 about 4.8 percent of patients have a significant
11 elevation to greater than three times upper limit
12 of normal from a normal baseline. That's compared
13 to the 0.8 rate that was seen with telithromycin.
14 Back to the conclusions. There is a clear
15 solithromycin exposure and ALT elevation
16 relationship which appears to be dose and duration
17 dependent, and this will be addressed in more
18 detail in the next presentation by my colleague,
19 Dr. Zhang.
20 It's important to remember that in this
21 development program of less than 1000 patients,
22 there were multiple toxicity patterns seen,

1 hepatocellular injury, cholestatic signatures, and
2 the definite possibility of a component of
3 hypersensitivity, as seen in the COPD patient.
4 Again, recall that in the three patients who
5 had significant elevations in the COPD trial, three
6 completely different patterns of injury were
7 actually seen.
8 No cases fulfilled all of Hy's law criteria,
9 but using the Rule of 3 in this very limited
10 database, the risk of severe DILI can really only
11 be capped at roughly one in 333.
12 As I showed you before, the likelihood of
13 severe DILI is known to be much less than that,
14 and, thus, we contend that the database is really
15 not large enough to accurately evaluate this risk.
16 The additional risk of increased exposure to
17 solithromycin through factors such as the
18 potentially unintended increased duration of
19 treatment, drug-drug interactions in the real
20 world, concomitant illnesses with other conditions
21 that may themselves have a potential to elevate
22 liver enzymes or affect the liver, and the

1 potential unadjusted use in renal failure all need
2 to be considered given the robust signal that is
3 seen in this very controlled clinical trial
4 population.
5 The risk of hypersensitivity in addition to
6 older macrolides or to solithromycin itself and its
7 potential role in severe solithromycin-related DILI
8 is really unknown. But the COPD patient offers
9 some tantalizing clues that this may be something
10 that could be seen in a wider population.
11 The aminotransferase signal for
12 hepatotoxicity seen with solithromycin in the
13 phase 3 trials is greater than was seen with
14 telithromycin in the phase 3 trials and, as I've
15 shown you, telithromycin was associated with severe
16 hepatic injury postmarketing.
17 Finally, although exploratory computational
18 modeling in DILIsym may suggest that solithromycin
19 does not have the same mechanism of hepatotoxicity
20 as erythromycin and possibly telithromycin,
21 nonetheless, the high observed incidence of hepatic
22 injury in this relatively small phase 3 safety

1 database suggests at least the potential that
2 solithromycin is actually causing injury through
3 additional pathways which are undefined by this
4 model, associated with DILI and which raise great
5 concern for safety.
6 Thank you for your attention.
7 **FDA Presentation - Yongheng Zhang**
8 DR. ZHANG: Good morning. My name is
9 Yongheng Zhang. I'm the clinical pharmacology
10 reviewer for this application.
11 I will cover four topics in this clinical
12 pharmacology presentation: PK highlights of
13 solithromycin, drug interactions, exposure-response
14 relationship for both efficacy and safety, and,
15 lastly, the dosing considerations.
16 This slide summarizes the PK attributes of
17 solithromycin. The absolute bioavailability was
18 estimated to be 62 percent following 400 milligram
19 oral relative to 400 milligram IV infusion.
20 Food does not affect absorption. Therefore,
21 solithromycin capsules can be taken regardless of
22 food. Tmax is two to four hours after oral

1 administration. Plasma protein binding is 81
2 percent. Volume of distribution is 400 liter
3 following 400 milligram IV infusion.
4 Solithromycin concentrations were estimated
5 to be higher in the epithelial lining fluid than
6 plasma based on PK data from healthy subjects.
7 Solithromycin is also both a substrate and
8 inhibitor of CYP3A and P-gp. It inhibits its own
9 metabolism. Solithromycin is a major component in
10 the circulation, with two minor metabolites. Each
11 present at less than 6 percent of the parent in
12 terms of AUC.
13 The terminal half-life of solithromycin is
14 8.5 hours following IV administration in healthy
15 subjects. Solithromycin is extensively metabolized
16 and mainly excreted in the feces. Urinary
17 excretion is a minor contributor, about 14 percent,
18 to the overall elimination.
19 A few noticeable PK features. Solithromycin
20 PK is nonlinear due to time dependent inhibition of
21 CYP3A and the saturation of intestinal P-gp. Its
22 PK is highly variable, even more so following oral

1 administration. Phase 3 PK data showed that
2 solithromycin exposure was higher in patients than
3 in healthy subjects.
4 Drug interaction of solithromycin centers on
5 the fact that it is both a substrate and inhibitor
6 of CYP3A and P-gp. As a substrate for both 3A and
7 P-gp, CYP3A and P-gp inducer, such as rifampin, can
8 drastically decrease solithromycin exposure.
9 Because solithromycin inhibits its own metabolism,
10 via CYP3A auto-inhibition, concomitant use of non-
11 CYP3A inhibitor is not expected to significantly
12 affect solithromycin exposure following a repeat
13 dose. For example, CYP3A inhibitor ketoconazole
14 increased a single-dose solithromycin AUC by 2.6-
15 fold. However, solithromycin AUC is predicted to
16 increase by 25 percent following repeat dosing of
17 both drugs.
18 For the CYP3A inhibitor, solithromycin can
19 significantly increase the exposure of a
20 concomitant CYP3A substrate. For example, it
21 increased the midazolam AUC by nine-fold.
22 Similarly, as a P-gp inhibitor, solithromycin can

1 increase the exposure of concomitant P-gp
2 substrates. In the case of digoxin, there was a 30
3 to 50 percent increase in AUC or Cmax. Therefore,
4 based on this information, an appropriate
5 management strategy regarding drug interaction
6 should be included in the label.
7 Next, I'm going to talk about E-R
8 relationship for both efficacy and safety. First,
9 let's compare solithromycin daily exposure in terms
10 of AUC by three dosing regimens, studied in two
11 phase 3 trials, 300 and 301.
12 In trial 300, the oral dosing regimen was
13 studied, 800 milligram loading dose on day one,
14 followed by 400 milligram QD for four days. The
15 treatment duration was five days.
16 The daily AUC ranges are shown in this box
17 plot. The blue box depicts the 25 percent to 75
18 percent distribution of daily AUC values, which was
19 also referred to as the interquartile range, as a
20 visual aid to compare exposure across dosing
21 regimen in the two studies. The two red dotted
22 lines representing the interquartile range of day

1 five AUC value in study 300 is added.
2 In trial 301, both IV-only and IV-to-oral
3 dosing regimens were studied, as you can see.
4 Following a 400 milligram IV dose for seven days,
5 the daily AUC, as the treatment goes on, becomes
6 higher and higher compared to the oral dosing
7 regimen studied in 300.
8 For the IV-to-oral dosing regimen, there are
9 six dosing scenarios depending on which day the
10 patient is ready for oral switch. As you can see,
11 regardless of the switch day, the daily AUC values
12 are also higher compared to the oral dosing regimen
13 in studied in 300.
14 To recap, besides a longer treatment
15 duration in 301 versus 300, the daily exposure is
16 higher in 301.
17 In the exposure-response analysis, shown in
18 this figure, the Y-axis shows the early clinical
19 response on day four, which is the primary efficacy
20 endpoint. The average daily AUC for the first 72
21 hours was used as the exposure matrix and is
22 represented by four quartiles, shown on the X-axis.

1 This analysis included all the patients in the ITT
2 population who had PK data, which is about 95
3 percent of the entire ITT population.
4 As you can see, with the increasing AUC from
5 quartile one to four, there is no clear change in
6 clinical response.
7 Similarly, when we look at the clinical
8 response at the end of the therapy from exposure
9 quartile one to four, with the increase in the
10 average daily AUC over the entire treatment, either
11 five days or seven days, there is no clear change
12 in clinical response.
13 Therefore, we concluded that a flat
14 exposure-response relationship was identified over
15 the exposure range observed in the phase 3 trials.
16 For an antibacterial drugs such as
17 solithromycin, the AUC over MIC ratio is the PK/PD
18 index associated with solithromycin efficacy in
19 animal models.
20 What is shown in this figure, the Y-axis
21 again is the early clinical response on day four.
22 The AUC/MIC ratio is used as an exposure matrix and

1 represented by four quartiles, shown on the X-axis.
2 This analysis included the patients in the
3 microbiological intent-to-treat population who had
4 both MIC and PK information, which is about half of
5 the MITT population. As you can see, with the
6 increase in AUC/MIC ratio from quartile one to
7 four, there is no clear change in clinical
8 response.
9 Similarly, when we look at the clinical
10 response at the end of therapy, with the increasing
11 AUC/MIC ratio from quartile one to four, there is
12 no clear change in clinical response.
13 Therefore, similar to the AUC response
14 relationship we discussed in the earlier slide, we
15 concluded that AUC/MIC ratio response relationship
16 was also flat over the AUC/MIC range observed in
17 the phase 3 trials.
18 For exposure-response analysis of safety,
19 the incidence of ALT elevation is of particular
20 interest. As was presented in the safety
21 presentation, there was a higher incidence of ALT
22 elevation in study 301 compared to study 300.

1 Specifically, the incidence of ALT elevation higher
2 than 3-fold of upper limit of normal is 9.1 percent
3 in study 301 compared to 5.3 percent in study 300.
4 This liver enzyme elevation is likely to be
5 dose-dependent. First, in phase 1 dose escalation
6 studies, the ALT elevation was identified as a
7 dose-limiting factor. Secondly, as shown in the
8 previous slide, overall daily exposure is higher
9 and the treatment duration is longer in 301
10 relative to 300.
11 To further illustrate the potential
12 correlation between the incidence of ALT elevation
13 and solithromycin exposure, a logistic regression
14 analysis using phase 3 data from both trials 300
15 and 301 was conducted and showed the correlation
16 between the probability of ALT elevation higher
17 than 3-fold of upper limit of normal, depicted in
18 Y-axis, and solithromycin exposure depicted in
19 X-axis.
20 The exposure matrix here used was the
21 average daily exposure two days prior to the ALT
22 measurement.

1 In summary, this E-R relationship on safety
2 suggests the increase in the incidence of ALT
3 elevation was associated with an increase in
4 solithromycin exposure.
5 Now, let's move to dosing considerations.
6 First, let's talk about the three dosing regimens
7 proposed by the applicant. Oral dosing regimen,
8 day one, 800 milligram loading dose, followed by
9 400 milligram oral once daily for four more days.
10 IV-only dosing regimen is 400 milligram daily, 60
11 minutes, IV infusion, seven days. The IV-to-oral
12 dosing regimen starts with 400 milligram IV daily
13 dose; when IV-to-oral switch criteria are met,
14 receiving 800 milligram oral load on the day of
15 switch, then followed by 400 milligram oral once
16 daily to the end of seven days of treatment. Here,
17 as you can see, I use oral switch on day four as an
18 example.
19 These three dosing regimens were studied in
20 phase 2 and phase 3 trials. In addition, for
21 patients with baseline creatinine clearance less
22 than 30, the applicant proposed to modify the three

1 dosing regimens by a 50 percent daily dose
2 reduction from day two to the end of therapy, while
3 retaining the same dose on day one. These three
4 reduced dosing regimens have not been studied in
5 the clinical trials.
6 The proposal was based on the dedicated
7 renal impairment PK study, population PK, and
8 physiologically-based PK predictions.
9 Based on the review team's analysis, we
10 concur with the proposed oral-only and IV-only
11 dosing regimen, including the proposed dose
12 reduction in patients with severe renal impairment.
13 However, for the IV-to-oral dosing regimen, we
14 suggest alternative dosing by the removal of the
15 oral loading on the day of IV-to-oral switch.
16 Instead of the oral load, a maintenance dose of 400
17 milligram or 200 milligram for patients with severe
18 renal impairment is proposed. This maintenance
19 dose is consistent with the maintenance dose
20 proposed for the oral-only dosing regimen.
21 This alternative dosing is based on the
22 following three considerations. First, the removal

1 of the oral load may potentially reduce the
2 increased risk of ALT elevation observed in study
3 301. As shown in this graph earlier, it is the
4 daily AUC comparison by dosing regimens in the two
5 phase 3 studies, 300 and 301. For each patient,
6 the oral load dose of 800, indicated by the arrows,
7 resulted in the highest daily AUC in the entire
8 seven-day treatment period.
9 This oral load, along with the IV dose and a
10 longer treatment duration, may have contributed to
11 the increased incidence of ALT elevation observed
12 in study 301, as we discussed in the exposure and
13 ALT elevation relationship.
14 Secondly, the removal of oral load is not
15 expected to compromise the efficacy. PK simulation
16 results, shown in this graph, suggest that patients
17 can transition with 400 milligram instead of 800
18 milligram oral load and still maintain daily AUC at
19 or exceeding day five AUC in study 300, indicated
20 by these two red dotted lines. Plus, the seven day
21 treatment, we do not expect the efficacy to be
22 compromised.

1 In other words, we believe that when
2 patients meet the criteria for IV-to-oral switch,
3 they can use the same maintenance dose, which is
4 400 milligram oral, as those patients in 300.
5 The third consideration is that the
6 alternative IV-to-oral dosing regimen is simpler
7 than originally proposed. Therefore, it would help
8 reduce the potential for dosing error.
9 To recap, we discussed the important PK
10 features of solithromycin. There is no food
11 effect, higher ELF exposure than in plasma, PK is
12 nonlinear, and PK also has a higher variability.
13 Drug interactions are expected because
14 solithromycin is both a substrate and inhibitor of
15 3A and P-gp. For E-R relationship, a flat E-R
16 relationship for efficacy was identified over the
17 exposure range observed in the phase 3 trials. We
18 do see the association between the incidence of ALT
19 elevation and exposure.
20 For dosing, we propose alternative IV-to-
21 oral dosing regimen by the removal of the oral
22 load. This can simplify the dosing regimen and can

1 potentially reduce the risk of ALT elevations
2 observed in Studies 300 and 301, without
3 compromising the efficacy.
4 This concludes my presentation. Thank you
5 for your attention.
6 **Clarifying Questions to the Presenters**
7 DR. BADEN: I'd like to thank the three
8 agency speakers for covering a lot of data and
9 providing more information for the committee. I'd
10 like to open this up to clarifying questions of the
11 committee.
12 Dr. Lo Re?
13 DR. LO RE: This is Vincent Lo Re, from the
14 University of Pennsylvania.
15 The sponsor showed us one of the -- this
16 question actually is for Dr. Gopinath. The sponsor
17 showed us one of the eDISH plots, electronic drug-
18 induced serious hepatotoxicity plots, that seemed
19 to identify three cases that met Hy's law
20 biochemical criteria, though were not Hy's law, and
21 one of which was moxifloxacin.
22 In looking at the briefing book that we were

1 given, it looks like there was a difference, that
2 there are five cases that are solithromycin that
3 meet the Hy's law biochemical criteria, none for
4 moxifloxacin.
5 I'm wondering what the difference is. I'm
6 interested in knowing -- I didn't see in the
7 description of the telithromycin experience if
8 there was an eDISH plot for that by which we could
9 at least compare. And then to further put it into
10 clinical context, at least for me, just to get a
11 sense of how often in the context of clinical
12 studies do we see any cases meeting Hy's law
13 biochemical criteria.
14 DR. GOPINATH: Thank you for your questions.
15 I'm going to ask Dr. Avigan to address the eDISH.
16 DR. AVIGAN: The difference actually is
17 superficial. The difference really has to do with
18 whether some of those cases that would have been
19 plotted on that right upper quadrant as having
20 biochemical criteria that would be consistent with
21 Hy's law would be filtered out, because at face
22 value, they were clearly not drug-induced liver

1 injuries.
2 The difference really has more to do with
3 sort of the editing of certain cases which were
4 prima facie not drug-induced liver injuries.
5 We have no dispute or there's really no
6 inconsistency. That first graph, which shows the
7 population effects, is really a starter to then
8 pick cases of interest out and look at them
9 individually for their clinical course and their
10 differential diagnosis. So at the end of the day,
11 the risk assessment is not that first graph. It's
12 the assessment of individual cases and the
13 composite conclusion of risk based upon the
14 analyses that include individual case reviews.
15 There is no disagreement there.
16 With reference to your other question about
17 what do we see in the world of clinical trials with
18 drugs that turn out to be problematic, that's an
19 interesting question and we don't have a full
20 repertoire of every eDISH plot for all clinical
21 development programs that have been done in the
22 past, because to some extent, some of this data for

1 some of these trials is quite old.
2 In the case of telithromycin, this wasn't
3 done on the graph, but I can tell you that from
4 what we heard in the case of the telithromycin
5 clinical development program at the time when it
6 was initially presented to the FDA in 2000, and
7 there was that very nice review that was quoted,
8 there were no cases that would have been plotted in
9 the right upper quadrant and, in fact, there was
10 not much of an imbalance in contrast to here to the
11 right lower quadrant, where there was an imbalance,
12 as to which many of the cases that were then showed
13 to you were described in a few examples shown to
14 you of clinical course in individual cases.
15 They were from the right lower quadrant 5X
16 the upper limit of normal. There is really no
17 dispute here about the fact-finding.
18 The final point about other drugs that have
19 turned out to be problematic, the answer to that
20 with reference to finding out a signature of
21 certain drugs that are idiosyncratically
22 hepatotoxic is that it depends.

1 Different drugs actually pose different
2 reasons why there's a risk for hepatotoxicity.
3 With reference to the idea of exposure-related and
4 duration of treatment-related risk effects, a drug
5 that is a poster child is bromfenac, which is a
6 drug where it was studied for short-term use for
7 pain management, an NSAID, a number of years ago
8 and it turned out that in short treatment trials of
9 ten days or less, there was no signal seen. I
10 mean, it was basically a clean drug.
11 Yet, once the drug was being used and also
12 studied in longer exposure treatment protocols for
13 osteoarthritis and rheumatoid arthritis for periods
14 that were substantially longer, over 30 days, there
15 was a very dramatic hepatocellular injury signal
16 seen. So it depended on the use pattern.
17 In that case, even in the clinical trials,
18 as I recall, most of the hepatotoxicity signatures
19 seen in the clinical trial itself was just
20 transaminases. But once the drug was actually put
21 out there and was used in clinical practice for
22 longer periods of time, there was the accrual of

1 hepatic failure cases, severe liver injuries, about
2 50 cases of severe liver injuries, four liver
3 failures or even more, and the drug was withdrawn.
4 Part of the challenge in this particular
5 development program is to define the conditions in
6 which there is a possible concern for really
7 ramping up risk, where we see a signal and from
8 that are trying to infer is there an effect on risk
9 in certain ways in which this drug could be used
10 with what we so far know about it in the absence of
11 a Hy's law case in this particular very small
12 development program.
13 DR. BADEN: Dr. Levine?
14 DR. LEVINE: Thank you. Dr. Levine, I'm the
15 industry representative. I had a question on the
16 FDA's safety presentation. It's on Slide 20 and
17 it's just regarding the structure-activity
18 relationship.
19 The slide states -- it strikes me as a
20 categorical statement regarding what might be
21 expected with solithromycin based on the structural
22 relationship to the other ketolide, telithromycin.

1 Does the agency also interpret anything
2 quantitatively, like in terms of numbers needed to
3 harm, based on this type of analysis, number one;
4 and, number two, did the agency conduct a similar
5 evaluation for solithromycin with the other
6 macrolides?
7 DR. GOPINATH: Thank you for your question.
8 My FDA colleague who actually did the analysis is
9 here and I'd like to ask Dr. Stavitskaya if she
10 would just come and answer the question about the
11 methodology and how that [inaudible - off mic].
12 DR. STAVITSKAYA: Thank you for the
13 question. The software that we used for our
14 particular analysis is called Leadscope and the
15 software itself is actually calculating the
16 similarity using
17 With reference the Tanimoto similarity index.
18 The way it does it is actually it considers
19 the presence and absence of particular sub-
20 structural features within the molecule that is in
21 question and also any other molecules or any other
22 drugs that we have within that particular system.

1 It actually looked at series of chemicals or
2 a series of drugs that were within there. So this
3 is not the only one that was within this system.
4 However, that's the one that was identified to be
5 the most similar to it based on the sub-structural
6 features.
7 DR. LEVINE: Can you address the
8 interpretation, it was purely categorical or
9 quantitative?
10 DR. STAVITSKAYA: It's actually
11 quantitative.
12 DR. LEVINE: In terms of the implications
13 for hepatotoxicity.
14 DR. STAVITSKAYA: It's actually looking at
15 the different drugs within the system and
16 identifying whether there are similarities within
17 the two and then actually using that in order to
18 say whether it's going to be hepatotoxic.
19 It's looking to see that if other drugs that
20 are very similar to it are also known hepatotoxins.
21 Does that answer the question?
22 DR. BADEN: Dr. Andrews:

1 DR. ANDREWS: I have a question, not on
2 hepatotoxicity, but on the symptoms. Consumers
3 care about symptoms. I was struck in the
4 difference I saw in both Dr. Rubin's presentation
5 about the difference between symptoms improving
6 compared to soli versus moxi. I'm not going to
7 even try.
8 (Laughter.)
9 DR. ANDREWS: In the IV-to-oral study, but
10 not in the oral study, and then also looking at the
11 company's analysis at short-term follow-up, looking
12 at resolution of all the symptoms is about 50
13 percent and it's a little lower with soli versus
14 moxi, but a little higher in the IV.
15 I wonder if that's because you can tell
16 which one you're getting because it's an acidic
17 solution and that sort of fit with the infusion
18 site reactions are much higher in the soli versus
19 moxi.
20 I guess I'm getting around to
21 whether -- should we be using, instead of
22 investigator-reported symptom reports, should we be

1 asking patients about their symptom reports?
2 DR. RUBIN: This is Dan Rubin, FDA. You
3 raised a number of important points.
4 On the unblinding issue, maybe the sponsor
5 could comment in more detail about that from the
6 study reports. I don't recall there being very
7 many cases of accidental unblinding.
8 In terms of differences of results at
9 different endpoints based on different symptoms,
10 there was a fair amount of noise about those
11 different assessments. So I wouldn't be prepared
12 to say that there's any type of interaction for the
13 primary analyses. The results did look very
14 similar in the two trials, in both arms.
15 As far as complete resolution of symptoms,
16 it is known that some of them, like cough, will
17 take longer to resolve. I didn't focus on that in
18 my presentation.
19 Then for patient-reported outcomes, maybe
20 either Dr. Turner or Dr. Das could say more detail
21 about this, but there is effort from the
22 Foundations for the National Institutes of Health

1 to come up with a patient-reported outcome for
2 community-acquired pneumonia. Unfortunately, it
3 wasn't available in time to use in this trial.
4 DR. BADEN: Dr. Rubin, just to follow-up on
5 that comment, since there was a 10 percent
6 difference, could that unblinding have impacted the
7 results or subanalyses can show that there's no
8 difference whether or not that unblinding occurred?
9 It's not unblinding, but perceived unblinding.
10 DR. RUBIN: Right. These were designed as
11 double-blind trials and accidental unblinding was
12 supposed to be captured and there wasn't a lot of
13 it reported. But if you're asking if there was
14 unblinding, could it have made a difference --
15 DR. BADEN: I didn't ask it correctly. If
16 those who had symptoms with the infusion made the
17 self-perception of what they were receiving, I
18 presume the results are insensitive to that self-
19 perception, if that were to have occurred.
20 DR. RUBIN: I see. You're asking in the IV-
21 to-oral trial, because there were those infusion
22 site reactions, if the patient somehow realized

1 that, knew that they were on solithromycin.
2 DR. BADEN: Then the subjective cough,
3 because the outcomes are not necessarily a
4 laboratory test, but a subjective test. I would
5 presume the results would be insensitive to
6 that -- it's not unblinding, but a self-perception.
7 DR. RUBIN: Right. To be honest, I'm not
8 sure exactly how the results would be impacted by
9 that.
10 DR. GOPINATH: This is Ramya Gopinath. The
11 only other point that I would make is that recall
12 that there were a significant number of patients
13 with underlying asthma or COPD. Sometimes it is
14 hard to evaluate the resolution of these symptoms
15 in somebody who may have chronic sputum production
16 or cough.
17 DR. BADEN: A follow-up?
18 DR. ANDREWS: Yes, because I guess the
19 concern is that the symptoms look better under soli
20 versus moxi, but the clinical response is worse.
21 You wonder if the investigator symptom
22 possible -- whether if you looked at patients'

1 responses on their symptoms, would that track
2 better with the clinical response and then it would
3 affect maybe dosing. It might affect whether it's
4 effective in the IV arm.
5 DR. RUBIN: Right. In the IV arm, at the
6 SFU 12 to 17 days after baseline, you'd have the
7 numerical point estimate for the treatment
8 difference favored solithromycin on the symptom
9 endpoint, but disfavored solithromycin on the
10 investigator-assessed clinical response endpoint.
11 We tried to look into why that was and to
12 see if it was anything other than chance and, to be
13 honest, couldn't make a determination that it was.
14 I think in one of my slides I showed the
15 different reasons for investigator-assessed
16 response and there wasn't really enough granularity
17 to say exactly why some of these patients were
18 being called treatment failures other than, say, a
19 perceived need for additional therapy or a
20 perceived lack of resolution.
21 DR. BADEN: Mr. Mikita?
22 MR. MIKITA: This is a follow-on question.

1 I really appreciate both the sponsor's and the
2 agency's presentations. I promise there's going to
3 be some questions. I appreciate Dr. Avigan's
4 initial explanation.
5 My concern is on the fact that there is a
6 crying need for antibiotics. There's also a crying
7 need for safe antibiotics.
8 My question centers on this. It seems to be
9 that there is a concern on the agency's part about
10 the safety of this data. The agency has become
11 hyper vigilant as a result of the telithromycin
12 experience. Therefore, if sponsors are going to be
13 confined to doing these things in the isolation of
14 a clinical trial, which is, by definition, not
15 always practical, as Dr. Re said at the beginning
16 of the questions after the sponsor, then are you
17 saying that we are so risk averse because of the
18 telithromycin lessons learned that this package
19 fails on the basis of a lack of safety data or is
20 it a lack of population and the lack of numbers and
21 the lack of sample with respect to the safety data
22 or is the presentation -- having worked with the

1 sponsor, are you concerned at the sponsor never
2 directly responded to your concerns and either
3 characterized them as idiosyncratic or cover
4 themselves by saying, well, the drug is not
5 supposed to be prescribed that way, the drug is
6 supposed to be prescribed this way?
7 As Dr. Re says, that's not real world.
8 That's not going to happen. I know there's a lot
9 of questions in there. But what does this sponsor
10 do and what do other sponsors do now in the face of
11 this very, very large shadow cast over by the
12 telithromycin comparison? Thanks.
13 DR. COX: A lot of questions in there. Let
14 me try and step through a few different points.
15 I think what we're trying to do is really
16 just present the data that we're seeing from the
17 clinical trials and provide you with our objective
18 assessment of what it is that we're seeing.
19 You're bringing up telithromycin. Yes,
20 telithromycin was another member of the ketolide
21 class. And as we work through science, we try and
22 learn from past experiences. Oftentimes, there are

1 lessons that can help you to understand future
2 situations. So we are always trying to learn from
3 the past.
4 With regard to weighing all this, I think
5 that's really where we're looking for the committee
6 to provide some opinion, some advice on this. We
7 hope that the presentations that have been provided
8 will help to give you the information that will
9 help you to work through this.
10 With advisory committee meetings, we
11 oftentimes are bringing the more challenging
12 questions that we face to the committee and we
13 recognize that. We value the deliberations of the
14 advisory committee in helping to work through the
15 challenging benefit-risk scenarios that we
16 sometimes face.
17 I hope that helps to address your questions,
18 Mr. Mikita.
19 MR. MIKITA: Yes, Vincent. It's good to see
20 you.
21 DR. BADEN: On that note, which essentially
22 summates our charge, it is past 12:35, we will

1 break for lunch. There are many questions from
2 panel members both from the sponsor's presentation
3 this morning and the agency's presentation that we
4 will resume with after lunch. So fortify
5 yourselves.
6 (Laughter.)
7 DR. BADEN: We will now break for lunch.
8 We'll reconvene again in this room in one hour from
9 now at 1:30. Please take any personal belongings
10 you may want with you at this time.
11 Committee members, please remember that
12 there should be no discussion of the meeting during
13 lunch amongst yourselves, with the press, or with
14 any member of the audience.
15 Thank you. See you at 1:30.
16 (Whereupon, at 12:37 p.m., a lunch recess
17 was taken.)
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3 A F T E R N O O N S E S S I O N
4 (1:31 p.m.)
5 **Open Public Hearing**
6 DR. BADEN: if you all can take your seats,
7 we'll resume in one or two minutes.
8 (Pause.)
9 DR. BADEN: So we shall resume our business.
10 Both the FDA and the public believe in a
11 transparent process for information gathering and
12 decision making. To ensure such transparency at
13 the open public hearing session of the advisory
14 committee meeting, FDA believes that it is
15 important to understand the context of an
16 individual's presentation.
17 For this reason, FDA encourages you, the
18 open public hearing speaker, at the beginning of
19 your written or oral statement, to advise the
20 committee of any financial relationship that you
21 may have with the industry, its product, and if
22 known, its direct competitors. For example, this

1 financial information may include the industry's
2 payment of your travel, lodging, or other expenses
3 in connection with your attendance at the meeting.
4 Likewise, FDA encourages you, at the beginning of
5 your statement, to advise the committee if you do
6 not have any such financial relationships.
7 If you choose not to address this issue of
8 financial relationships at the beginning of your
9 statement, it will not preclude you from speaking.
10 The FDA and this committee place great importance
11 in the open public hearing process. The insights
12 and comments provided can help the agency and this
13 committee in their consideration of the issues
14 before them.
15 That said, in many instances and for many
16 topics, there will be a variety of opinions. One
17 of our goals today is for this open public hearing
18 to be conducted in a fair and open way, where every
19 participant is listened to carefully, and treated
20 with dignity, courtesy, and respect. Therefore,
21 please only speak when recognized by the
22 chairperson. Thank you for your cooperation.

1 As we open the open public hearing
2 component, I'd like to note that we received about
3 a dozen letters commenting on this application,
4 which were very helpful, and has been appreciated
5 by the membership, and has been carefully
6 considered and reviewed.
7 I would like to now ask speaker number 1 to
8 step up to the podium, introduce yourself. Please
9 state your name and any organization you are
10 representing for the record.
11 DR. PRICE: Good afternoon. My name is
12 Lance Price. I have no financial conflicts of
13 interest to report. I even paid for my own Uber
14 ride over here.
15 So I'm a molecular microbiologist and a
16 professor at the Milken Institute School of Public
17 health in Washington, D.C. and I also direct the
18 Antibiotic Resistance Action Center, where we're
19 combining cutting-edge research with strategic
20 communication and science-based policy to try to
21 preserve the usefulness of antibiotics for future
22 generations.

1 So as the center's director, I'm regularly
2 asked to speak about antibiotic resistance. And
3 usually, I spend most of my time talking about
4 improving antibiotic stewardship both in human
5 medicine and animal production.
6 But today, I want to focus my comments on
7 our desperate need for new antibiotics. So over
8 the past few decades, we've seen two clashing
9 trends. We've seen the rapid emergence of multi-
10 drug resistant bacteria and also the precipitous
11 decrease in new drug development.
12 The clanging of these two trends has been
13 reverberating in the form of infections that are
14 increasingly difficult to treat. And for the first
15 time in our lives, we're facing a time when we
16 could be infected by bacteria that are untreatable
17 with our current antibiotics.
18 Now, I'm an optimist and I have no doubt
19 that we'll bring new antibiotics to market, but if
20 we don't change the pace at which we do this, we
21 will all have to trudge through a time when even
22 common bacterial infections could be deadly.

1 This is going to dramatically change our
2 lives, so everything from what procedures can take
3 place in a hospital to what it feels like to shake
4 somebody's hand or ride public transportation.
5 I think it's important to remind ourselves
6 of what happened to our previous antibiotics, too.
7 Many if not all of them have been squandered
8 through inconsiderate use. So I say inconsiderate
9 because so many people, including physicians,
10 patients, livestock producers use antibiotics
11 without consideration for society as a whole.
12 Stuart Levy, the godfather of antibiotic
13 stewardship, professor at Tufts University, and the
14 guy who started the Alliance for the Prudent Use of
15 Antibiotics, once described antibiotics as societal
16 drugs to try to help us understand that one
17 person's abuse of an antibiotic can lead to
18 resistant bacteria that can spread to somebody else
19 and prevent them from using that same antibiotic.
20 So we have to recognize the societal nature
21 and change the way we use antibiotics. So we need
22 some other things as well, some very practical

1 things. We need rapid diagnostics that can
2 differentiate viral from bacterial infections. We
3 need diagnostics that can determine bacterial
4 species and determine what they're susceptible or
5 resistant to.
6 We need to invest in the developing world to
7 provide clean water and better hygiene to reduce
8 illnesses and the dissemination of drug-resistant
9 bacteria. And we need vaccines and we need to
10 invest in alternate strategies to treat infections
11 that leave good microbes behind. But among all
12 these things, while we need all of these things,
13 the fact remains that, today and into the
14 foreseeable future, antibiotics are the best things
15 we have for treating infections.
16 So we have to find ways to increase the pace
17 of new antibiotic development while ensuring their
18 public safety. Now, many of our challenges are a
19 result of market failures. So we are asking drug
20 companies. We are speaking out of both sides of
21 our mouths. Right?
22 We're asking drug companies to bring new

1 antibiotics to market while at the same time asking
2 them to use them as little as possible. So it's no
3 wonder that a lot of drug companies are getting out
4 of this market. And we need to come up with new
5 incentives to bring them back into the market and
6 new management structures that will preserve the
7 utility of antibiotics.
8 But these are way beyond my expertise.
9 However, despite these challenges, companies like
10 Cempra are still willing to work in this difficult
11 environment and are even seeking narrow indications
12 for their antibiotics to help with our stewardship
13 efforts.
14 I think this is commendable and we do need
15 these drugs. So we have to find a way to help
16 these companies determine if their drugs are safe
17 and, if they are, increase the pace at which these
18 drugs are brought to the clinicians.
19 So I'm here for two simple, I think simple,
20 requests. I'm here to ask the FDA to do all in
21 their power to help expedite the process of
22 bringing new, safe, effective antibiotics to market

1 and then continue to find ways to reduce
2 unnecessary antibiotic use in both human medicine
3 and animal production.
4 I think a world full of untreatable bacteria
5 is not inevitable. It's not inevitable. We can
6 change our course. But we have to make this change
7 a national priority. And I think you guys have the
8 power to do this. Thank you.
9 DR. BADEN: Thank you. Will speaker
10 number 2 step up to the podium and introduce
11 yourself? Please state your name and any
12 organization you are representing for the record.
13 DR. TULKENS: Okay. I'm Paul Tulkens. I'm
14 a pharmacologist from the University of Louvain,
15 Brussels, Belgium. The next slide will show you my
16 disclosures. I have been -- for the trip to come
17 to here, to Washington, but I also worked for many
18 pharmaceutical companies, and I have past
19 experience with the European Medicine Agency.
20 I think I will start by saying the
21 following. Some people should not die. This
22 person that you see here is the one who discovered

1 the mode of action of penicillin with Strominger,
2 and he died from a pneumococcal infection due to a
3 resistant bacteria.
4 The next slide shows you the risk of
5 community-acquired pneumonia. We still do have
6 mortality. And you see that we get something like
7 5 percent mortality even if we treat patients
8 correctly. And the reason why we have this
9 mortality is because, with some of those patients,
10 we do have a resistance problem and the treatment
11 is not adequate.
12 This is based on a large German database.
13 Now, we produce a paper on the multi-resistance of
14 pneumonia, and I'll show you what the result of our
15 investigation was.
16 We do have now in Europe about 18 percent of
17 our strains that are non-susceptible to
18 amoxicillin. We have about 30 to 40 percent
19 resistance to clarithromycin and azithromycin. And
20 we even see resistance coming to levofloxacin.
21 In comparison, we have even the MIC
22 distribution of solithromycin for a number of

1 strains in Europe. And as you can see, the figures
2 are very low, exactly, those that we have seen this
3 morning. So we are in need of drugs that are able
4 to be used in place of clarithromycin and
5 azithromycin, which will no longer be used.
6 Now, we also may ask the questions about
7 safety. We produced a paper about a couple of
8 years ago about the safety of antibiotics for liver
9 toxicities, those within the clinical practice.
10 And we found out that erythromycin will cause an
11 increase in amino transferase. Clarithromycin will
12 show a hepatotoxic profile similar to
13 levothyroxine.
14 The azithromycin will show also elevated
15 enzymes in about 2 percent of the patients and
16 documented in children. The references are shown
17 on the slide. So with a long story short, we do
18 see that we have elevated enzymes with
19 erythromycin. We do have elevated enzymes with
20 clarithromycin. And we do have elevated enzymes
21 for azithromycin, as indicated from the label use
22 in the U.S. today.

1 So the message is very simple in a nutshell.
2 First of all, we lack new antibiotics, and we have
3 the problem of non-susceptibility and resistance of
4 [indiscernible] pneumonia, which is a real problem.
5 Solithromycin may show excellent in vitro activity
6 against multi-resistant streptococcus
7 [indiscernible] isolates.
8 The problem is that, in the absence of this
9 drug, we may actually be forced to use either high
10 doses of amoxicillin, including a combination with
11 clavulanic acid, which we know to be hepatotoxic,
12 or we may use quinolones, but quinolones have a
13 problem that have been underlined by your
14 organization a couple of months ago.
15 Solithromycin, the hepatic safety profile
16 is, at the end of the day, not different from that
17 of current approved macrolides to elevation of
18 liver enzymes.
19 The way the company proposes to use the
20 compound for about 7 days is exactly what is needed
21 to solve the problem for community-acquired
22 pneumonia and avoiding risk. And therefore, the

1 solithromycin may be the long way to really save
2 macrolide active against resistance pneumoniae for
3 both IV and oral administration.
4 We'd like to have this compound because it's
5 usable as monotherapy not only against
6 streptococcus pneumoniae, but also against the
7 other organisms, including the atypical that we
8 cannot reach if we use only beta-lactams. Thank
9 you for your attention.
10 DR. BADEN: Will speaker number three step
11 up to the podium and introduce yourself? Please
12 state your name and any organization you're
13 representing for the record.
14 DR. HEIL: Hi, good afternoon. My name is
15 Emily Heil and I'm speaking today on behalf of the
16 society of Infectious Disease Pharmacists.
17 I'm an assistant professor at the University
18 of Maryland, School of Pharmacy, and I practice as
19 an infectious diseases clinical pharmacy specialist
20 and antimicrobial stewardship coordinator at the
21 University of Maryland Medical Center, although my
22 views today do not necessarily reflect the views of

1 the university. I am not a consultant for any
2 pharmaceutical companies with antibiotics in
3 development and I was not paid for this appearance
4 today.
5 The Society of Infectious Diseases
6 Pharmacists, or SIDP, is a professional
7 organization dedicated to promoting the appropriate
8 use of antimicrobials, and we support practice,
9 teaching, and research in infectious diseases. Our
10 members work with other clinicians and
11 antimicrobial stewardship programs that provide
12 oversight to the appropriate prescription of
13 antibiotics.
14 SIDP does not comment on individual drugs.
15 However, we do support the continued antibiotic
16 development. We support innovative pathways for
17 antibiotic research, development, and approval,
18 given significant unmet need.
19 Community-acquired pneumonia or CAP
20 continues to burden our healthcare system and,
21 along with influenza, remains the leading cause of
22 infection-related mortality in the United States,

1 primarily striking elderly patients and patients
2 with comorbidities.
3 In addition, admissions and re-admissions to
4 hospitals for community-acquired pneumonia are
5 rising with close to 1,000,000 hospitalizations and
6 143,000 re-admissions each year, costing our
7 healthcare system an estimated $17 billion. As the
8 U.S. population ages, the clinical and economic
9 burden of CAP is only anticipated to get worse.
10 This disease state affects the healthcare
11 continuum, impacting patients receiving treatment
12 in the community and in the hospital depending on
13 disease severity. Optimizing treatment of this
14 disease and working to reduce re-admissions
15 associated with this disease is a top charge of our
16 antimicrobial stewardship program at my institution
17 and likely other programs around the country.
18 One of the mainstays of CAP treatment are
19 the fluoroquinolone antibiotics. Fluoroquinolones
20 are public enemy number one for people like me, who
21 spend their days trying to minimize adverse effects
22 associated with antibiotic exposure and also to

1 slow the antibiotic resistance train that's
2 barreling down the tracks at us.
3 Fluoroquinolone has remained one of the top
4 antibiotics associated with C. difficile infection,
5 which is another infection associated with
6 significant morbidity and mortality.
7 Additionally as everyone in this room knows,
8 fluoroquinolones are associated with a host of
9 potential toxicities, as was recently published in
10 an FDA drug safety communication about their use.
11 When you're caring for a patient who was
12 formerly a runner that has been sidelined by tendon
13 rupture or an elderly patient experiencing
14 hallucinations, you remember just how important it
15 is to limit the use of these drugs to situations
16 where there are not alternatives.
17 Additionally, as one of the most commonly-
18 prescribed antibiotic classes, resistance to the
19 fluoroquinolones is on the rise and this class of
20 medications is known to drive resistance, including
21 methicillin resistance, staph aureus, or MRSA.
22 New antibiotic options, particularly

1 fluoroquinolone sparing options that are available
2 orally and can be used outpatient are needed to
3 optimize community-acquired pneumonia treatment
4 while minimizing antibiotic adverse effects.
5 In general, continued support for new
6 antibiotic development is desperately needed.
7 Thanks to policy changes like the GAIN Act and some
8 of the work done here at the FDA, we've certainly
9 seen some new antibiotic approvals recently.
10 But we still need to build on these changes
11 to bring forth a more robust pipeline of
12 antibiotics that's urgently needed. Thank you.
13 DR. BADEN: Will speaker number 4 step up to
14 the podium and introduce yourself? Please state
15 your name and any organization you're representing
16 for the record.
17 DR. CARLIN: Thank you. My name is Brian
18 Carlin. I am currently a practicing physician in
19 western Pennsylvania and I practice pulmonary
20 critical acre and sleep medicine there.
21 My drive down this morning from Pittsburgh
22 is being reimbursed by Cempra, but I am here on my

1 own behalf. I am not receiving any other
2 compensation for any of my other travel expenses.
3 The reason I'm here today -- it's important
4 to me and it's also more important to my patients
5 in regards to the issues of antibiotics. I've been
6 in practice for the last 28 years. In addition, I
7 see patients in both the inpatient and outpatient
8 arenas. And I am a former training program
9 director for Primarily Critical Care Fellows at
10 Allegheny General Hospital in Pittsburgh.
11 In addition, I participate actively in
12 several national organizations, the National Lung
13 Health Education program, American College of Chest
14 Physicians, the National Board for Respiratory
15 Care, and the American Thoracic Society.
16 I believe that there's currently a need for
17 newer antibiotics. I see various infections in my
18 clinical practice in the inpatient and outpatient
19 arena, whether regards to COPD exacerbations,
20 pneumonia, sepsis, C. diff infections, just to name
21 a few.
22 Certainly, the availability of newer

1 antibiotics will be helpful in managing these
2 infections. In regards to the management of COPD,
3 it's projected that over $50 billion will be spent
4 in this country in managing COPD in the year 2020.
5 Most of this is spent when people are sick
6 with an acute exacerbation or pneumonia. And the
7 cause of these, as many of you know, are due to
8 bacterial types of infections. In addition, as has
9 been mentioned just previously, greater than 20
10 percent of those patients who are admitted to the
11 hospital with a COPD exacerbation are re-admitted
12 within a 30-day period, prompting CMS to initiate
13 monetary penalties for those hospitals that have
14 higher-than-average rates of readmission.
15 This certainly affects the overall
16 healthcare system and it also affects each
17 individual patient. And here's an example of what
18 I mean just with a patient by the name of Mr. H.
19 He was admitted to the hospital with COPD
20 exacerbation that eventually required tracheostomy
21 and long-term ventilation.
22 He came to me at a long-term acre facility,

1 a skilled nursing facility, actually, that was
2 designed to take care of patients such as him.
3 Prior to his admission to me, he was actively
4 golfing and actively traveling, but a six-month
5 illness really debilitated him significantly.
6 He required multiple re-admissions back to
7 the acute care hospital and had recurrent
8 pneumonias that were actually due to a multiply-
9 resistant bacterial organism that was actually only
10 sensitive to an inhaled antibiotic therapy.
11 Fortunately, after several rounds of this
12 inhaled antibiotic therapy, he improved and was
13 eventually, after another couple months, able to
14 get decannulated and sent him without ventilator
15 support. The burden to him and his family,
16 absolutely tremendous, absolutely tremendous, the
17 burden to the healthcare system, also absolutely
18 tremendous, nine months in a hospital stay, re-
19 admissions, and the like.
20 He isn't alone. I've seen this with many
21 other patients and I think all my colleagues that I
22 could ask have seen this as well. That's why I'm

1 here. The total number of antibiotic agents
2 introduced from when I started practice from 1988
3 to 1992 was 14.
4 In 2004, only three new agents were
5 introduced. With the growing number of resistant
6 organisms, I feel that the development and
7 introduction of newer agents that can effectively
8 treat such organisms is absolutely essential and a
9 critical need for our patients, so we can provide
10 them the best patient outcomes.
11 I also think it's important to have
12 therapies available in both intravenous and oral
13 form. Many critical-care pulmonologists like
14 myself have had patients who have improved
15 initially on intravenous therapy only to be
16 switched to another type of oral therapy, as that
17 was what was available, requiring in some instances
18 a switch back, as the patient had failed that
19 switch to the oral therapy.
20 The availability to have an antibacterial
21 agent that is available to both intravenous and
22 oral forms would be ideal to help in the management

1 of our patients. With the development of newer
2 therapies, we should be able to reduce the overall
3 morbidity and mortality associated with the care of
4 patients that have, in my instance, lung disease
5 and critical care illness and, absolutely most
6 importantly, I feel that we should be able to
7 improve the patient's quality of life with these
8 more targeted and personalized therapies. Thank
9 you.
10 DR. BADEN: Will speaker number 5 step up to
11 the podium and introduce yourself? Please state
12 your name and any organization you're representing
13 for the record.
14 DR. ROBLES: Good afternoon. My name is
15 Aymarah Robles. Thank you for allowing me the
16 opportunity to address the panel. My travel has
17 been reimbursed by the sponsor, but my time has
18 not. I have no professional relationship with the
19 sponsor and no financial stake in the outcome of
20 this meeting. My opinion is my own.
21 I'd like to tell you briefly about my
22 background as a clinician. I spent approximately

1 20 years in academic primarily critical care,
2 medicine, and was the ID pulmonologist and
3 associate director of the inpatient AIDS unit at
4 SUNY Downstate, Brooklyn, New York.
5 For the past 11 years, I have been
6 practicing primarily critical care medicine in a
7 community hospital in Miami. As a pulmonologist, I
8 am acutely aware of the problem of community-
9 acquired bacterial pneumonia and of the growing
10 problem of antibiotic resistance, which is
11 particularly high in my neck of the woods.
12 With macrolide resistance reaching over 50
13 percent, solithromycin would provide a good
14 alternative to current treatment regimens. In
15 particular, the ability to use solithromycin and
16 macrolide-resistant and multi-drug-resistant
17 infections would be extremely helpful.
18 Because it's much less likely to cause
19 resistance, it would fit well with current
20 guidelines for antibiotic stewardship. The studies
21 presented this morning show comparable efficacy to
22 a standard respiratory fluoroquinolone and the

1 safety profile is good, including the low potential
2 for C. diff-associated diarrhea.
3 From a clinical standpoint, the IV site
4 reactions, which are common to macrolides, are
5 manageable. The daily oral dosing provides a good
6 option for outpatient management as well as for
7 enhanced patient adherence.
8 The availability of effective oral dosing
9 will reduce hospitalizations and associated
10 complications. I'm here because, given the high
11 rates of antibiotic resistance, I have patients
12 right now in my practice who would benefit from
13 this drug.
14 While the idiosyncratic liver problems of
15 telithromycin raise an understandable concern,
16 regarding solithromycin, some form of postmarket
17 surveillance should provide clinicians with
18 additional pertinent information.
19 In the meantime, this is an important
20 macrolide to make available for the specific
21 condition of community-acquired bacterial pneumonia
22 to deal with the very serious problem of antibiotic

1 resistance.
2 As a clinician, I strongly urge the panel
3 and the FDA to consider the approval of
4 solithromycin. Thank you for your time.
5 DR. BADEN: Will speaker number 6 step up to
6 the podium and introduce yourself? Please state
7 your name and any organization you're representing
8 for the record.
9 DR. REESE: Good afternoon, ladies and
10 gentlemen. My name is Dr. Celeste Reese, and I'm a
11 board-certified family medicine physician out of
12 Birmingham, Alabama. My only disclosure is that my
13 travel has been reimbursed by the sponsor today.
14 However, I have no financial stake in the outcome
15 of this meeting.
16 Here's what I do. I'm a local urgent care
17 physician out of Birmingham, Alabama, pretty busy.
18 We see or I see about 50 to 60 patients a day. I
19 work about 20 shifts a month. And so why I came
20 today is just to share a little bit with you about
21 what happens to me a little bit every day at work.
22 The increasing resistance of antibiotics in

1 the treatment of community-acquired pneumonia is a
2 growing problem. It's something that I see every
3 day as I stand on the front lines, treating
4 patients on an outpatient basis with pneumonia.
5 The first case I'd like to share with you is
6 a 65-year-old female that's relatively healthy.
7 Only history of disease is hypertension. She was
8 started on a Z-PAK by her family physician. She
9 saw me about four days later with worsening of
10 symptoms, a high fever, discovered to have
11 pneumonia, needed antibiotics, was therefore sent
12 to the hospital.
13 With the new black-box label warning of the
14 fluoroquinolones, the risk of starting patients on
15 these drugs is something that limits the treatment
16 of patients that come in with community-acquired
17 pneumonia.
18 Another recent example, there's a 42-year-
19 old healthy gentleman, relatively healthy, had been
20 coughing for about three weeks, placed on a Z-PAK
21 by me, returned to the clinic two weeks later with
22 a persistent pneumonia that was just resistant to

1 azithromycin.

2 I could go on, and on, and on about other

3 examples, but I came to share with you guys today

4 that, being someone who's a family medicine

5 physician, board certified, I do urgent care. I

6 see a lot of patients every single day. And the

7 increasing resistance with using azithromycin is a

8 growing, increasing problem, and I would simply

9 love to have another choice in the treatment of

10 this disease. Thank you.

11 **Clarifying Questions to the Presenters (continued)**

12 DR. BADEN: That concludes the number of

13 speakers who requested to speak. Anyone else wish

14 to make comments? Hearing none, the open public

15 hearing portion of the meeting has now concluded

16 and we will no longer take comments from the

17 audience.

18 I would like to resume now to where we left

19 off before lunch, asking clarifying questions of

20 either the sponsor or the agency, and we will

21 resume from the sponsor list of questions where Dr.

22 Honegger, we weren't able to get to you this

1 morning. But I think it's fair to ask issues to
2 either the agency or the sponsor at this point.
3 DR. HONEGGER: Okay. Thank you. Is it okay
4 if I ask two unrelated questions.
5 DR. BADEN: Okay.
6 DR. HONEGGER: The first one is about the
7 legacy of telithromycin. The question I will give
8 to the FDA. In terms of telithromycin, without any
9 ALT increased signals seen in the phase 3 trials,
10 there still was this risk of idiosyncratic DILI,
11 and, in the case of solithromycin, there actually
12 is the ALT increase.
13 But even if there weren't, the drugs
14 are -- there's some structural similarity. My
15 question is, when reading about antibiotic-
16 associated DILI, it seems like there are some
17 genetic associations, mostly related to molecules
18 that present the T-cells, HLA molecules.
19 I was wondering if genomic studies have been
20 conducted in telithromycin to know if there are HLA
21 associations.
22 DR. AVIGAN: Well, that's a very interesting

1 and important question. And at this time, with
2 this particular drug reaction, the answer is, we
3 don't know. So we haven't yet identified such an
4 enrichment, but I would be very interested in
5 hearing if the sponsor has any information. I can
6 say a couple of things about HLA markers for drug
7 reactions and DILI.
8 There are an evolving number of drugs -- one
9 example is amoxicillin some clavulanic acid --
10 where there's a class 2 HLA marker, which enriches
11 for the risk. And there are other examples as
12 well. Lumiracoxib is another.
13 So one of the take-home messages with HLA
14 markers and DILI is that they tend to be drug
15 specific, so different drugs actually have
16 different HLA haplotype associations, which are to
17 some extent empirically discovered, but I would now
18 defer to the sponsor.
19 DR. BADEN: Dr. Fernandes, you have some
20 thoughts on this?
21 DR. FERNANDES: Yes. Thank you very much.
22 So when we first got solithromycin, we really

1 worked extremely hard to say, what is it, why is
2 telithromycin different from the older macrolides.
3 I had a lot of experience with macrolides
4 coming from that and having developed erythromycin.
5 So we looked at it. We talked to a lot of
6 chemists. And for a chemist who is working in the
7 central nervous system, it was very obvious.
8 They saw the pyridine and they basically
9 told me a self-respecting anti-bacterial chemist
10 should not be putting a pyridine on the molecule
11 because central nervous system chemists use this in
12 milligram amounts like nicotine, analogs of
13 nicotine.
14 Here, telithromycin was given an 800-
15 milligram amount for 7 to 10 days in large amounts,
16 of course. And we have shown conclusively this
17 work was done by Dr. Daniel Bertrand, that binds
18 the alpha-7 nicotinic acid receptor in the eye.
19 A question which was asked at the 2006
20 advisory committee meeting for Ketek was why were
21 young women addressed. And Dr. Bertrand has
22 already published in 1988 that progesterone

1 sensitizes these receptors and that's why young
2 women were most susceptible to the visual effects.
3 It's the same receptor, the exact same
4 receptor in the liver. And if you read the
5 fantastic work of Dr. Kevin Tracey, where he
6 describes inflammatory reflex, and if you block
7 that telithromycin, you are going to get DILI
8 because you have this rapid necrotic cell death
9 caused by TNF alpha.
10 That is being released into the liver and
11 has blocked. The actions cannot be blocked
12 anymore. So that is the reason we decided to use a
13 molecule without any pyridine in it. I hope that's
14 clear.
15 DR. HONEGGER: Well, it makes sense to try
16 to avoid that interaction with the acetylcholine
17 receptor, but still, it was an idiosyncratic
18 reaction, so it seems there must be some genetic
19 association or there may be one that's rare. And
20 so it seems that an HLA association still seems
21 possible. And if these drugs are structurally
22 similar, although I don't know how close 85 percent

1 is and what the likelihood that they would have the
2 same epitope, for instance, seems like something to
3 consider.
4 DR. FERNANDES: I mean, I'm sure there
5 possibly would also be genetic things because
6 you're most susceptible if you have certain
7 genetics. I certainly acknowledge that. Thank
8 you.
9 DR. HONEGGER: The second question is just
10 kind of addressing the narrow therapeutic window of
11 this drug. It seems that high doses or prolonged
12 doses are associated with what's usually an
13 asymptomatic ALT elevation.
14 Because the drugs seem to have good efficacy
15 regardless of the quartile of the AUCs or AUC over
16 MIC, is there any reason to consider a trial of
17 dosing at, like, 200 milligrams for 5 days for oral
18 therapy, even though maybe that wasn't predicted to
19 be optimal on the PK data?
20 Then secondly, is there a possible role for
21 therapeutic level monitoring during therapy, for
22 instance on inpatients? I'd be curious to get

1 those.

2 DR. BADEN: Dr. Fernandes?

3 DR. FERNANDES: In antibiotic development,

4 we always try to optimize the dose for efficacy,

5 especially in a serious disease. I'd like to call

6 upon Dr. Ambrose, who did the work for us to

7 determine the dose, and then I will address some

8 lower doses for the long-term. It's okay.

9 DR. AMBROSE: So when we think about

10 identifying a dose that we're going to bring into

11 treatment of infectious disease, in this case

12 pneumonia, as mentioned by Dr. Bhavnani earlier, we

13 bring in animal data first.

14 We forecast doses using the animal data and

15 early pharmacokinetic data. There we go. So this

16 is one of the plots that we look at in making these

17 kind of decisions. And what you're looking at on

18 the left-hand side on the X axis is total drug ELF

19 AUC to MIC ratio, and change in log CFU in the

20 lungs of neutropenic mice.

21 As you move from left to right on that X

22 axis, you see more and more drug effect. That blue

1 box and whisker plot up at the top is the
2 distribution of AUC to MIC ratios expected in
3 patients. It's a simulation using the weighted AUC
4 to MIC distribution.
5 What we want to do is, we want to push the
6 dose upwards such that we're getting it to the
7 upper plateau of effect for the selected regimen to
8 go into patients. What we don't want to do is
9 slide down that exposure response curve. The
10 further you slide down that curve, the less
11 effective you become.
12 This particular picture is very reminiscent
13 of what you'd see with meropenem, if we put the
14 same picture up for meropenem. It would be very
15 strong up on the upper plateau of the exposure
16 response relationship.
17 So could we study a dose of 200 milligrams?
18 Sure. But the patients that would be most at risk
19 are those with elevated MIC values. So this is
20 what happens. This is the same dose of
21 solithromycin with MIC values now fixed at .12,
22 .25, and .5. And you can see it begin to slide

1 down that slope of the exposure response
2 relationship.
3 So what you'd be giving up by dropping the
4 dose too low is the patients that have the elevated
5 MICs, oftentimes the reason the drug is being
6 developed, at risk for suboptimal exposures.
7 DR. FERNANDES: I'd like to make one more
8 comment. I'm sure Paul will also agree that in
9 infectious disease, you want to have a few
10 multiples above the MIC to prevent resistance
11 development and preserve that antibiotic, so we try
12 to get a little bit higher than what is absolutely
13 required for those MICs.
14 Now, for the other indications which were
15 testing, the COPD, is longer term. And this was an
16 exploratory study and we don't need 400 for that,
17 but we have to start there because that was what
18 our chosen dose was and now we are dialing back.
19 So I want you to know that, for CAP, it's 5 to 7
20 days of the dose effect. But for other things,
21 it's not picked and we're dialing back.
22 DR. BADEN: Thank you. Dr. Weina?

1 DR. WEINA: Pete Weina from Walter Reed. So
2 we've been kind of dancing around in the shadow of
3 Ketek here, with the hepatotoxicity and some of the
4 other issues.
5 The safety data, though, was presented
6 primarily on 856 people with actual dosing of the
7 drug and that's wonderful because you want to see
8 how it's going to be actually used. But I didn't
9 see anything presented and I didn't see in the
10 briefing packet any real hard look at the phase 1
11 data.
12 The reason I'm just wondering if somebody
13 could comment on that is because there's different
14 types of dosing that's done and getting a good idea
15 of other types of effects that may have potentially
16 been seen or maybe a signal that's seen at higher
17 doses or for longer periods of time with the dose
18 adjusting from the phase 1.
19 Even if you just told me everything's cool,
20 that makes me feel a whole lot better than just not
21 seeing the data.
22 DR. GOPINATH: Thank you for your question.

1 So in phase 1, there were about 7.5 percent of
2 people in the total population who had ALT
3 elevation greater than the upper limit of normal.
4 If you recall, there were two patients that I
5 presented who both were healthy people and had
6 greater than 5 times.
7 Obviously, the phase 1 population is quite
8 heterogenous because there's different protocols
9 and some of them were exposed to different doses
10 and durations. So one of the patients that I
11 presented just had a single dose. The other one
12 had 3 800-milligram IV doses.
13 That dose is not used in the subsequent
14 trials.
15 DR. WEINA: I just need to be clearer, then.
16 You are absolutely right. You did present the
17 stuff on the hepatotoxicity. I am asking about
18 anything else that might have been seen. Because
19 we are focusing so much on hepatotoxicity, nobody
20 has said anything about any other kind of signal
21 that may have been seen at all.
22 DR. GOPINATH: While Dr. Fernandes is going,

1 let me just tell you that there were patients who
2 had the same sorts of adverse events, the other
3 adverse events that we had outlined, so some people
4 with nausea and vomiting, et cetera, those kind.
5 The visual disturbances -- there were 2 patients
6 who had blurring of vision, one who had asthenopia,
7 tired eyes, and that all happened in the phase 1
8 trials. Dr. Fernandes?
9 DR. FERNANDES: Yes. So having done
10 phase 1s on other macrolides, I could compare
11 between this and other macrolides and that's
12 actually very good because, within a class, you can
13 expect certain things.
14 We had expected a lot more belly cramps, a
15 lot more nausea and vomiting. For instance,
16 telithromycin, I think there was a lot of nausea
17 and vomiting at the 800-milligram dose. We saw
18 very little of that. We saw very little of that.
19 So we did see ALTs, and we knew the liver,
20 as was noted, is an organ, so as soon as you see
21 ALTs, we dial back. And so it was remarkable. On
22 the other end, there was nothing from the cardiac

1 effects. GI effects were very minimal. We have
2 been using the 1,000 milligrams for the gonorrhea
3 study and very, very minimal effects.
4 DR. BADEN: If I understand Dr. Gopinath,
5 the phase 1 studies used a higher dose and, with a
6 higher dose, there seems to be a toxicity signal.
7 And that's part of the reason the lower dose, the
8 400 milligrams, was chosen.
9 DR. GOPINATH: I think that's fair to say.
10 I mean, obviously, in the phase 1 trials, there
11 were several different regimens tried. And so the
12 doses differed. Some were crossover studies. Some
13 were ascending-dose studies.
14 So there really was quite a heterogenous
15 population. But overall, from that data and even
16 from the phase 3 data, it does seem that, if you
17 increase the exposure, there is more of a problem.
18 I should just add that one of the slides that I did
19 not present was, in the phase 3 trials, a
20 creatinine clearance of less than 30 mLs per minute
21 was actually an exclusion criterion.
22 So anybody with renal failure was excluded.

1 However, there were actually 9 patients who, in the
2 phase 3 trials, did have a creatinine clearance of
3 less than 30 mLs per minute. And the sponsor has
4 proposed, which is supported by our clinical
5 pharmacology review team, that the dose for renal
6 failure be halved because the exposure is much
7 higher.
8 Indeed, in those 9 patients who were exposed
9 to the regular dose and duration, 2 of the 9, so 22
10 percent, had significant ALT elevations above three
11 times the upper limit of normal.
12 DR. BADEN: Then I will recognize myself for
13 a question to Dr. Gopinath. Again, in one of your
14 slides, I think you said there were 6 in the
15 solithromycin group that had antimicrobial failure
16 or infection progression of some of the severe
17 outcomes.
18 Did you do that same analysis for moxy?
19 Because the issue of the reason for failure may
20 matter in that, if there's more failure for
21 antimicrobial inadequacy versus more failure for
22 toxicity or side effect, that might be useful

1 particularly in severe cases.

2 DR. GOPINATH: Yes. Thank you for that

3 question. It's an important one. I'll just

4 preface that remark by just reminding ourselves

5 that these are really sick patients. And some of

6 them, especially the hospitalized ones, were sick

7 enough to be hospitalized.

8 Many of them did have some confounders. 2

9 of the 6 patients had another microbiological

10 reason that they had failed. So for example, one

11 of them was infected with pseudomonas and the other

12 one had, I think it was, klebsiella along with a

13 gram positive.

14 So that was one potential problem. There

15 were a couple of others in whom it's always hard to

16 try to determine these things post-hoc when you

17 have not seen the patient. From what we could

18 gather from the narrative, it did look like there

19 was at least a component of the fact that they

20 weren't quite being treated with what they really

21 needed.

22 We did look at the same type of analysis

1 with moxifloxacin and, again, with the data that we
2 were presented, which obviously we don't have
3 access to all the data that's relevant, it did seem
4 that there were a couple of patients, 2 or 3
5 patients, if I recall, who did also seem to fail or
6 did progress on moxifloxacin.
7 DR. BADEN: So look similar given the data
8 available between the groups?
9 DR. GOPINATH: Given the data available, I
10 mean, it's hard to tease out all the confounders as
11 well.
12 DR. BADEN: Thank you. Dr. Daskalakis?
13 DR. DASKALAKIS: I actually have a question,
14 I think, both for the sponsor and the FDA regarding
15 adverse events. One of the things that we haven't
16 seen is sort of the age-old question potentially
17 but not necessarily is, is there any stratification
18 of these adverse events based on race and
19 ethnicity?
20 I ask that because, since the study was
21 mainly individuals of Caucasian descent mainly in
22 Europe, we have about 10 percent of the folks

1 studied who are African-American. I'm just curious
2 if you have any data beyond that.
3 DR. FERNANDES: Dr. Das, do you want to
4 address that, or Oldach?
5 DR. OLDACH: David Oldach. So when we
6 looked at ALT elevations in particular and tried to
7 find, then, the at-risk population for them -- I'm
8 waiting for a slide to come up -- we really didn't
9 find that age, or gender, or race predicted ALT
10 elevation.
11 The best predictors of ALT elevation were
12 exposure and ALT elevation at baseline. And I'm
13 not sure that we're going to be able to get the
14 slide up in time, but when looking at those
15 questions, we did not find that any of those three
16 parameters were predictive.
17 DR. DASKALAKIS: A direct follow-up, then,
18 actually, for the FDA is, given the size of the
19 population that was evaluated, that were African-
20 American and not of Caucasian descent, is that a
21 strong enough signal of safety to be able to
22 reliably not identify an at-risk population?

1 DR. AVIGAN: I can make a brief comment. So
2 just by looking at other examples, where there
3 might be an effect of demographics, race, on risk,
4 and HLA, an example actually is the TR1501 and
5 amoxicillin clavulanic acid, which was discovered
6 and primarily found in northern Europeans and
7 published.
8 That risk, if you have that allele, is still
9 very small. It's actually 1 in 1,000 for a serious
10 cholestatic hepatitis. So the point about that is,
11 you'd have to have an enormous study in a case-
12 controlled fashion to be able to tease out such a
13 question of differential risk.
14 DR. BADEN: To just follow that up, given
15 that we have 1,000 subjects studied, we can assess
16 or the data available to us assesses for about a 1
17 in 300 risk for all populations, not even smaller
18 populations. Is that a fair encapsulation?
19 DR. AVIGAN: Right. So one of the key take-
20 home messages from my review, at least from my
21 understanding of what the issue is, is, where can
22 we say the risk is, where we can assign the capping

1 of risk based on the fact that we never saw a
2 severe or serious liver injury.
3 But we were all this other kind of injury in
4 a larger population and, based on this rule-of-
5 three concept and the idea that there were 1,000
6 treatment subjects or just a little bit less than
7 that, we could say that at least the risk, if there
8 is a risk for serious liver injury, is less in a
9 homogenous population where risk is attributable in
10 a homogenous way, 1 in 330, but we couldn't assign
11 it a number that's less than that.
12 DR. BADEN: Thank you. Dr. Boyer?
13 DR. BOYER: Yes. So I got very confused by
14 what you're talking about with the 1 in 300 risk
15 and how you came to that number. One, I would
16 argue you did have 1 serious adverse drug reaction
17 in the study population. Whether it fits an
18 artificial rule or not, it was still a serious drug
19 episode of drug-induced liver injury that looked
20 like it might be a hypersensitivity reaction.
21 So I'm confused on how, because if it's 1 in
22 300 patients are going to have a serious hepatic

1 injury, that's terrible. And it's a little unclear
2 to me how you actually arrived at that number.
3 DR. PROSCHAN: I can tell you how they
4 arrived at that. That comes from doing an upper
5 confidence limit for the probability of event,
6 given that you've observed 0 out of N, then an
7 approximate upper confidence limit for that
8 probability is about 3 out of N, 3 over N.
9 DR. AVIGAN: Right. I don't want to
10 disagree with you because I to some extent agree
11 that there are many caveats to just making a kind
12 of padunk number.
13 The point is, the general point is, the
14 larger the test exposure population is without a
15 serious event, the more confidence we have that the
16 event, if it occurs, is more rare. So the question
17 is more kind of arithmetic or mathematics to say,
18 if we've studied 1,000 people and we never saw
19 liver failure, and we never saw what we call a
20 severe enough hepatocellular injury, this is from
21 our experience in other drugs, to cause jaundice.
22 With hepatocellular injury, we would then

1 say that it would be likely that we wouldn't see a
2 Hy's law case, another Hy's law case in a treatment
3 population less than 330 people, where if we were
4 to extrapolate the liver failure in 1 in 3,000, but
5 I agree with you that's a high number, so the take-
6 home message is, maybe we haven't -- the question
7 is, have we tested enough people to feel
8 comfortable with where the risk may lie to say that
9 we haven't seen an event.
10 DR. BOYER: So for Isoniazid, which has this
11 same problem, you have a lot of people who get
12 increased liver tests and very few of those get
13 severe hepatic injury. What would that number be
14 for Isoniazid?
15 DR. AVIGAN: Right. So these are general
16 ballpark figures, so there's a few percent of
17 people on Isoniazid that get robust ALT elevations
18 and about .1 percent have serious liver injury,
19 something like 1 in 1,000.
20 That's based on different studies and their
21 different numbers, but in that ballpark. So one of
22 the practical questions for an empirical clinical

1 trial, the safety experience, is how many people do
2 you want to study when you see a liver signal but
3 you haven't seen the severe end of the spectrum to
4 feel comfortable that, if you have serious liver
5 injury with that drug, it's below a certain level
6 of risk. And that's what the question is.
7 DR. BOYER: The other thing I wanted to ask
8 was, women have a normal ALT that's half of what
9 men have. So when the analysis was done on the
10 upper limit of normal, was that taken into account
11 when you defined it? Because 40 in a female can be
12 twice their upper limit of normal and I wonder if
13 that was looked at in the trials.
14 DR. GOPINATH: We did not differentiate
15 between a different upper limit of normal between
16 men and women and that was not provided, so
17 everybody was considered to be -- upper limit of
18 normal was defined the same for men and women.
19 DR. BOYER: My last question is, do you feel
20 comfortable, given what you've been saying, to give
21 this potentially hepatotoxic drug to people with
22 chronic liver disease such as NASH?

1 DR. AVIGAN: I think that's going to be one
2 of the questions, of course, for the committee to
3 ponder. There are different groups that may have
4 patient populations that may have susceptibility to
5 outcomes that are different than the general
6 population for different reasons.
7 One of course is the liver disease
8 population, where there may not be an increased
9 risk for an event, but the outcomes may be more
10 problematic if the event occurs. But that would be
11 a matter of speculation.
12 The other group are of course those patients
13 who get longer-duration treatment, where over time,
14 there's a build-up effect of a drug in liver, an
15 exposure effect, or patients who have PK effects
16 because of drug-drug interactions, or renal
17 insufficiency.
18 So these are different scenarios where we
19 were asking whether there might be an inherently
20 different risk than the general risk measure across
21 the whole study population.
22 DR. FERNANDES: Perhaps Dr. Gholam is here.

1 He's been using solithromycin in the NASH patients
2 and he can give you real-life experience. I don't
3 think he has prepared slides. Maybe he does, but
4 he's around.
5 DR. GHOLAM: My name is Pierre Gholam. I am
6 an associate professor of medicine at Case Western
7 Reserve University School of Medicine and the
8 medical director of the Liver Center of Excellence
9 at University Hospitals. I have served as a
10 consultant for the sponsor and I am compensated for
11 travel and time.
12 The NASH exploratory study is an open-label
13 pilot that basically plans to enroll 12 patients
14 with biopsy-proven NASH through an entry biopsy at
15 baseline, give 13 weeks of solithromycin, and then
16 look at biopsies following the end of treatment to
17 look at the outcome.
18 We've already enrolled 10 patients, six of
19 which have full datasets. Some of these data have
20 been presented in part today. We have so far seen
21 a fairly good safety and tolerability of
22 solithromycin, which is really the main focus of

1 the pilot. As was mentioned in the FDA
2 presentation, there was 1 patient who experienced
3 asymptomatic elevation, ALT, isolated ALT, up to
4 four times the upper limit of normal.
5 This resolved within 10 days and did not
6 recur when the patient was re-challenged 16 days
7 later. The patient actually started out with a ALT
8 of 51 and his ALT at the end of treatment was 36.
9 His two biopsies were compared and he had an
10 improvement in his histological activity score by
11 two points, and stability fibrosis, and no evidence
12 of eosinophilia.
13 So that's just a snapshot of what the study
14 is.
15 DR. BADEN: Thank you. Dr. Proschan?
16 DR. PROSCHAN: I guess I'm just trying to
17 figure out why the sponsor feels confident that
18 this is not going to be causing major liver
19 problems.
20 They talk about the fact that, well, yes, it
21 could cause a problem in maybe 1 in 100,000 and it
22 wouldn't be observed. But as we've seen, it could

1 be a lot more probable than that and still not be
2 seen.
3 So given that the FDA has shown slides from
4 other studies and other indications that these
5 elevated liver results have been seen in other
6 trials, what makes you so confident that we're not
7 going to see another telithromycin story here?
8 DR. BADEN: Dr. Fernandes?
9 DR. FERNANDES: The first is that we are
10 using this for 5 to 7 days in CAP. We are not
11 pursuing this in simple upper respiratory tract
12 infections. That's a very important difference
13 between what telithromycin was developed for versus
14 this.
15 We also are planning to be careful with
16 citizens to follow this, even after approval, if
17 approved. And I would like to call upon Dr. Oldach
18 to describe what we plan to do. He mentioned a
19 little bit during his presentation, but perhaps he
20 could clarify that.
21 DR. OLDACH: David Oldach. So the point we
22 want to stress is that we are committed to a 5- to

1 7-day course and to helping prevent longer-term use
2 through our educational programs.
3 Our MSL team will be talking with physicians
4 around the country and it's very clear to us that
5 this drug at that dose is a 5- to 7-day drug, full
6 stop. And that's going to be our commitment to
7 educate clinicians about this.
8 Now, in terms of our enhanced
9 pharmacovigilance, this first slide, we talked
10 about this before. We will initiate this as soon
11 as the drug rolls out if it is approved. And that
12 is to work with healthcare systems so that we can
13 look at outcomes in real time or as close to real
14 time as possible. So we will continue to monitor
15 experience with the drug not only in our own
16 ongoing trials, we will educate that the 5- to 7-
17 day regimen is the regimen, period, and we will
18 also monitor outcomes very carefully.
19 Again, we want to use this drug or see this
20 drug used for patients that really need it, for
21 patients with life-threatening pneumonia. Thank
22 you.

1 DR. BADEN: Dr. Green, you have a follow-on
2 question?
3 DR. GREEN: Yes. This is a direct follow-
4 up. It was going to be my question later, but it
5 really is the right timing.
6 So you're wanting us to give approval with
7 the plan that you'll do this very tight vigilance
8 afterwards and we're getting a sense that maybe we
9 need to study more patients to demonstrate risk.
10 So tell me how many severe events, liver events, do
11 you need to identify in your pharmacovigilance
12 before you voluntarily pull the drug back? Is it
13 1? Is it 2? Is it 4?
14 I think that we're concerned about the risk.
15 If we already saw a signal now, this wouldn't be
16 much of a conversation. So do you guys have a plan
17 already what you'll do when you see your first
18 event or if you see your second event?
19 DR. WATKINS: Paul Watkins, University of
20 North Carolina. So let's assume it is a Ketek.
21 We heard from the FDA there's a little over
22 5 events per 100,000 individuals in the

1 postmarketing experience with Ketek. That's 1 in
2 20,000. The rule of three says you would need a
3 trial of 60,000 to detect that with 95 percent
4 confidence. And of course, if it were a clinical
5 trial, that would not involve treatment beyond the
6 7 days or probably concomitant medications, et
7 cetera.
8 So I think it's important if you're going to
9 talk about an additional clinical trial to exclude
10 the risk of Ketek. That's an amazing trial.
11 DR. GREEN: That's not the question I asked.
12 The question I asked is, assuming you got your
13 approval and you're doing your vigilance, does the
14 company have a plan when you see your first or
15 second event, what will you do? You're monitoring,
16 but then there has to be a response to the signal
17 when you find it.
18 DR. WATKINS: Yes. Of course we agree.
19 Part of that plan will include our communication
20 plan and reporting plan with the FDA. If we see an
21 event, the first job will be, just as in the DILIN
22 Network, to determine whether or not that event

1 appears to be related to a particular drug.
2 Sometimes these things happen and they're
3 not. So I couldn't stand here today and say, "We
4 see 2, or 3, or 1 event, that, that would lead to a
5 pulling of the drug from the market." But what we
6 will do for sure is evaluate every event,
7 communicate clearly with the FDA, and through
8 advice from our hepatic safety advisory board about
9 those events when they occur.
10 If it turned out that there was a drug that
11 there was a Ketek-like signal, then we will respond
12 responsibly. I mean, I think the message we want
13 to convey today is that we are committed to the
14 responsible use of this antibiotic, that we want it
15 to be available for its beneficent effects, and we
16 have no more desire to harm patients than any of
17 you.
18 We will monitor it very carefully, but we
19 can't set up a priori rules without understanding
20 the context of what we'd be saying.
21 DR. BADEN: Dr. Boyer, you have a follow-on
22 question?

1 DR. BOYER: Yes. So physicians are
2 notorious for not following instructions. And one
3 way to control for this is to control the way it's
4 prescribed and to the company to limit the
5 prescription for 5 days and that you can't renew
6 the prescription.
7 I mean, there are ways. Just relying on
8 surveillance is a risky business because you're
9 relying on physicians to report adverse events,
10 which we're not good at. Trying to control the way
11 the drug is prescribed, if you feel short-term
12 administration reduces the risk, it seems to me to
13 be a better way to deal with the problem.
14 DR. ABDULLAH: Munir Abdullah, regulatory
15 affairs, Cempra. So indeed, that's an excellent
16 point. And once, and if the drug is on the market,
17 we will put plans at the pharmacy level as well,
18 where a pharmacist will not prescribe or fill a
19 prescription for solithromycin for a second use.
20 These are all plans which will come into
21 play, not just the pharmacovigilance. This will
22 also be part of a comprehensive training and

1 communication and education program.
2 DR. BADEN: Dr. Scheetz?
3 DR. SCHEETZ: Thank you, Mark Scheetz. My
4 first question -- these again surround
5 pharmacometrics. My first question goes back to
6 what the proposed doses are in terms of whether or
7 not there's going to be a load. So are we not
8 suggesting a load for even the oral-only therapy?
9 The backdrop for why I ask this is, our
10 liver experts are telling us -- and I'm certainly
11 not a liver expert -- that there are several
12 mechanisms of injury here, one being
13 hepatocellular. And there's a decent exposure
14 response curve with this hepatocellular enzymatic
15 release, shown by the FDA and the sponsor.
16 It is a relatively flat curve, but you're
17 looking at a percentage going up of about a
18 doubling, a doubling effect of this ALT greater
19 than 3 times the upper limit of normal. So there's
20 a pretty clear exposure response curve there from
21 the serum.
22 I have not seen any data yet that really

1 shows us what the concentrations look like when we
2 transit from the serum to the lung, which would
3 help us understand whether or not we need a load
4 for this drug.
5 We've heard that there's a double-edged
6 sword. We saw some excellent data from Dr.
7 Bhavnani, Dr. Ambrose, and those were ELF data.
8 They showed that there is a very good exposure
9 response for efficacy. We're also seeing that
10 there's exposure response for toxicity. And
11 there's likely some sort of exposure response for
12 this idiosyncratic event, but we're probably never
13 going to figure out what it is.
14 We call things idiosyncratic when we don't
15 have answers for them. Maybe it's effect
16 modification, HLA, as our liver experts can tell
17 us. So I'm just still trying to figure out what
18 the proposed dosing is and what that might mean
19 once we get into populations where we're going to
20 see much more variability.
21 With this oral therapy, we're certainly
22 going to see very large variabilities in serum

1 concentrations that then probably translate to even
2 more variability in liver concentrations.
3 DR. FERNANDES: So for the older dosing, we
4 do recommend 800 as a loading dose and the primary
5 reason is, you want to get steady state almost on
6 the very first day because this is a serious
7 disease.
8 Much of the damage would happen on the very
9 first day. After that, the dose is lowered to 400
10 and you can see by the fifth day, whether you gave
11 the load or not, it is the same. Where we do agree
12 with the FDA's recommendation is to take away the
13 loading dose if you were to switch from IV to oral,
14 where we have seen increased numbers of ALTs.
15 We assume some of those ALTs will go away
16 and also some of the pain may go away because
17 you're increasing solubility at that point.
18 DR. SCHEETZ: So my quick follow-up question
19 would be, do you have data that suggests that you
20 are not getting adequate epithelial lining fluid
21 concentrations on day 1, not the serum
22 concentrations, rather the epithelial lining and

1 alveolar macrophage concentrations.
2 DR. FERNANDES: That's [inaudible - off
3 mic].
4 DR. BHAVNANI: Sujata Bhavnani. In the core
5 presentation, the average of the first 48 hours was
6 presented in terms of target attainment relative to
7 ELF concentrations.
8 So if I can reorient us to this, if you look
9 at the blue lines, the solid blue lines, you can
10 see that, that represents ELF PK/PD target
11 attainment. And so I think the question was, is
12 there adequate exposure at the effect site early in
13 the therapy. And the answer is yes, with the
14 loading dose for the oral regimen.
15 DR. SCHEETZ: What would it look like if
16 there was no load?
17 DR. BHAVNANI: That would be much less
18 favorable. It would take 5 days or more to reach
19 steady state and it would be much lower.
20 We actually have some target attainment
21 results to show you. Early in our deliberations
22 about dose, we did look at what the impact would be

1 of not giving a load. And so here, you can see 800
2 milligrams followed by 400 milligrams daily and
3 what the target attainment would be at the upper
4 margins of the MIC distribution.
5 But relative to no load, that is much lower
6 and less favorable.
7 DR. BADEN: Dr. Gripshover?
8 DR. GRIPSHOVER: Hi. So I guess my question
9 is for the FDA, but it may go for both and/or the
10 sponsor. So I noticed there was more
11 hepatotoxicity in the IV to oral one.
12 So I wondered, one, if some was the renal,
13 which you addressed a little bit. That had been
14 one of my questions there. I think there were more
15 people that have renal insufficiency in that group
16 than the other. And we know that those people had
17 more liver problems.
18 Also, is there any time course of the ALST
19 in the elevations? So does it happen after the
20 switch or is it early on? We never saw it. I
21 don't think we never had a graph that showed which
22 at your various time points we find the elevations.

1 Thank you.

2 DR. OLDACH: So I will present the clinical

3 trial data and then Dr. Bhavnani will talk about

4 modeling.

5 So first, we'll go back to the time-to-peak

6 elevation. The analysis presented by the FDA

7 suggested that many of the ALTs occur after dosing

8 in late. But when we look at the number of those

9 PK LTs that occurred after the end of treatment

10 visit, so day 11 through 15 or after day 15, you

11 can see that the number of these patients and the

12 percentage goes down substantially.

13 So the majority of these ALT elevations

14 occur either while on drug or shortly after

15 completion of study drug. But your question

16 specifically was about ALT elevations with renal

17 failure. And if I could have the slide, yes. This

18 is PK/PD. This is for Dr. Bhavnani, if I could

19 have the ALT elevation by -- that's the one. Okay.

20 Thank you. And so here, we look at the frequency

21 of ALT elevation by quartiles of peak plasma

22 solithromycin exposure.

1 You can see that, although there is an
2 increase, a slight increase in rate, the rates of
3 greater-than-threefold elevation, actually, between
4 the lower exposures and the high exposures in the
5 oral study on top and in the IV-to-oral study on
6 the bottom do not differ greatly.
7 For a greater-than-3x7 to 10 percent is more
8 notable than we observed for the oral study. So in
9 the IV study, there's a bit of a signal, but we
10 also have a slide that has the ALT elevation by
11 renal function. And I'll pull that up in just one
12 moment.
13 Okay. With renal impairment, there was a
14 bit more ALT elevation, as pointed out, and our
15 adjustment for that is to reduce the dose. So we
16 recognize that the ALT elevations are exposure
17 related and, with renal impairment, there is higher
18 exposure, so we are going to recommend that a lower
19 dose be sued in patients with severe renal
20 impairment. And Dr. Bhavnani was going to present
21 the PK/PD.
22 DR. BHAVNANI: So we had the opportunity to

1 look both at phase 1, 2, and 3 data and develop a
2 model, but our most robust model was based on the
3 phase 3 data.
4 In that data, we had baseline ALT, day 4,
5 day 7. And so we were able to develop a multi-
6 variable model looking at different impacts of
7 different variables. And as was described by Dr.
8 Oldach, exposure was the most important and
9 prominent variable.
10 But in doing so, we were able to look at
11 time course relative to the days that ALT was
12 measured. And we saw that, consistent with the
13 observed data, ALTs did come down on day 7 for the
14 upper margins of the population that had higher
15 elevations.
16 But just to show you the impact of the
17 simulation in the context of the question that was
18 recently asked about balancing safety and efficacy,
19 if you look at the blue bars, that shows you the
20 impact of the IV to oral with the 800-milligram
21 load on the probability of ALTs greater than 3
22 times the upper limit of normal on day 4 over

1 different days of switching relative to the same
2 dosing regimen if a 400-milligram dose had been
3 used.
4 Then you can look at that same contrast no
5 day 7. So this helps us understand the previous
6 question, what is the impact of not giving the oral
7 load and what does the probability of ALT look like
8 on the different days that ALT was measured in the
9 clinical trial.
10 DR. BADEN: Then a follow-on question? Then
11 we'll add you. So then I'll recognize myself for
12 two questions on efficacy.
13 One is a generic question to both the agency
14 and the sponsor. Efficacy is based on a
15 noninferiority margin. 10 percent was chosen or 15
16 percent. What is the justification for that
17 noninferiority margin.
18 DR. RUBIN: This is Dan Rubin, FDA. So the
19 justification is provided in some detail in the
20 guidance document that we developed for treatment
21 of community-acquired bacterial pneumonia, that
22 it's not perfect data.

1 It is based on looking at very old studies
2 of patients who did not receive adequate treatment
3 and comparing early symptom response in those
4 patients to those who did receive adequate
5 treatment and finding a large difference at the
6 approximate time point.
7 Then some fraction of that was preserved to
8 form a 10 percent noninferiority margin.
9 DR. BADEN: I think it's important, in
10 looking at that, to make sure that not all failure
11 is equal. And there may be disproportionate
12 severity of failure in both groups.
13 Along the lines of the efficacy, I asked the
14 sponsor previously about the activity in macrolide-
15 resistant pneumococcus, which presumably is one of
16 the primary reasons for developing this.
17 Otherwise, it'd use a macrolide.
18 I guess my question to the agency is, they
19 show data on 2 dozen macrolide-resistant cases
20 where it seems to work. How do we weigh the level
21 of evidence given the numbers? It's 1,000
22 patients. They were able to definitively show in

1 22 or 24, depending on how you look at it.
2 How do you think or how should we think
3 about the strength of the evidence when it comes
4 down to those kinds of numbers for the target
5 pathogen.
6 DR. COX: Yes. So I mean, the numbers are
7 small. I mean, it's a subgroup. It is a baseline
8 characteristic, though, so I think it is okay to
9 look at them.
10 I'm doing this just from recollection, but I
11 think if you look at the numbers from study 300 and
12 301, things jump around a little bit as you look at
13 one study to the next. So I think that's probably
14 a product of the small numbers that we're seeing
15 there.
16 DR. BADEN: But do you like 30, 60? Is
17 there statistical guidance on how one thinks about
18 pathogen-specific activity? I've heard different
19 numbers bandied about in other settings or overall
20 gestalt given the pre-clinical and clinical data.
21 DR. COX: So usually, I mean, there is no,
22 I'd say, magic number. I'll jump back in time a

1 little bit. We used to give out claims for
2 penicillin-resistant strep pneumo. Usually, when
3 we looked at the database to see how a drug
4 performed against strep pneumo, we were interested
5 in really the total body of evidence in treating
6 that particular organization. And in particular,
7 the cases that were more severe, the cases that had
8 bacteremia, and then would sort of work our way on
9 this pyramid to the patients that had penicillin-
10 resistant strains.
11 So I mean, I think that's at least one way
12 to sort of think about the data. I mention that,
13 too, because that was prior to the change in the
14 breakpoints in penicillin, when penicillin
15 resistance was something that we actually
16 encountered more frequently in clinical trials.
17 With the change in the break points, those
18 penicillin-resistant strains obviously became much
19 more difficult to determine or actually to enroll
20 in a clinical trial.
21 One other thing not to lose sight of is, I
22 mean, it's the strains in essence that remain

1 susceptible to solithromycin, where we would expect
2 a positive outcome. So the macrolide resistance is
3 not a determinative factor per se. And I think
4 it's important not to lose sight of that, too.
5 DR. BADEN: Dr. Proschan, do you have any
6 follow-on comment?
7 DR. PROSCHAN: Follow-on to your first
8 question -- I think it's important to remember
9 that, regardless of whether you think 10 percent is
10 a good noninferiority margin, it actually ruled out
11 more than 5.5 percent.
12 So even if you disagree with that, they did
13 better than that.
14 DR. BADEN: The point estimates were
15 overlapping heavily, but still, I think the
16 efficacy is in relation to that pre-defined
17 characteristic that's important to keep in mind.
18 Dr. Fernandes, do you have a comment?
19 DR. OLDACH: So on the topic of
20 pneumococcus, since that's the most common and most
21 important pathogen, the first point I'd like to
22 make is that we worked hard to make a

1 microbiological diagnosis, but the infectious
2 disease docs in the crowd are going to know that
3 it's very difficult to actually get an etiologic
4 diagnosis.
5 So if we found 24 macrolide resistant with
6 perfect diagnostics, that might have been 50 or
7 100. So we'd ask you to look at the overall MITT
8 population, then look at the performance in
9 pneumococcus, because some of our pneumococcal
10 diagnoses were based on nasopharyngeal quantitative
11 PCR, where we didn't have an isolate to test, and
12 some of those may have been macrolide resistant.
13 But if we look at the most important circumstance,
14 which would be bacteremia with pneumococcus --
15 everybody would accept that, that is sort of the
16 perfect pneumonia patient for a CAP trial.
17 Here's how we did with bacteremia by white
18 blood cell count in all patients on solithromycin
19 versus moxifloxacin. The blue line is
20 solithromycin and here's how we did with body
21 temperature in patients with pneumococcal
22 bacteremia. And by the way, included among this

1 were pneumococcal bacteremia cases on
2 solithromycin, 1 with macrolide resistance, some
3 treated with oral 5-day therapy.
4 Overall, in our pneumococcal bacteremia
5 group, there were four treatment failures. One was
6 a patient who developed phlebitis, and was switched
7 to alternative oral therapy, and Augmentin was
8 used. But that patient had a response like this
9 prior to the switch.
10 Another was a patient who was successful in
11 therapy at the end of treatment, but had a chest x-
12 ray that is not yet resolved, so the clinician
13 prescribed erythromycin.
14 So we know that we saw a significant
15 beneficial effect of the drug comparable in broad
16 picture looks to moxifloxacin, even in patients
17 with bacteremia, including macrolide-resistant
18 bacteremia. Thanks.
19 DR. BADEN: Thank you. Dr. Daskalakis?
20 DR. DASKALAKIS: Demetre Daskalakis. So I
21 just have a question, I think, more for the agency,
22 but then potentially also for the sponsor

1 around -- my nagging concern is, I hear the need
2 for this new antibiotic, which I think in general
3 we have a need for new antibiotics.
4 My vision that this will accidentally become
5 the Z-PAK part 2 and that people with not very
6 severe disease and with pneumonia in the eye of the
7 beholder rather than the way it was defined in the
8 study, which actually there was radiologically
9 proven 48 hours after start as well as symptoms.
10 What are the ways that we account consider to limit
11 the use of this drug to people with really
12 significant pneumonias from the regulatory
13 perspective as well as from the sponsor's
14 perspective?
15 DR. COX: This is Ed Cox. So the way that
16 we think about this at least is, I mean,
17 essentially through product labeling and describing
18 where we think the benefit-risk is achieved. So
19 that would be the way to essentially convey the
20 information about where the benefit-risk would be
21 acceptable.
22 There are obviously practical challenges as

1 you take care of a patient with pneumonia with
2 regards to diagnostic uncertainty and other things
3 that you face in the setting, which may be a time
4 when physicians are working to quickly get therapy
5 on board, so there are obviously practical issues
6 here that need to also be taken into consideration,
7 too.
8 DR. AVIGAN: Can I just weigh in, also? I
9 think one of the challenges, of course, is that
10 you're locked into a Goldilocks conundrum, that you
11 want to treat patients who are not too well, that
12 really have pneumonia, but at the same time, you
13 want to reserve treatment for only 5 to 7 days and
14 not longer. But you have also the more sick
15 patients in the hospital setting who are getting
16 perhaps IV therapy, who may need longer treatment
17 for a bad pneumonia. And then the question becomes
18 how are you going to also manage them. So you have
19 to consider both ends of the clinical severity
20 spectrum if you want to really consider what the
21 constraints are with it that are being discussed.
22 And that's very challenging.

1 DR. BADEN: Dr. LoRe?

2 DR. LORE: Yes. So given all that we've
3 heard about hepatotoxicity, if the drug of
4 solithromycin is approved, has the sponsor come up
5 with some plan on the timing of the measurements of
6 the liver amino transferases and other liver
7 function tests, especially given that we've heard
8 some of the hepatoxicity is occurring after the
9 discontinuation of the drug?

10 DR. FERNANDES: So in our plans, currently,
11 of course, there are some other ongoing studies,
12 which is the pediatric studies. We'll have some
13 other clinical studies, which will run, and we will
14 certainly be managing those very closely.

15 But in the pharmacovigilance, it will be
16 reporting based on symptoms. David, would you like
17 to take that, please?

18 DR. OLDACH: At this time, with a 5- to 7-
19 day treatment course, we are not recommending that
20 ALT profiles be done and we are committed to a 5-
21 to 7-day course. If somebody were to need the drug
22 for longer than that, it would be prudent to check

1 ALTs.

2 But in terms of gathering more data for you,

3 we have plans to do real-time, real-life protocol,

4 which we will also roll out. This is not passive

5 collection of data or even active collection of

6 data, but we are in discussions as well to collect

7 more safety data in a rapid time course by working

8 with a network of urgent care and emergency wards

9 in the U.S. that use an integrated data and

10 electronic medical record with real-time reporting

11 to be able to come back and say a 3:1 randomization

12 solely versus standard of care, what the ALTs were

13 over time, and the patients being treated to build

14 that ALT database.

15 But for routine use and treatment of

16 pneumonia, for a 5- to 7-day course, we're not

17 recommending that ALTs need to be performed based

18 on our observations.

19 DR. BADEN: Dr. Boyer, a follow-on question?

20 DR. BOYER: Yes. So you have no re-exposure

21 data. Is that correct, where you have patients who

22 had increased liver tests and then got re-exposed,

1 because a concern about that approach would be sort
2 of like the story with Halothane, where somebody
3 got exposed to Halothane, they had elevated liver
4 tests and a fever, nobody looked at that, and they
5 got re-exposed, and then they had a sever reaction?
6 So do we have re-exposure data on people
7 with elevated liver tests?
8 DR. GOPINATH: No. We do not. I'm sorry.
9 Go ahead.
10 DR. OLDACH: No. I'm sorry.
11 DR. GOPINATH: Go ahead.
12 DR. OLDACH: Okay. We have limited data in
13 this regard. One case was already presented to you
14 by Dr. Gholam, an individual who had an ALT
15 elevation in the NASH protocol and then was re-
16 challenged with drug and actually did clinically
17 quite well with re-exposure and had a liver biopsy
18 at the end of treatment, which was improved over
19 his baseline.
20 We also did repeat exposures in patients in
21 our initial phase 1 trials where we tested IV and
22 oral to determine bioavailability, but there was no

1 particular injury in the antecedent exposure, so
2 that we can't -- it doesn't fit the criterion
3 you're describing. So at this time, beyond that
4 limited experience, we have not repeat dose
5 patients who had an ALT elevation previously.
6 I guess I'd come back to our view that the
7 DILIsim work has really helped us to define what
8 causes an ALT elevation with solithromycin. And I
9 do respect and understand that hypersensitivity at
10 some rate may occur.
11 But what we've seen in our clinical trials
12 is exposure related ALT elevations had generally
13 resolved rapidly. And so on that basis, we aren't
14 anticipating that there will be a significant
15 problem.
16 DR. BADEN: Dr. LoRe, a follow-on question?
17 DR. LORE: Yes, just a follow-up. So given
18 all the concerns that we've had that we potentially
19 don't have a large enough sample size of patients
20 to adequately assess the liver signal, I'm just a
21 little surprised that there isn't a more formal
22 plan to, in the pharmacovigilance study, actually

1 formally have a timing of the measurement.
2 Has that at all been considered at all with
3 regards to -- you're just going to wait until
4 symptoms? That seems somewhat, I don't know,
5 cavalier.
6 DR. OLDACH: In the phase 4 or post-approval
7 study that I described, we will actually write that
8 protocol. And it will include liver function
9 testing.
10 In the pharmacovigilance, where we're trying
11 to pull data from millions of patients, millions of
12 patient lives, here, we'll be looking for the
13 outcomes that are of concern from the point of view
14 of DILI, or hypersensitivity, or a serious drug
15 reaction.
16 So from that, we want to cast a wide net,
17 and do that properly, and adequately to truly
18 collect important data for the FDA and for us to
19 understand the drug.
20 In the phase 4 study that I just mentioned a
21 few minutes ago, we will write into that protocol
22 ALT collection since we'll be collaborating with

1 clinical science in that work.
2 DR. BADEN: Dr. Gopinath, do you have a
3 comment?
4 DR. GOPINATH: Thank you. I just wanted to
5 also respond, the complicating factor in this whole
6 thing is also the fact that most patients are
7 asymptomatic, even if they have an ALT elevation.
8 So I think that is one of the challenges
9 that we felt was key to trying to monitor the
10 safety of this drug in use, because, in a course of
11 5 to 7 days, if you don't specifically think or
12 check for liver enzymes, you may miss people who
13 have an elevation, get better on their own, or have
14 an elevation and don't get better. And so you
15 really don't know what's going on because many of
16 them don't have symptoms.
17 DR. BADEN: Dr. Lee, you had a follow-on
18 comment?
19 DR. LEE: Yes. I think the thing that we're
20 struggling with here is the small sample size.
21 So this is my fourth ADCOM. And I was at
22 two of the Ketek ADCOMs as well as the ximelagatran

1 and, in all of those, we had over 3,000 patients to
2 review. I think that's the challenge we've got.
3 So the question is, from FDA or the sponsor, are
4 you okay -- is it that urgent; maybe it is -- that
5 we only are looking at 800 or 900 patients here
6 rather than 3,000 or 5,000. Ximelagatran, for
7 example, had 4 Hy's law cases, but they had close
8 to 5,000 exposures for, as I recall, three to six
9 months.
10 DR. BADEN: Dr. Cox, do you have a comment?
11 DR. COX: Yes. So I mean, I think you're
12 sort of getting to the question that we're looking
13 to get advice on from the committee. And I realize
14 that we've tried to bring together a variety of
15 expertise here today, expertise on the efficacy
16 side and also the safety side. And I think,
17 really, that is the question for the committee and,
18 in essence, what we will get to is, we get to the
19 questions, which are along the lines of what do we
20 know about efficacy here, has efficacy been shown,
21 and what about the risks.
22 With that question around risk is the issue

1 of acceptability of risk, given the potential
2 benefits and the uncertainty surrounding the
3 current estimates with regards to what we know both
4 for efficacy and risk. So I think that really is
5 what we're hoping to hear more from the committee.
6 More on that, Dr. Lee, or --
7 DR. TESH: No. We have to keep comments
8 very short because we need to get to break and then
9 have time for the discussion around the voting.
10 DR. LEE: My recollection was that
11 telithromycin was not approved the first time.
12 They asked for more data and came back with a
13 12,000-person study the second time around.
14 DR. COX: Yes. That is correct and just in
15 brief, you're correct that the initial advisor, the
16 first advisory committee for telithromycin, the
17 safety database, was somewhere between 3,000 and
18 4,000. Ramya had the number on her slides.
19 Given the hepatic safety risk, there was a
20 study that was done in respiratory tract infections
21 to try and gather more data to further understand
22 the hepatic safety risks, 12,000 patients per arm.

1 And it gave it in essence or it was intended to
2 give some interval bounding with regards to risk,
3 if you will, because it's hard with very infrequent
4 events to capture those in a clinical trial of a
5 certain size, but certainly if you see those events
6 in a trial of that size, ten that would be
7 concerning. So it was almost sort of a step-wise
8 approach, if you will.
9 That study had all sorts of problems with
10 regards to data integrity and data reliability,
11 which is a whole sort of separate chapter. But
12 then you're correct also that it did go back to a
13 second advisory committee in 2004, I believe it
14 was. It was approved in 2004, so an advisory
15 committee prior to its approval.
16 Was it 2003? Okay. So it happened a little
17 bit before the approval in April of 2004. And
18 then, with the hepatic safety events that were
19 noted postmarketing, it went back to advisory
20 committee in December of 2006. So that's sort of
21 the chronological history of telithromycin and the
22 sequential bounding over time and increasing

1 information with regards to the safety issues with
2 the drug.
3 DR. FERNANDES: We've also grown with the
4 stewardship and the fact is, this is only for CAP,
5 not for other respiratory tract infections.
6 So we cannot throw a broad net to do trials.
7 It has taken us almost three and a half to four
8 years to enroll the two trials, so you must
9 remember the time and the benefit to the patient,
10 which will be missing.
11 DR. BADEN: Thank you. Last question, Dr.
12 Weina, and then we'll be able to go to break.
13 DR. WEINA: Pete Weina, Walter Reed. I just
14 want to get some context from the agency for
15 listening to this and that's the whole issue of
16 risk management versus risk avoidance.
17 I'm trying to understand where we have
18 things like, where's the threshold. We have things
19 like Augmentin, where we have liver effects on 1
20 out of 2,500. And it's still on the market and
21 we're using INH all the time.
22 A lot of times, we don't track the liver

1 enzymes for a lot of these drugs. And if they're
2 asymptomatic and they have elevated LFTs, who cares
3 as long as they get better? Right? But we know
4 that a bunch of them don't. With all the liver
5 effects that are out there, where's that threshold?
6 Where do you say, "This drug should definitely not
7 be out there," versus, "What the heck? We're going
8 to continue to use it because we need it," things
9 like INH.
10 DR. AVIGAN: So I mean, in essence, that's
11 what advisory committees are to help us tell,
12 because this is benefits and risks.
13 So if you have a trivial indication and you
14 have an uncertain risk for something quite serious,
15 even though it might be rare, or one in 500, or
16 1,000, or 5,000, we wouldn't tolerate it if it's a
17 life-saving drug where you save a lot of people and
18 it has a benefit in relation to other drugs that
19 are available for the same purpose. There are no
20 other drugs for the same purpose.
21 Then of course it has a different point of
22 view. I would say that, with INH, actually,

1 clinicians who treat patients with TB with INH
2 actually do follow liver test results. It is part
3 of a guideline and so, although it's true that, in
4 the real world, often, in this kind of context,
5 these liver tests wouldn't be done, but I think
6 that, again, the augmented example actually is not
7 a perfect example because, there, it's a
8 cholestatic injury.
9 They tend not to go into liver failure.
10 Here, what we're sort of looking at is the
11 uncertainty of what would we get in the
12 hepatocellular side of the ledger. So we don't
13 know that we would get it, but we see more mild
14 hepatocellular injuries, which are very frequent.
15 So the question is, do we need a larger exposure
16 experience to feel more confident that this is not
17 going to be a problem.
18 DR. WEINA: But 3,000 for Ketek wasn't
19 enough.
20 DR. AVIGAN: This is a matter of judgment.
21 DR. WEINA: Yes.
22 DR. BADEN: We will now take a 10-minute

1 break. Panel members, remember there should be no
2 discussion of the meeting topic during the break
3 amongst yourselves or with any member of the
4 audience. We will resume at 3:15 sharp.
5 (Whereupon, at 3:05 p.m., a brief recess was
6 taken.)
7 **Questions to the Committee and Discussion**
8 DR. BADEN: Can everyone please take their
9 seats? It is 3:15. The committee will now turn
10 it's attention to address the task at hand, the
11 careful consideration of the data before the
12 committee as well as the public comments. I would
13 like to remind the public observers that while this
14 meeting is open for public observation, public
15 attendees may not participate except at the
16 specific request of the panel.
17 We'll be using an electronic voting system
18 for this meeting. Once we begin the vote, the
19 buttons will start flashing and will continue to
20 flash even after you have entered your vote.
21 Please press the button firmly that corresponds to
22 your vote. If you are unsure of your vote or you

1 wish to change your vote, you may press the
2 corresponding button until the vote is closed.
3 After everyone has completed their vote, the
4 vote will be locked in. The vote will then be
5 displayed on the screen. The DFO will read the
6 vote from the screen into the record. Next, we'll
7 go around the room, and each individual who voted
8 will state their name and vote in the record. You
9 can also state the reason why you voted as you did
10 if you want to. We'll continue in the same manner
11 until all the questions have been answered.
12 We will read the questions and have
13 discussion with the agency to make sure we all
14 understand the questions and if there are any
15 nuances that need to be vetted prior to discussion
16 and prior to voting.
17 DR. NAMBIAR: Thank you, Dr. Baden. At
18 today's meeting, we've discussed the benefits and
19 risks of solithromycin for the treatment of
20 community-acquired bacterial pneumonia. As you've
21 heard, the applicant is seeking approval of
22 solithromycin for the treatment of CAPB in patients

1 18 years of age and older. You've heard
2 presentations from the FDA and the applicant
3 regarding the safety and efficacy of this product
4 for the proposed indication and heard comments
5 submitted to the open public hearing.
6 Based on the information provided to you in
7 the briefing documents, the presentations, and
8 discussions today, we week your input on three
9 voting questions. From an efficacy standpoint,
10 you've heard that both phase 3 trials met the
11 prespecified NI margin for the primary endpoint of
12 early clinical response. From a safety
13 perspective, you've heard about the signal of
14 hepatotoxicity that was seen in both in the CABP
15 and non-CABP trials and the higher incidence of
16 infusion site reactions in patients treated with
17 solithromycin.
18 We would appreciate receiving your advice on
19 these issues, and as always, in addition to your
20 words, we greatly value and benefit from the
21 rationale you provide to support your decision sand
22 any recommendations you might have regarding these

1 applications.
2 So with that, the first question we have for
3 you is, has the applicant provided substantial
4 evidence of the efficacy of solithromycin for the
5 treatment of community-acquired bacterial
6 pneumonia. If your answer is yes, please provide
7 recommendations for labeling, and if no, please
8 discuss additional studies or analyses that are
9 needed.
10 DR. BADEN: I open to the committee
11 discussion of this question to make sure that we
12 all understand the implications, as stated. I
13 guess this question is straightforward.
14 DR. NAMBIAR: Go on to the second question?
15 DR. BADEN: Sure. We can go through the
16 three questions.
17 DR. NAMBIAR: The second question is, has
18 the risk of hepatotoxicity --
19 DR. BADEN: We are going to vote. Prior to
20 voting, let's make sure we understand what each
21 question means, because once we start voting, I
22 think that will change the discussion. So we'll

1 discuss each of the -- right now, we'll discuss the
2 three questions, and if there's any issue about
3 what the question means or the intent, or what do
4 you mean by efficacy, or what do you mean by
5 toxicity, we discuss that now so people agree upon
6 the questions.
7 We'll continue with question 2 as stated to
8 make sure we all agree with what it means.
9 DR. NAMBIAR: The second question is, has
10 the risk of hepatotoxicity with solithromycin been
11 adequately characterized? If yes, please provide
12 any recommendations for labeling. If no, please
13 discuss additional studies that are needed to
14 further characterize the risk.
15 DR. BADEN: Any questions about how this
16 question is worded?
17 (No response.)
18 DR. BADEN: Then I guess we'll read question
19 3.
20 DR. NAMBIAR: Question 3 is do the efficacy
21 results of solithromycin for the treatment of CABP
22 outweigh the risks, including hepatotoxicity? If

1 yes, please provide any recommendations for
2 labeling. If no, please discuss additional studies
3 or analyses that are needed.
4 DR. BADEN: Dr. Green?
5 DR. GREEN: If we can get a clarification on
6 how the process will go from here. I don't have a
7 specific question on this. So will we do three
8 votes silently, and then we'll respond to our
9 results? Just so I understand the process.
10 DR. BADEN: So the process is, I wanted to
11 go over the three questions to seek clarification
12 as to the intent of the question to make sure that
13 there was no ambiguity of what was being asked.
14 Then if there's any discussion about the content of
15 what we've heard today, we should discuss. And
16 then we'll vote individually. And after each
17 question is voted upon, we'll go around and give
18 our rationale or key issues associated with how
19 each of us voted.
20 I will say that it is very important to the
21 agency to hear our reasoning. I think whether we
22 say yes or no is actually probably less important

1 than what is it that we're concerned about or
2 supportive of, and why. So the reasoning behind
3 each of our votes I think will be taken extremely
4 seriously.
5 DR. GREEN: So just to clarify, we will have
6 voted on 1, discussed; voted on 2, discussed before
7 we actually cast our vote for 3.
8 DR. BADEN: Correct. When you say
9 discussed, we'll go around, and everyone will
10 explain their rationale for each vote one at a
11 time, because I think it's too much to do it all in
12 bulk.
13 DR. BOYER: It's unclear to me if you answer
14 no on 2, how you could answer yes on 3.
15 DR. BADEN: One can imagine different
16 scenarios where one could weigh 1 and 2
17 differently, and 3 could go either way.
18 So if there are no questions about the
19 intent of the three questions, then is there any
20 other discussion the committee would like to have
21 amongst ourselves about the data presented to
22 clarify our thinking prior to casting our first

1 vote? Dr. Proschan?
2 DR. PROSCHAN: Yes. I think the question
3 Dr. Weina brought up earlier is really the key
4 because --
5 DR. BADEN: Which question?
6 DR. PROSCHAN: You know, about how do you
7 balance the trade-offs between having a drug
8 available that might be great for multi-drug
9 resistant pneumonia, and you might be saving
10 someone's life by giving them that drug versus
11 knowing, if you knew -- I'm not saying you do know,
12 but versus knowing that one out of every however
13 many, 20,000 or whatever, people are going to die
14 from liver disease because of giving the drug, to
15 me that's key.
16 Obviously, in Ketek, they decided that 1 in
17 20,000, which was the estimate we heard, is too
18 much. It's not being used anymore. So it seems to
19 me it's really tough to figure out what is that
20 magic number at which you would say, okay, forget
21 it; I'm not going to use this.
22 DR. BADEN: Dr. Weina, if I can characterize

1 what I heard you say earlier on this point, in
2 part, it's risk management. Many medicines have
3 side effects and benefits, and then how one weighs
4 the weight of each. But I don't wish to speak for
5 you.
6 DR. WEINA: No. I think you hit the nail
7 right on the head. I've had surgical colleagues
8 that I've brought patients to that were very, very
9 sick and asked them to operate because they needed
10 surgery done, and they thought the patient would
11 die when they were going to do the surgery. So
12 what their comment to me was, is, "Well, yes, the
13 patient may die, but I don't have to be the one to
14 kill them."
15 It depends upon what type of clinician you
16 want to be. If you think that the disease is bad
17 enough that you would take the risk for a certain
18 number of people, it's going to be different for
19 all of us.
20 DR. BADEN: I guess I would ask Dr. Boyer
21 and Dr. Lee, INH. There is a medicine that has
22 side effect and benefit, including potential

1 serious hepatic side effect, yet we use it. So one
2 could say that it's favorable in 1, concerning in
3 2, but acceptable in 3, or am I mis-weighing those
4 issues?
5 DR. BOYER: They must not want me to talk.
6 There we go.
7 I think we've got to make sure that we're
8 talking about the study that they performed. And
9 the study that they performed was in community-
10 acquired pneumonia, and they showed efficacy. They
11 didn't show life-saving. They didn't use this in
12 multi-drug resistant organisms.
13 So I don't really think we could say that,
14 but that's not what they studied. So we need to
15 focus on what they studied, and they showed
16 efficacy. So there are other drugs out there that
17 are as effective as this drug in treating
18 community-acquired pneumonia, and it's the same.
19 So then in that context, the question comes up
20 about the risks.
21 So INH is a rather unique drug in the
22 treatment of tuberculosis. I think it's used less

1 now, but it's still used I think for prophylaxis of
2 people who get positive skin tests. And there's
3 controversy about monitoring liver tests because so
4 many people get elevated liver tests. That's not
5 predictive of the adverse drug reaction the
6 individuals get, but it's still felt to be a very
7 important drug for which there are poor
8 alternatives, but there are alternatives for this
9 drug. So I think every drug is different, as is
10 this one.
11 DR. BADEN: Dr. Lee?
12 DR. LEE: Yes. Just briefly, I think we'd
13 love to get rid of Isoniazid, but it's still the
14 keystone to treatment. So the question really
15 becomes, is solithromycin so important because of
16 C. diff and all the other issues, that it trumps
17 the concerns that we have about hepatotoxicity.
18 DR. BADEN: Mr. Mikita?
19 MR. MIKITA: Yes, very quickly. I just want
20 to underscore the fact that there are a lot of
21 smart people on this advisory committee, but there
22 are also a lot of smart docs taking care in

1 stewarding these drugs. And I'm not going to die
2 of spinal muscular atrophy, but one day I will die
3 of a respiratory illness. And I want my physician,
4 who I trust implicitly, to have options.
5 So I would just -- I know that we're looking
6 at data, and the data are what the data are. But
7 if we're going to talk about the practical impact
8 of what we're talking about, it is about each
9 individual life, and a lot of us need options.
10 Thank you.
11 DR. BADEN: So I would like to curtail
12 discussion that is leading to how we think about
13 the ultimate analysis, but rather the discussion to
14 make sure that the questions as worded make sense
15 to us and don't create logical impossibility, which
16 was more of what I was getting at about the
17 question raised by Dr. Boyer about 1 and 2
18 intersecting with 3, because they do intersect, but
19 I want to make sure that the three questions make
20 sense to each of us, they are interrelated but
21 they're independent. And then after we vote for
22 each question, we'll be able to explain our

1 rationale directly to the agency.
2 So other questions about the questions to
3 make sure that when we vote, people understand what
4 we're voting on.
5 (No response.)
6 DR. BADEN: If not, then I guess we should
7 go to our first vote. If there are no questions
8 concerning the wording of the questions, we'll now
9 open to the question to discussion/vote.
10 Question number 1, has the applicant
11 provided substantial evidence of the efficacy of
12 solithromycin for the treatment of community-
13 acquired bacterial pneumonia? If yes, please
14 provide a rationale for labeling. If no, please
15 discuss additional studies/analyses that are
16 needed.
17 Please press the button on your microphone
18 that corresponds to your vote. You have
19 approximately 20 seconds to vote. Please press
20 firmly. After you have made your selection, the
21 light may continue to flash. If you are unsure of
22 your vote or you wish to change your vote, please

1 press the corresponding button again before the
2 vote is closed.
3 (Vote taken.)
4 DR. BADEN: Has everyone voted? So we will
5 show the results of the vote, and then we'll go
6 around the room and provide -- even though it's a
7 unanimous vote of yes, there still are insights to
8 provide the agency and the sponsor about issues we
9 may be concerned about to further provide data to
10 the community.
11 So we will start on the --
12 DR. TESH: For the record, there are 13
13 votes for yes, zero for no, zero abstentions, and
14 zero no voting.
15 DR. BADEN: Thank you. So we will now start
16 with Dr. Boyer as to any thoughts related to the
17 evidence of efficacy.
18 DR. BOYER: As far as labeling, it seems
19 it's 5 to 7 days. And it sounds like from what was
20 said, loading dose appears to be required, whether
21 it's oral or IV, to achieve levels high enough for
22 efficacy.

1 DR. SCHEETZ: Mark Scheetz. I voted yes. I
2 think the 13 to zero vote shows that they've pretty
3 much met the FDA's guidance for CABP. I agree that
4 there should be some hard limiting to 5 to 7 days.
5 I'm a pharmacist, and I haven't practiced in the
6 community in a long time. But I can tell you that
7 when I was there, that's a data-poor zone.
8 So when patients transition from the
9 hospital to the community pharmacy, sometimes
10 you're not sure what their name is, knowing exactly
11 how many days of therapy they received of
12 solithromycin is going to be difficult. I know the
13 FDA has mechanisms to make sure that that hand-off
14 goes well, and I encourage them to use those.
15 In terms of the load, we talked about that a
16 bit. It sounds like the load is necessary for the
17 oral therapy, oral-only therapy. I still don't
18 know if I've seen enough data to suggest that it's
19 necessary for the IV to oral switch. That depends
20 on what day you make the IV to oral switch.
21 I'd caution that I don't know that the serum
22 concentrations are the way to actually make that

1 assessment. So I think the current FDA assessment
2 is based on the serum concentrations. I would
3 suggest that -- I'd probably look at the target
4 concentrations. Thank you.
5 DR. PROSCHAN: I'm Michael Proschan. I
6 voted yes. They met the noninferiority criteria,
7 but they also did better than that because, as I
8 said, they ruled out basically 5 and a half percent
9 increase. I think there's been no disagreement.
10 The FDA agrees that it worked. Their analysis
11 indicated that it worked. Obviously, the sponsor
12 also agreed that it works. So I think that's not
13 in question.
14 DR. ANDREWS: This is Ellen Andrews. I
15 voted yes, but maybe not as enthusiastically as
16 others, because I would still like to see
17 patient-centered, patient-reported outcomes,
18 whether people are feeling better and not just what
19 an investigator reports for them. I would like to
20 see a lot more in terms of -- I know I'm not
21 supposed to talk about other studies if I voted
22 yes, but looking at lower doses and whether the

1 loading is really, really necessary, and also
2 tracking liver enzymes over time, a study look at
3 that and whether you can then key that
4 to -- because it seems that there are
5 people -- this is a drug that attacks the liver,
6 and most people recover from that, but some don't.
7 Can we find out which ones are not going to, and
8 when we can know that as soon as possible and
9 discontinue the drug.
10 MR. MIKITA: Yes. Steve Mikita. I voted
11 yes. I believe it's a narrowly construed and
12 straightforward question. I believe, like others
13 have said, that the sponsor has met its burden.
14 And any concerns can certainly be mitigated by
15 effective labeling. Thank you.
16 DR. HONEGGER: Jonathan Honegger. I voted
17 yes. Like others, I was convinced that they met
18 the noninferiority target. The package labeling as
19 well as other mechanisms to directly interact with
20 pharmacies would likely be important to make sure
21 that the short courses are adhered to.
22 DR. WEINA: Pete Weina. I voted yes, and

1 just with a quick caveat, and that is that the
2 question was stated as substantial evidence. I
3 think a better way of putting it would be adequate
4 evidence rather than substantial.
5 I just become concerned with what was
6 already brought up in our discussion, and that is
7 the issue of once the genie's out of the bottle,
8 it's going to end up getting used like the Z-Pak
9 part 2. And there really needs to be some adequate
10 controls in place of some type, whatever you can
11 do.
12 I agree with the oral. I think the data is
13 good for that, but I have a significant concern
14 about using the loading dose on the switch and
15 think that the recommendations of not going with
16 the loading dose seems -- at least the evidence
17 that was presented is better.
18 DR. GRIPSHOVER: Hi. I'm Barb Gripshover,
19 and I voted yes because I agree with everyone else.
20 I think it certainly showed that it was noninferior
21 moxifloxacin. I think I agree with we need to make
22 sure, like everyone said, about the short course.

1 But I think the other thing, we need to also make
2 sure to emphasize that this is only for pneumonia
3 and not for otitis and bronchitis. That's the
4 other way they go down Z-Pak number 2, is
5 broadening the respiratory.
6 So I think that needs to be clear as well.
7 And I agree. I think I wouldn't load -- I agree
8 with no load when you go from IV to oral.
9 DR. BADEN: Lindsey Baden. I also voted
10 that substantial evidence of activity was
11 demonstrated. In addition to comments already
12 made, additional considerations, I think the data
13 on resistant pathogens has to be expanded. And
14 there's only so much one can do in an initial study
15 given the challenges of diagnostics, but I think we
16 need to be careful in assuming that it works the
17 way we think it should work for different bugs with
18 different mechanisms, with different levels of
19 emerging resistance. And even macrolide
20 resistance, as presented, had different mechanisms,
21 and that has to be more carefully looked at.
22 I think the issue of threshold for

1 use -- and I think this is important for this
2 compound and important in general for the agency to
3 consider -- is one of the problems with antibiotics
4 is we think they have no side effects and only
5 benefit. Every medicine has risk and benefit, and
6 therefore we really need to push the issue of
7 benefit, that it's the population with the disease
8 that can benefit, and how we can strengthen the
9 label to the agency and strengthen the education to
10 the sponsor that it isn't misused because then
11 we'll all lose something if it's misused.
12 Drug interactions, we didn't touch much on,
13 but it was alluded to. That I think is very
14 important with the 3A4 pathway. And then the renal
15 issue was implied already that the dosing needs to
16 be carefully considered in renal issues, and one
17 needs to think carefully in individuals who already
18 have a compromised liver until more data are
19 available.
20 DR. GREEN: Michael Green. I voted yes. So
21 I have some of the same thoughts as been already
22 mentioned by other members of the committee, that

1 they certainly met the statistical and design
2 burdens that were following the guidances of the
3 FDA.
4 I want to reiterate what Dr. Baden said
5 about trying to get more data on resistant
6 organisms. At least one of the follow-ups that was
7 in the data sets suggested that there might have
8 been a bit of inferiority with MRSA. And while
9 there are not that many of those infections, when
10 they occur, they can be really horrific.
11 In terms of labeling, I just want to
12 reiterate the thought that you said to limit it
13 really to just CABP, and maybe even in the labeling
14 discourage its use for other things. I think the
15 company's already told us that they are going to
16 follow the FDA's recommendation and not use a
17 second load when they go from the IV to oral, and I
18 support that.
19 Then I would consider in their package
20 insert recommending against the use in people with
21 preexisting liver conditions because I think it was
22 a contraindication to enter the study, and

1 therefore we have no idea how this drug will work
2 in that setting. Thanks very much.
3 DR. DASKALAKIS: Demetre Daskalakis. I'm
4 going to be brief so I don't restate a lot of
5 what's already been said. But I think that
6 the -- I voted yes. I think a couple of important
7 points are, again, to do whatever we can from the
8 perspective of regulatory and at the pharmacy side
9 to make sure this is only prescribed for people who
10 have a community-acquired bacterial pneumonia. The
11 5 to 7-day issue is very important, and those
12 regulatory aspects need to be in place as well at
13 the pharmacy side.
14 I want to restate that I do agree with the
15 no-post IV load, but that the loading dose with
16 oral seems to make sense. Ultimately, I wanted to
17 then also echo Dr. Baden, which is even though
18 we're not being asked about what future studies
19 should happen, I think that studies focusing on
20 multi-drug resistant bacteria are critical if we're
21 assuming that this agent is one that has a role in
22 the armamentarium against them. Thank you.

1 DR. LEE: William Lee. I voted yes as well.
2 I have very little else to add, except that the
3 list of 3A4 metabolized drugs is quite long, and
4 only three or four have been tested. So more
5 testing along that line, as Dr. Baden suggested, is
6 very important, and at least should be listed in
7 the package insert.
8 DR. BADEN: Dr. Lo Re?
9 DR. LO RE: Vincent Lo Re. I voted yes. I
10 thought both the sponsor and the agency concurred
11 about noninferiority. I agreed with the fact that
12 for the IV to PO switch, that potentially avoiding
13 the loading dose for PO would be helpful. I feel
14 strong about the 5 to 7-day duration. I think
15 there wasn't really enough data on patients with
16 preexisting liver disease.
17 I would echo Dr. Baden's suggestion about
18 getting more data in this population because,
19 potentially, given the prevalence of chronic liver
20 disease, this will be very important to understand.
21 And I think given what we've heard about the
22 hepatotoxicity, I think that would be very

1 important to highlight the potential of
2 hepatotoxicity and to assess -- to at least include
3 some measurement and timing for liver
4 aminotransferases in liver function tests. Thanks.
5 DR. BADEN: I think that concludes the
6 comments on the first vote. I think I need to
7 briefly summarize all of the comments. Hard 5 to
8 7-day treatment. One loading dose, not two. More
9 data on resistant pathogens. More data on
10 populations at risk, and probably throw into that
11 not just liver/renal, but also neurologic with
12 myasthenia gravis, given it was excluded, the drug
13 interaction issue. And then how to push the
14 community on all sides to not use it unnecessarily,
15 so really patients who have the disease of
16 question. And in the study at least, it was
17 radiologic confirmation.
18 Let's move to question 2. Has the risk of
19 hepatotoxicity with solithromycin been adequately
20 characterized? If yes, please provide any
21 recommendations for labeling. If no, please
22 discuss additional studies that are needed to

1 further characterize the risk.
2 The voting, as previously stated, is press
3 your button, and it will keep blinking until
4 everyone has voted.
5 (Vote taken.)
6 DR. BADEN: The voting is now complete.
7 DR. TESH: For the record, there is yes, 1
8 vote; 12 no votes; zero abstentions; and zero
9 nonvoting.
10 DR. BADEN: For discussion of question 2, we
11 will start on the left with Dr. Lo Re.
12 DR. LO RE: So the question was, has the
13 risk of hepatotoxicity with solithromycin been
14 adequately characterized? I voted no. I felt that
15 the sponsor -- for a couple of reasons. I felt
16 that the sponsor had suggested to abandon the oral
17 loading dose after switching from IV, and I felt
18 like it was really unclear how this might change
19 the drug's hepatotoxicity profile.
20 We really weren't presented with data on ALT
21 elevations after initiation of solithromycin among
22 persons who previously used macrolides or other

1 structurally related drugs, or patients with
2 chronic liver disease. And I felt that this was
3 important to characterize the hepatotoxicity
4 profile.
5 I was concerned that there were relatively
6 small sample sizes within the phase 2 and 3 trials
7 that might not be really sufficient enough to
8 adequately characterize the hepatotoxicity risk.
9 As an infectious disease physician, I recognize the
10 need for new antimicrobial agents, especially with
11 the rise of antimicrobial resistance. But I think
12 we need to ensure these drugs safety prior to
13 release into the market. I need to make sure that
14 we first do no harm. So I think we need larger
15 patient samples to really confirm the safety of
16 this drug.
17 DR. LEE: Yes. William Lee. I voted no as
18 well. It's hard to know where to start with
19 further studies. I think the FDA in phase 4 could
20 require formally a study where there is a larger
21 number of patients enrolled, even just for the 5 to
22 7 days, with adequate ALT follow-up, not just

1 during but post.
2 Obviously, in the second tier, there's going
3 to be a need for some sort of further monitoring or
4 consideration of when a patient a year later gets
5 reexposed, and maybe these large databases are the
6 way to go for that. I think that's very important.
7 As Dr. Boyer suggested, multiple exposures often
8 leads to this adaptive immune response.
9 DR. DASKALAKIS: Demetre Daskalakis. I
10 voted no. I don't think that the sponsor has
11 adequately characterized the hepatotoxicity or the
12 potential for more extreme hepatotoxicity.
13 In terms of additional studies, I think that
14 it is about numbers and sample size. And so I
15 think that the strategy in terms of what kind of
16 study that should be is one that I think needs to
17 be discussed more. So whether that is increasing
18 the phase 3 studies and doing more of them, or
19 doing a phase 4 study after release that has very
20 stringent and very focused observation of hepatic
21 parameters, not only extreme outcomes, but also
22 outcomes that may portend more extreme outcomes,

1 which means liver function testing as part of the
2 story for being in those studies and aggressively
3 so.
4 I think it's also critical to better
5 characterize some racial and ethnic minorities in
6 the United States. That's really I think sort of
7 surly missing, understanding that 10 percent are
8 African American. I didn't see any comment on what
9 percent were Latino or Latina. So I think it's an
10 important thing to think about in establishing the
11 phase 4 or whatever strategy approaches to increase
12 the end in understanding the liver toxicity
13 potential for this drug.
14 DR. GREEN: Michael Green. I voted no. I
15 think all the infectious disease specialists at
16 this table understand the incredible need for new
17 agents and new drugs. And actually, in response to
18 that need, the FDA has created these expedited
19 pathways that allow studies to come for approval
20 with much smaller numbers than they did before.
21 Using noninferiority as a strategy leads to
22 being able to conclude from an antimicrobial

1 basis -- effectiveness is found. But the safety
2 side of the equation is not necessarily going to be
3 fulfilled when you use these smaller numbers. And
4 while we heard that certain aspects and the
5 difference in the compound between telithromycin
6 and solithromycin, maybe make it not going to be a
7 telithromycin-like agent. We also heard that
8 there's a lot of similarity.
9 So I think we need larger numbers and
10 perhaps creative study designs to really answer the
11 question because my concern is that if we approve a
12 drug, and then it ends up having to be withdrawn
13 again, people's confidence -- the confidence of
14 those of us who prescribe medicines, the confidence
15 of the patients that we take care of, the
16 confidence in the FDA, the confidence in -- and
17 actually the confidence in the sponsors -- will all
18 go away.
19 So rather than making a mistake on small
20 numbers, I think we need more data.
21 DR. BADEN: I also voted that the
22 hepatotoxicity has not been adequately

1 characterized. I think the ALT, the evidence of
2 liver injury in the phase 1, as well as the 2-3
3 data sets are concerning, as well as the history of
4 the class. I think that the issue of what sample
5 size is needed to detect idiosyncratic reactions is
6 a salient one, and it may be tens of thousands
7 rather than hundreds. And that creates complexity
8 in how best to characterize it, but it doesn't
9 diminish the need to do so.
10 I think the other comments about different
11 groups may be at different risks also needs to be
12 sorted out. There's also more than hepatotoxicity,
13 but the hepatotoxicity signal obviously is the one
14 of greatest concern.
15 DR. GRIPSHOVER: Hi. Barb Gripshover. I
16 also voted no. And I feel, again, that numbers is
17 the biggest issue.
18 DR. BADEN: Talk into the microphone.
19 DR. GRIPSHOVER: Again, I'm worried that we
20 just haven't seen enough people treated with this
21 to know. The one other group that I'm worried
22 about is renal people because we know that they're

1 having higher levels. So I think that -- maybe
2 that gets down more to the next question on risk-
3 benefit. But that's a situation I think we need to
4 study better, too, the extra risk there.
5 DR. BADEN: Dr. Weina?
6 DR. WEINA: Pete Weina. I as well voted no.
7 In addition to what was already said, all I would
8 say is that what is adequate characterization, I
9 think, given the taint of the third generation
10 macrolide on the entire class, is going to create a
11 problem. And I think the suggestion of tens of
12 thousands, or even more, are going to be really the
13 rule until we even start to feel comfortable with
14 not having that shadow hanging over us.
15 DR. BADEN: Dr. Honegger?
16 DR. HONEGGER: Jonathan Honegger. I also
17 voted no. I agree that the search for
18 idiosyncratic findings will be difficult, but we do
19 larger studies to at least get us to a point where
20 we feel that the benefit is matching the potential
21 risk. I also feel like this needs to be evaluated
22 in other races, as has been mentioned. The effects

1 of retreatment may be in healthy controls as well
2 as in people with infection.
3 DR. BADEN: Mr. Mikita?
4 MR. MIKITA: Yes. Being the lone descending
5 vote, I don't want anyone in this room to come away
6 with the fact that this was a knee-jerk or
7 emotional reaction. I believe that both the
8 sponsor and FDA have proceeded with their
9 expertise, and that they have considered the data.
10 I believe that we're kind of raising the bar to a
11 level because of the telithromycin specter too
12 high.
13 I think that there are risks inherent in
14 these kinds of drugs, and I believe that with
15 labeling, and with stewardship, and with
16 post-surveillance that a lot of the concerns can be
17 addressed. I think confidence can be introduced in
18 those practitioners in the communities who know
19 their patients. And I think it's unfortunate that
20 the climate is such that there is an invitation for
21 those to develop these drugs, and yet there is such
22 hesitancy over a single event when many, many

1 patients are dying of this disease every day.
2 Thank you very much.
3 DR. ANDREWS: Ellen Andrews. I voted no. I
4 agree that we obviously need more tests. We need
5 more studies with more people. But as Stephen just
6 pointed out much better than I could, time means we
7 might catch a few more, and we might be more
8 diligent and save some people from liver damage,
9 but how many people are going to die or be harmed
10 because of the disease. Their resistance levels
11 are already up to 50 percent and going higher. And
12 how long does it take to do massive clinical
13 studies? It takes a long time.
14 So I think it's really important, though,
15 for the FDA, if they choose to approve this, to be
16 really strong about the studies that they're going
17 to require going forward. I love the ICD-10 idea.
18 I don't know if that's happening elsewhere, but
19 that's a way to get postmarket surveillance of very
20 large groups.
21 Also, the connection to payers I think is
22 really important because you can educate doctors as

1 much as you like, but if you say -- payers have
2 other ways to influence physicians, and they're
3 prescribing beyond 5 to 7 days, and also to educate
4 them. Value-based purchasing provides an
5 incredible opportunity, and opportunities to also
6 get to very large populations. So I think that's
7 exciting.
8 DR. PROSCHAN: Michael Proschan. I voted
9 no. I just felt like there was enough evidence
10 presented that I really have substantial concerns
11 about the liver safety. I think the FDA's
12 presentation gives me a lot of concern, especially
13 taking not only these studies but other studies
14 that have used solithromycin.
15 As mentioned about what will be the
16 confidence in the FDA, or the company for that
17 matter, I think that's especially true when people
18 are going to say, you had this other story here
19 with telithromycin, and you still didn't get it
20 when you saw these signals. So I definitely think
21 there needs to be more safety information.
22 Now, I don't call for a clinical trial to

1 rule out the 1 in 20,000 because you just can't do
2 that. But I certainly would feel more comfortable
3 if I had another larger phase 3 trial. And I'm not
4 talking about tens of thousands, but even a couple
5 thousand per arm, I would certainly feel a lot
6 better than I feel right now. And I don't feel any
7 better knowing that the company says, well, you
8 can't predict these things. That doesn't make me
9 feel any better. That makes me feel worse.
10 DR. SCHEETZ: Mark Scheetz. I voted no. I
11 do think the company characterized some things
12 adequately, that being really hepatotocellular
13 injury as shown by cellular enzyme release. Our
14 liver experts have told us that that may or may not
15 predict the idiosyncratic reaction, which I think
16 is what we're all worried about. I think the
17 committee has almost universally suggested larger
18 patient numbers in order to tease out whether or
19 not -- tease out really what that risk of the
20 idiosyncratic reaction is.
21 Dr. Green was telling us about how we're
22 going to smaller patient sizes in order to approve

1 drugs, and I certainly agree with that. And one of
2 the mechanisms forward for that is using something
3 like a PK/PD approach, where we have very
4 well-characterized mechanisms that we know then
5 later go on to predict true outcomes. So using
6 some of the mic models, so on and so forth, the CFU
7 studies, those all correlate really well with
8 outcomes in patients.
9 In safety, I'm not sure we have as good of
10 data. I'm a little bit troubled that we don't know
11 the mechanism of the idiosyncratic reaction, that
12 in effect defines it as idiosyncratic. If we knew
13 the mechanism, I think you could have more
14 confidence in smaller patient sample sizes, leading
15 to approval.
16 So I voted no. I'm not sure -- until we
17 know a lot of these mechanisms of the idiosyncratic
18 and make them no longer idiosyncratic, it will be
19 hard for companies to give us the safety data they
20 need before they can potentially get approved.
21 DR. BOYER: I'm Tom Boyer, and I voted no
22 because I think there are two phenomena looking at

1 the data that are going on here, one which I think
2 is reasonably well clarified. And that is, this is
3 a direct hepatotoxin perhaps mediated by
4 mitochondrial injury that tends to get better. So
5 that doesn't cause me huge concern because there
6 are so many drugs that cause transient elevations
7 of transaminases that don't lead to serious liver
8 disease.
9 The concern is the one case of jaundice.
10 And when you think about it, if you had a 1 in
11 10,000 risk, and out of 800 patients -- or out of
12 10 patients who got prolonged exposure, one patient
13 turned yellow -- but what are the odds that in this
14 one study, that one patient of 1 in 10,000 happened
15 to be in the study, happened to get the drug, and
16 happened to turn yellow?
17 So I think the concern is that's not the
18 number, that the number is less than that. And I
19 think the FDA is trying to make some estimates of
20 what that risk is. And if you know what the risk
21 is, you can define the size of the study to
22 determine whether or not that risk is real or in

1 fact it was 1 in 10,000, and the company was
2 incredibly unlucky. I'm not going to Vegas with
3 these guys.
4 I think you need more data, and you can do
5 it now, to design a study to look at risk. The
6 other thing is, as Dr. Lee pointed out, we need
7 later numbers, even after patients have come off
8 the drug. So if you're going to do a trial, you
9 need to document that two or three weeks later,
10 they don't have a rise in their liver tests that
11 might -- as we see with clavulanic acid.
12 So I think there are some things that could
13 be done to enhance the safety profile and make
14 everybody feel better about the risk-benefit for
15 this drug.
16 DR. BADEN: So the committee raised many
17 themes in their consideration of the
18 characterization of hepatotoxicity, including how
19 well LFTs were measured, both during treatment and
20 post-treatment. Struggling with the issue of
21 sample size and how does one adequately power that,
22 particularly for rare or less common events.

1 Whether this needs to be done in a study setting
2 versus postmarketing, it needs to be done.
3 The re-exposure question, how they engage
4 others in the monitoring, potentially payers or
5 others, and that the difficulty in predicting the
6 toxicity were themes. In favor of the
7 hepatotoxicity or that we understand it, risks are
8 inherent, and this can be handled with labeling
9 stewardship, monitoring, and we have to keep an eye
10 on the unmet need.
11 So having summarized question 2, we'll now
12 look at question 3. Do the efficacy results of
13 solithromycin for the treatment of community-
14 acquired bacterial pneumonia outweigh the risks,
15 including hepatotoxicity? If yes, please provide
16 any recommendations for labeling. If no, please
17 discuss additional studies, analyses that are
18 needed. Please vote.
19 (Vote taken.)
20 DR. BADEN: The voting is complete.
21 DR. TESH: For the record, the vote is yes,
22 7; no, 6; zero abstentions; and zero nonvoting.

1 DR. BADEN: This is why you have an odd
2 number of committee members.
3 (Laughter.)
4 DR. BADEN: We will start on the right,
5 Dr. Boyer.
6 DR. BOYER: Tom Boyer. Well, you could have
7 predicted my vote from what I asked the question
8 of. I just -- if this drug were one of a kind drug
9 treating a disease for which there was no other
10 therapy, then I would feel differently, I think.
11 But I don't feel that way, and I think there is a
12 significant risk associated with this drug, and I
13 think that outweighs its efficacy.
14 DR. SCHEETZ: Mark Scheetz. I voted yes. I
15 really wish I could have voted the mean or the
16 median here, which is maybe. The reason I say
17 maybe is because I think it really depends on the
18 situation, and I think the labeling will have to
19 define that very carefully. Should this drug bleed
20 into otitis media? Should this drug bleed into
21 other areas where there's going to be expanded use?
22 I think the answer is clearly no, not until we have

1 much, much more data.
2 I was fortunate to sit around this table
3 when we discussed the risk of the fluoroquinolones,
4 and even when there's almost infinitesimal risk,
5 that translated to patients standing up out in that
6 audience, that had very real toxicities, very
7 life-threatening toxicities. So I think that can
8 happen here.
9 I also think that we do need to have a
10 better way to approval of antibiotics, and there is
11 a true need in CAPB. I could very easily come up
12 with multiple scenarios where the patient might not
13 have any other therapy other than this, and if it's
14 not available, that patient would be at risk.
15 So I think a lot of this has to center
16 around risk-benefit, and I think there are a number
17 of postmarketing strategies that can be employed to
18 really give physicians that option to use this
19 treatment, but to also know that this is not the
20 first treatment they should be grabbing off the
21 shelves for your run-of-the-mill, I think, even
22 CABP.

1 DR. PROSCHAN: I'm Michael Proschan. I also
2 voted no. This is tough for me because, obviously,
3 I'm not a physician, so it's very hard for me to
4 judge how much the benefits are of having another
5 agent to use in case someone doesn't get benefit
6 from other drugs. So it makes it very difficult
7 for me to balance benefit and risk. But I am
8 concerned enough about the safety that I just -- I
9 would feel very bad if I voted yes and the same
10 thing happened as happened with telithromycin,
11 which I see as a real possibility. So I had a
12 tough decision, but overall, I felt like I had to
13 vote no.
14 DR. ANDREWS: Ellen Andrews. I voted yes.
15 I also worry a lot about that scenario, that not
16 unlikely scenario. And I would feel like we could
17 wait if the bugs would just slow down and not get
18 resistant so fast. Then we'd have time to do the
19 studies, and we don't really. And there are people
20 who need drugs for these infections.
21 I do think -- I understand the public was
22 not -- it was a scandal at the time, but I think

1 people understand there are no easy answers.
2 There's always a trade-off. I think people can get
3 that. I think we can help people with that
4 confidence concern that you had. I think it's
5 inevitable either way. People are going to feel
6 that you didn't do enough or that you did too much.
7 That's why they get the big money at FDA.
8 MR. MIKITA: I'm delighted not to be alone
9 on this one.
10 (Laughter.)
11 MR. MIKITA: It takes courage to vote, and
12 it takes courage to stand on a wall and say I'm
13 going to develop drugs for this particular disease,
14 and I'm willing to put in safeguards to make it as
15 safe as possible. Nothing's a hundred percent
16 certain in this life. And when you're dealing with
17 people's lives, there's got to be a trade-off
18 because there are a lot of sick people, and the
19 drugs that you use are not always a hundred percent
20 safe for a hundred percent of those patients.
21 But in this case, I believe that the
22 efficacy data clearly outweigh those array of

1 worries and concerns that are not surprising, but
2 they can be addressed by a package of labeling and
3 the other types of precautions, and safeguards, and
4 postmarket analyses that can ensure, and invite,
5 and encourage other drug developers to bring their
6 genius to the FDA and to the patients like me that
7 need them. Thank you.
8 DR. HONEGGER: Jonathan Honegger. I voted
9 no. I definitely recognize there is a need for
10 antibiotics for pneumonia and macrolide-resistant
11 pneumococcus, avoiding excess risk of C. diff and
12 other adverse effects of the other options for
13 pneumonia.
14 But with 7 percent risk of an ALT rise
15 that's significant and the history of Ketek, I feel
16 that additional studies are needed in the phase 3
17 level before approval, not in the tens of
18 thousands, a range necessarily to rule out a rare
19 risk of DILI, but in the thousands to evaluate for
20 a moderate or high risk of DILI. Then in phase 4,
21 we can do further evaluations to quantify the risk
22 of DILI if it's lower.

1 Also, just a perspective, I don't know where
2 the science of risk-benefit is at, but it would be
3 interesting if FDA, or even pharmaceuticals, would
4 quantify different levels of DILI versus offsets of
5 C. diff and other adverse effects. And maybe it
6 wouldn't be as meaningful as our own judgment, but
7 it would be nice to see.
8 DR. WEINA: Pete Weina. I voted yes. I had
9 a hard time with it until I started to think about
10 what we could do with the labeling. And part of it
11 is, if there was a very strong hepatotoxicity
12 warning on there, or potential hepatotoxicity, or
13 the signal that's there, it may slow down this
14 whole idea of Z-Pak part 2 syndrome because people
15 would be really concerned about just kind of
16 tossing it to anything, number one.
17 Number two, I think it opens up a
18 conversation between the clinician and the patient
19 about risks associated with it. And unfortunately,
20 that's not a conversation that takes place as often
21 as it should. I'm concerned about waiting to get
22 more data, how long is it going to get, to get the

1 right number, whatever that right number is, if
2 it's another thousand, or 5,000, or 10,000, to get
3 to the answer.
4 I don't think we know what that answer is
5 going to be. It might be a little better to get to
6 it, and a little faster to get to it and be able to
7 settle this in phase 4 than in doing another
8 phase 3, and then having to come back.
9 I'm really concerned about having some tools
10 in our toolbox because everything -- again, we're
11 left with one drug that works in no time at all,
12 and the next thing you know, everything looks like
13 a nail because all we've got is a hammer left in
14 our toolbox. I'd like to have the options. We
15 just need to use it with caution like we use other
16 hepatotoxic drugs.
17 DR. GRIPSHOVER: Hi. Barb Gripshover. I
18 voted yes, but I also echo that it was more like
19 maybe, or partial might even be a better way. I
20 think that when I'm thinking of the risk-benefit,
21 for oral, I actually think it's more important for
22 oral. We don't have any good oral therapy for

1 community-acquired pneumonia other than quinolones
2 right now, whereas for IV, we still can do a
3 beta-lactam and another macrolide.
4 So we have the -- and the IV formulation
5 also looked more toxic. So maybe if we started it
6 with a oral and collected more data on that, with a
7 phase 4, we could then feel more comfortable going
8 with IV as one strategy. That's what I was
9 thinking.
10 DR. BADEN: I also voted yes. I think that
11 there are real safety concerns, which are difficult
12 to answer given the uncertainties of exactly what
13 those concerns are. There is also a real need for
14 antibiotics, particularly oral antibiotics, for
15 organisms that are becoming more and more
16 resistant. And this is the balance that we have to
17 make, and we have to accept the fact that
18 medications have side effects.
19 I would commend both the sponsor and the
20 agency, that if this is not handled responsibly,
21 then we will relive Ketek. On the other hand, if
22 it is handled responsibly, we can have another

1 antimicrobial that we can use. However, it will be
2 difficult to know safety until we've looked at it
3 in a thousand, 5,000, 10,000, 100,000, a million,
4 with all the complexity. But it's a very, very
5 difficult balance, and it is very hard to develop
6 antimicrobials; hence, we have so few new ones.
7 Thus, I favor yes.
8 DR. GREEN: Michael Green. I voted no.
9 I've been struggling with this specific balance
10 question since I opened up my CDs from the FDA and
11 started reading about what looked like efficacy
12 that was demonstrated and toxicity that was raised.
13 What do we know? Telithromycin is a
14 ketolide. And it's interesting because I think
15 when telithromycin came out, they said it's
16 ketolide. They said it's a new class. When we've
17 been hearing about solithromycin, we've been
18 calling it a macrolide, in some ways to
19 intentionally separate it from its association with
20 telithromycin. And yet, structurally it looks a
21 lot alike, although it clearly has some
22 differences.

1 Unfortunately, we don't really know whether
2 the differences between solithromycin and
3 telithromycin, versus the similarities between
4 these two compounds, predict whether or not it will
5 have this signal.
6 My next concern is that we desperately need
7 antibiotics, and I've spent the last 20 years of my
8 career being interested in antibiotic resistance.
9 I do antimicrobial stewardship. I've done
10 resistance epidemiology, both in the community and
11 in the hospital setting for my entire career, and
12 I'm desperate to see new drugs.
13 We need them for our sick patients; it's
14 absolutely true. One of the things about this
15 particular recommendation and indication they're
16 looking for is it's not just for the patient who's
17 going to be hospitalized, who's going to have the
18 most severe infection. It potentially will also be
19 for the person who's got mild to moderate illness
20 in the community.
21 It turns out that there are still drugs that
22 are available. You might have to use two drugs as

1 opposed to one. You can use high-dose amoxicillin
2 to overcome penicillin non-susceptibility in
3 Streptococcus pneumoniae. I'm a pediatric
4 infectious disease person, and that is what we do
5 in our setting. We actually have less of a concern
6 or issue with the atypicals, at least in our very
7 young children. And for that, there's no issue I
8 think, or no real issue, of resistance in the
9 atypicals yet to the macrolides.
10 Having said that, I actually asked a
11 question which could have swayed my vote. I was
12 trying to give the sponsor a potential out because
13 they were putting this great surveillance in place.
14 And so I asked them, what level of signal will make
15 you pause, make you stop, make you hold, make you
16 withdraw, and I couldn't get an answer.
17 If they would have told me one or two cases
18 would make them pause, I could have voted yes with
19 an understanding that they would try to work out
20 some sort of an understanding with the FDA,
21 although I don't know whether that's even
22 precedented or not. And yet, we couldn't get that.

1 And I really do fear that we haven't answered the
2 question.
3 Having said that, I'm not smart enough to
4 know exactly how to do the study to get at
5 answering the risk, so I'm ambivalent. I'm
6 absolutely desperate to see new drugs. I'm so
7 thrilled that there are companies that are still
8 trying to do drug development, because if they
9 don't do it, we won't have them. And yet, I think
10 that this is a drug that is a ketolide, and we have
11 not addressed the issue of whether the signal that
12 we see will mean it is or it's not telithromycin
13 part 2. Thanks very much.
14 DR. DASKALAKIS: Demetre Daskalakis. I
15 voted no, which was really a no on the side of
16 maybe, mainly because of the fact that we don't
17 really have the full story of hepatotoxicity. I
18 think that that's where I can't really decide and
19 feel confident in a yes, given that that's still
20 missing.
21 I think that from the perspective of other
22 steps, a vote for no for this question is not

1 necessarily a vote for no for recommending
2 approval. That's not what this question asks. So
3 I put that out there to say that I vote for no with
4 the idea that potentially being very stringent if
5 this drug is recommended for approval since we do
6 need new antibiotics, especially oral antibiotics
7 for these conditions that reduce the risk of some
8 of the other complications of fluoroquinolones.
9 I think that it's critical that the, again,
10 phase 4 studies are very rigorous and very clear.
11 And I also want to bring up the idea of is this a
12 place where we think about a REMS, where we create
13 something where we realize that there's an
14 associated risk with the drug, and that we give
15 some tool to be able to allow patients to access
16 it, but shift the risk balance by creating some
17 sort of clear documentation that this is a piece of
18 the story of this drug as you use it in your
19 practice.
20 DR. LEE: Will Lee. Yes. This was a very
21 agonizing vote. I think the history of DILI at the
22 FDA was that in '99, there were two drugs approved,

1 troglitazone and Rezulin, that both had to be
2 withdrawn in the next couple of years. And since
3 then, the FDA's been incredibly risk-adverse with
4 one exception, and that's cancer drug. The
5 tyrosine kinase inhibitors get a free ride. We
6 know they have toxicity, but every patient has
7 cancer. And they usually have metastatic cancer,
8 so they're tolerant -- the FDA tolerance of
9 hepatotoxicity is huge, or at least higher than it
10 is with any other drug.
11 So since 1999, there's been essentially
12 nothing, not even telithromycin. It never was
13 withdrawn except eventually by the company. So FDA
14 has not withdrawn a single drug since 1999 because
15 I think they've been relatively risk-averse.
16 Now, this drug clearly has a strong
17 hepatotoxicity signal, however, I think we heard
18 Dr. Fernandez say that it took there and a half
19 years to get 880 patients. My concern is that we
20 keep discouraging companies from going forward.
21 Perhaps the FDA has to come up with something
22 different, a provisional approval with the

1 understanding that we're in the post-Ketek world,
2 we're in the post -- we're 18 years since 1999, and
3 we have to come up with a new strategy to allow the
4 phase 4 studies to go forward.
5 We have much better pharmacovigilance,
6 presumably, all these huge databases that we and
7 raw from. And I think we need to come up with
8 somehow a better paradigm, maybe stronger labeling
9 but also perhaps some way to acknowledge. The
10 C. diff issue is huge, the quinolone resistance
11 issue is huge, and the potential death from the
12 primary disease is huge. We've got to be able to
13 figure out where the balance is.
14 DR. LO RE: Yes. I voted no. I felt that
15 the risk outweighed the benefits. I was swayed by
16 the FDA's analysis, and the identification of a
17 hepatotoxicity signal was a major concern for me.
18 In particular, I thought that the evidence of acute
19 liver injury among the healthy phase 1 volunteers
20 with liver aminotransferase levels that continued
21 to rise after discontinuation; the imbalance in the
22 ALT elevations within the solithromycin treatment

1 arms compared to the levofloxacin in the phase 2
2 studies and moxifloxacin in the phase 3 studies;
3 and the case of acute hepatocellular jaundice from
4 the COPD trial, especially when no such case
5 existed where it was observed in the telithromycin
6 experience, made me feel that the risk of this drug
7 might outweigh its benefits.
8 I felt that more evidence to quantify the
9 risk of hepatotoxicity of the drug is needed. And
10 particularly, there's been some discussion about
11 the use of large databases. I felt that without
12 even some guidance on how clinicians should measure
13 liver function tests in real-world settings, that
14 it's going to be difficult to assess that without
15 that.
16 I feel that if we proceed without better
17 estimating the hepatotoxicity risks and more cases
18 of severe acute liver injury develop after
19 approval, then confidence in the FDA, sponsors, all
20 of us as advocates and providers is going to be
21 eroded.
22 DR. BADEN: So you have a split decision

1 from the committee, however, in hearing the themes,
2 it's not clear to me that it's a split decision. I
3 hear much more of a continuous decision and where
4 one falls on that risk-benefit with the challenges
5 of antibiotic, the unmet medical need, the
6 potential for postmarketing surveillance; labeling
7 and strengthening pharmacovigilance being one way
8 to mitigate and manage the potential benefit, and
9 then the issue of the signal is just too concerning
10 and needs to be better characterized before you can
11 accept that benefit.
12 I heard largely unanimity in what everyone
13 was saying, and then it comes to risk management,
14 and risk management with an eye to protecting the
15 confidence in the public. And I think the sponsor
16 has a serious responsibility in thinking about
17 that, and the agency as well and how this is
18 positioned. So there you have the committee's
19 deliberations.
20 I would like to -- Dr. Proschan?
21 DR. PROSCHAN: I just wanted to say, let the
22 record reflect that the committee did not feel it

1 was a logical inconsistency to vote no on 2 and yes
2 on 3.
3 (Laughter.)
4 DR. BADEN: At least six of us could be
5 deemed illogical, which is probably an
6 underestimate.
7 Before we adjourn, are there any last
8 comments from the agency?
9 DR. NAMBIAR: Thank you, Dr. Baden. On
10 behalf of the division and the Office of
11 Antimicrobial Products, we want to extend our
12 thanks and sincere appreciation to the committee
13 members for all of the discussions and advice
14 provided. We find the advice provided is extremely
15 beneficial to us as we continue to evaluate these
16 applications.
17 Our thanks also to the applicant for their
18 presentations and hard work on these NDAs. We also
19 want to thank the speakers at the open public
20 hearing for their comments. We wish all of you
21 safe travels, and thank you very much.
22 **Adjournment**

1 DR. BADEN: Closing comments? One, a cell
2 phone was left in the men's room at the
3 registration desk if you're missing one.
4 I would like to thank both the sponsor and
5 the agency for very thorough presentations of a
6 complex topic. I'd like to thank the committee
7 members for putting in the time and energy to think
8 this through as carefully and deliberatively as we
9 all did.
10 We'll now adjourn the meeting. Panel
11 members, please take all your personal belongings
12 with you, as the room is cleaned at the end of the
13 meeting day. All materials left on the table will
14 be disposed of. Please also remember to drop off
15 your name badge at the registration table on your
16 way out so it may be recycled. The meeting is now
17 adjourned.
18 (Whereupon, at 4:26 p.m., the meeting was
19 adjourned.)
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