ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

November 20, 2008

1   BARTH RELLER: Good morning. I'm Barth Reller

2   and I'd like to welcome you to the morning meeting, 20

3   November, 2008 of the Food and Drug Administrative

4   Anti-Infective Advisory Committee.

5   For topics such as those being discussed at

6   today's meeting, there are often a variety of opinions.

7   Some of which are quite strongly held. Our goal is

8   that today's meeting will be fair and open, a forum for

9   discussion of these issues, and that individual can

10   express their views without interruption.

11   Thus, as a gentle reminder, individuals will

12   be allowed to speak into the record only if recognized

13   by the Chair. We look forward to a productive meeting.

14   In the spirit of the Federal Advisory

15   Committee Act and the Government and Sunshine Act, we

16   ask that the advisory committee members take care that

17   their conversations about the topic at hand take place

18   in the open forum of this meeting. We are aware that

19   members of the media are anxious to speak with the FDA

20   about these proceedings. However, FDA will refrain

21   from discussing the details of the meeting with the

22   media until its conclusion. The press contact from FDA

1 for this meeting is Karen Riley who is standing center

2 stage.   Thank you, Karen.

3   Also, the committee is reminded to refrain

4 from discussing the meeting topic during the break.

5 Thank you.

6   I'd like to next have all of those about the

7 table introduce themselves.   And for variety we'll

8 start on my right at the far end of the table, with Dr.

9 Jim Steckelberg, who though not listed in the agenda is

10 a voting member of this morning's committee meeting.

11 Dr. Steckelberg.

12   JAMES STECKELBERG: Good morning, James

13 Steckelberg, Chair, Division of Infectious Diseases and

14 Professor of Medicine, Mayo Clinic, Rochester.

15   ALAN CROSS: Alan Cross, Infectious Disease,

16 University of Maryland at Baltimore.

17   ARTHUR LEVIN: Arthur Levin, Center for

18 Medical Consumers in New York and the consumer

19 representative.

20   MEL WEINSTEIN: Mel Weinstein, Professor of

21 Medicine, Pathology, Robert Wood Johnson Medical School

22 and Chief of Infectious Diseases, Director of the

1 Microbiology Laboratory, Robert Wood Johnson University

2 Hospital.

3   DEAN FOLLMANN: Dean Follmann, Head of Bio-

4 Statistics at the National Institute of Allergy and

5 Infectious Diseases.

6   KATHLEEN GUTIERREZ: Kathleen Gutierrez,

7 Pediatric Infectious Disease, Stanford University

8 Packard Children's Hospital.

9   CAROL KAUFFMAN: Carol Kauffman, Professor of

10 Internal Medicine at the University of Michigan and

11 Chief of the I.D. Section at the Ann Arbor V.A.

12   BUD WEIDERMANN: Good morning, I'm Bud

13 WEIDERMANN, Pediatric Infectious Diseases at Children's

14 National Medical Center in the George Washington

15 University in D.C.

16   JANIE KIM: Janie Kim, Designated Federal

17 Officer, FDA.

18   BARTH RELLER: Barth Reller, Professor of

19 Medicine and Pathology and Director of the Clinic and

20 Medical Microbiology Program at Duke University Medical

21 Center.

22   JOHN REX: John Rex, former Professor of

 1   Medicine in Infectious Diseases at the University of

 2   Texas Medical School at Houston. I'm currently Vice

 3   President for Clinical Infection at Astra Zeneca

 4   Pharmaceuticals.

 5   As Dr. Kim will later note, my role on the

 6   committee today is that of the nonvoting industry

 7   representative. In this role I represent regulated

 8   industry as a whole, rather than Astra Zeneca

 9   Pharmaceuticals or any other specific sponsor.

10   PETER KATONA: Peter Katona, Infectious

11   Disease Physician at UCLA.

12   KEMPER ALSTON: Kemper Alston, Infectious

13   Disease Physician at the University of Vermont College

14   of Medicine in Burlington.

15   MATTHEW GOETZ: Matthew Goetz, Professor of

16   Clinical Medicine, UCLA and Chief Infectious Diseases

17   at the V.A. Hospital in Los Angeles.

18   THOMAS FLEMING: Thomas Fleming, Professor of

19   Bio-Statistics at University of Washington.

20   JIM LEGGETT: Jim Leggett, Infectious

21   Diseases, Providence Portland Medical Center and Oregon

22   Health and Sciences University.

1   JACK BENNETT: I'm Jack Bennett, Senior

2   Investigator at IAID, Bethesda, Maryland.

3   TIMOTHY LESAR: Timothy Lesar, Director of

4   Pharmacy, Albany Medical Center, Albany, New York.

5   LEWIS NELSON: Lewis Nelson, I'm an Associate

6   Professor of Emergency Medicine and a medical

7   toxicologist from New York University School of

8   Medicine.

9   ED SEPTIMUS: Ed Septimus, Clinical Professor

10   of Medicine at the University of Texas Medical School

11   in Houston and Medical Director for Infection

12   Prevention at HCA Healthcare System in Nashville.

13   THAMBAN VALAPPIL: Thamban Valappil,

14   statistician here at FDA.

15   JOHN ALEXANDER: John Alexander, Medical Team

16   Leader, Division of Anti-Infective in Ophthalmology

17   Products.

18   MARK GAMALO: Mark Gamalo, statistician,

19   Office of Bio-Statistics, FDA.

20   KATIE LAESSIG: Katie Laessig, Deputy

21   Director, Division of Anti-Infective in Ophthalmology

22   Products, FDA.

1   ED COX: Ed Cox, Director of the Office Anti-

2   microbian Products, Cedar, FDA.

3   BARTH RELLER: Dr. Janie Kim will now read the

4   conflict of interest statement.

5   JANIE KIM: The Food and Drug Administration

6   is convening today's meeting of Anti-Infective Drugs

7   Advisory Committee under the authority of the Federal

8   Advisory Committee Act of 1972. With the exception of

9   the industry representative, all members and temporary

10   voting members of the committee are special government

11   employees or regular federal employees from other

12   agencies and are subject to the federal conflict of

13   interest laws and regulations.

14   The following information on the status of

15   this committee's compliance with federal ethics and

16   conflict of interest laws covered by, but not limited

17   to, those found at 18 U.S.C. Section 208 and Section

18   712 of the Federal Food Drug and Cosmetic Act are being

19   provided to the participants in today's meeting and to

20   the public.

21   FDA has determined that members and temporary

22   voting members of this committee are in compliance with

1 federal ethics and conflict of interest laws. Under

2 the 18 U.S.C. Section 208 Congress has authorized FDA

3 to grant waivers to special government employees and

4 regular federal employees who have potential financial

5 conflicts, when it is determined that the agency's need

6 for a particular individual's services outweighs his or

7 her potential financial conflict of interest.

8   Under Section 712 of the Food, Drug and

9 Cosmetic Act, FDA -- Congress has authorized FDA to

10 grant waivers to special government employees and

11 regular federal employees with potential financial

12 conflicts, when necessary, to afford the committee

13 essential expertise.

14   Related to the discussions of today's meeting,

15 members and temporary voting members of this committee

16 have been screened for potential financial conflicts of

17 interest of their own, as well as those imputed to them

18 including those of their spouses or minor children, and

19 for purposes of 18 U.S.C. Section 208, their employers.

20 These interests may include investments, consulting,

21 expert witness testimony, contracts, grants, CRADAs,

22 teaching, speaking, writing, patents and royalties and

1 primary employment.

2   Today's agenda involves a new drug application

3 NDA022-269, iclaprim, Arpida AG, for the proposed

4 treatment of complicated skin and skin structure

5 infection. This is a particular matter meeting during

6 which specific matters related to iclaprim will be

7 discussed.

8   With respect to FDA's invited industry

9 representative, we would like to disclose that Dr. John

10 Rex is participating in this meeting as a nonvoting,

11 industry representative acting on behalf of regulated

12 industry. Dr. Rex's role at this meeting is to

13 represent industry in general and not any particular

14 company. Dr. Rex is employed by Astra Zeneca.

15   We would like to remind members and temporary

16 voting members that if the discussions involve any

17 other products or firms not already on the agenda for

18 which an FDA participant has a personal or imputed

19 financial interest, the participants need to exclude

20 themselves from such involvement. And it exclusions

21 will be noted for the record.

22   FDA encourages all other participants to

1 advise the committee of any financial relationships

2 that they may have with any firms at issue. Thank you.

3   BARTH RELLER: The committee now looks forward

4 to hearing the presentation from the sponsor, Arpida

5 AG.

6   KHALID ISLAM: Thank you. Good morning. My

7 name is Khalid Islam, I'm the former C.E.O. of Arpida

8 and currently a member of the board of directors. On

9 behalf of Arpida I would like to thank the agency for

10 kindly inviting us to give this presentation and for

11 giving us the opportunity to put forward our rationale

12 for requesting an approval for iclaprim in this

13 indication.

14   I would also like to take this occasion to

15 thank the iclaprim review team at the FDA for all their

16 hard efforts and the dedication that they have given to

17 the review process.

18   As you'd realize it was a very proud moment

19 for us, as a very small company, to file the iclaprim

20 NDA with the FDA as a solution for infusion for the

21 indication of complicated skin and skin structure

22 infections. As we've heard over the last couple of

1 days, there is a pressing need for new antibiotics

2 which can overcome the problematic infections such as

3 those caused by MRSA, both hospital and community and

4 of course hetero-resistant VISA.

5   In this presentation we will provide evidence

6 that iclaprim, as a new antibiotic, will be a valuable

7 addition to the armamentarium to address this growing

8 issue -- concern.

9   After a brief introduction my colleague, Dr.

10 Mark Jones who is a senior program manager and leads

11 the Microbiology, will describe the pertinent

12 microbiological properties of iclaprim. Dr. Wayne

13 Dankner who acted as the medical monitor for the

14 iclaprim trials will describe the results of clinical

15 efficacy and safety. And Dr. Dankner has over two

16 decades of extensive experience with clinical trials

17 with anti-infective products.

18   Professor Wei, as you heard the other day, was

19 charging a million per minute so he's going to have a

20 very short presentation. And he will touch on some of

21 the statistical aspects. The clinical context,

22 including the medical need for new antibiotics will be

1   described by Dr. Vance Fowler. Dr. Fowler is an

2   infectious disease specialist.

3   And we also have some additional experts. For

4   cardiology, Dr. Peter Kowey. For hepatology, Dr. James

5   Lewis. And for statistics, Dr. Charles Davis. Dr.

6   Davis works as a statistical consultant with the

7   company.

8   And in the last 48 hours we have actually

9   heard a great deal about the problems facing the

10   medical community, particularly those associated with

11   hospital and community acquired MRSA and the toxin

12   production and release from community MRSA. We've also

13   heard about emerging challenges which may diminish the

14   usefulness of vancomycin and those that can also affect

15   daptomycin.

16   These are the current treatments in cSSSI.

17   And just to touch briefly, there are two major areas of

18   mechanisms infection that you're looking at, cell wall

19   and membrane inhibitors which include the Beta-lactams,

20   the glycopeptides and the lypoglycopeptides and two of

21   those we saw yesterday as well. And protein synthesis

22   inhibitors which include the oxazolidinones class

1 (linezolid) in particular, and tetracyclines

2 (tigecycline).

3   There are also emerging intolerance issue, for

4 example, with tigecycline there are problems with G.I.

5 intolerance and more recently, apart from the other

6 associated side effects for linezolid, there are also

7 issues not only with emerging resistance, and we've

8 heard several case reports in the last few years, but

9 also the recently described serotonin syndrome.

10   So the mechanism faction of iclaprim as a

11 dihydrophilic inhibitor -- react as an inhibitor DHFR

12 is distinct from the cell wall and protein synthesis

13 inhibitors that constitute the majority of the

14 antibiotics used today. Indeed we reason that a novel

15 drug with a differentiated mechanism faction provides

16 not only a means to bypass the problems associated with

17 resistance with these current classes, but also because

18 of the nature of the chemical structure, we'll also

19 avoid some of the side effect profiles associated with

20 these classes.

21   Now inhibition of DHFR, DHFR is involved in

22 the folate synthesis pathway, will result in the

 1   depletion of precursors which results in a shutdown of

 2   protein, RNA and DNA synthesis. And this obviously

 3   subsequently leads to bacterial death.

 4   There is good historical evidence that DHFR

 5   inhibitors are useful clinically and indeed

 6   trimethoprim which targets this enzyme, and you can see

 7   that on the left hand side, this is a (inaudible)

 8   structure of trimethoprim bound in the active pocket of

 9   the dihydropholic trajectories. This drug,

10   trimethoprim, has been extensively used for over four

11   decades and we have good clinical experience with this

12   drug. And it has proved to be safe, well tolerated and

13   effective.

14   We have used this structure base information

15   to design iclaprim which is actually shown on the right

16   hand side. And difference to trimethoprim, which is

17   shown on the left hand side, you can see that iclaprim

18   has several additional interactions with surrounding

19   amino acids within the active pocket. The result of

20   these additional interactions is an increased affinity

21   to dihydropholic trajectories and this enhanced binding

22   results in potent activity of this new DHFR inhibitor

 1   against gram-positive pathogens and in particular

 2   against MRSA, both community MRSA as well as hospital

 3   acquired MRSA.

 4   Now during this presentation you will see a

 5   number of properties which my -- which the subsequent

 6   presenters will be delineating for you. A targeted

 7   gram-positive spectrum of activity and potent activity

 8   against resistant bacteria, in particular against those

 9   problematic pathogens like MRSA, hetero-VISA, VISA,

10   vancomycin resistance, this drug demonstrates a rapid

11   bactericidal activity and a low propensity for

12   resistance development.

13   It shows, very importantly, very high

14   distribution in tissues and organs, a property which is

15   not so common and not so present in a number of the

16   current treatments. It also shows a low potential for

17   drug/drug interaction and shows a reduced impact on

18   commensal bacterial flora.

19   Last, but not least, this compound is also

20   orally bio-available. Oral development is currently in

21   Phase 2 clinical trials.

22   With that I would like to invite my colleague,

1 Mr. Mark Jones to walk you through the microbiological

2 properties of this compound. Thank you.

3   MARK JONES: Thank you, Dr. Islam. Iclaprim

4 is a new generation microbial DFHR inhibitor. It

5 belongs to the diaminopyrimidine group of antibiotics

6 of which trimethoprim is the best known representative,

7 and demonstrates potentiated binding to the bacterial

8 DHFR resulting in three key benefits. One, increased

9 potency against gram-positive pathogens. Two, rapid

10 bactericidal activity. And three, a low propensity for

11 the emergence of resistance.

12   Iclaprim demonstrates extensive tissue

13 distribution, a volume of distribution of around 120

14 liters in humans, no antagonism with over 30 different

15 antibiotics tested, inclusive of all major drug

16 classes. And, as Dr. Islam mentioned, is potentially

17 orally bio-available.

18   Iclaprim demonstrates potent activity against

19 key gram-positive pathogens in complicated skin soft

20 tissue infections. MIC90's presented in the slide are

21 derived from international surveillance study, testing

22 recent clinical isolettes from patients across the U.S.

 1   and Europe. These confirm the potency against staph

 2   aureus and the Beta-hemolytic Group A and Group B

 3   streptococci and noticeably demonstrate the

 4   independence of activity to methocilin resistance or

 5   susceptibility in the staphylococcal isolettes.

 6   Iclaprim demonstrates potent in-vitro activity

 7   against resistant MRSA phenotypes, against collection

 8   of H-VISA, ductomycin, linezolid, non-susceptible

 9   isolettes. The majority of isolettes are all -- are

10   inhibited at low concentrations demonstrating the

11   potential of iclaprim to treat these clinically

12   important, whether they albeit uncommon, phenotypes of

13   MRSA.

14   Against a sub-selection of MRSA confirmed as

15   community acquired, USA300 PVL positive strains,

16   iclaprim demonstrates equi-activity as compared with

17   hospital acquired strains. A key pharmacodynamic

18   property of iclaprim is its rapid sidle activity,

19   generally killing is seen after approximately six hours

20   to clinical isolettes of staph aureus which is

21   concentration independent as shown by the yellow and

22   orange lines in the histogram. Incidentally, killing

 1 is also seen for vancomycin resistant strain, the Van A

 2 Circle Pennsylvania isolette.

 3   Iclaprim demonstrates a low propensity for the

 4 emergence of resistance, both spontaneous and induced.

 5 In-vitro data show no emergency of resistance, a low

 6 frequency of less than ten to the minus ten. And in

 7 passage experiments, as shown in the graphic, when

 8 passaged in sub-MIC levels of iclaprim, clinical

 9 isolettes of staph aureus demonstrate small or no

10 changes in baseline MICs, which upon removal of drug at

11 day 17, returned to baseline.

12   Iclaprim consistently demonstrated efficacy in

13 animal models of infection. In classic mirroring

14 models of septicemia, peritonitis efficacy is

15 consistently demonstrated. Also for different

16 pathogens including resistant phenotypes MRSA,

17 including trimethoprim resistant MRSA. Efficacy was

18 also demonstrated by both oral and IV routes of

19 administration.

20   In considering microbiology from our Phase 3

21 clinical program, Phase 3 clinical microbiology is both

22 concordant with non-clinical studies and

1   representative. The etiology of pathogens from

2   patients at baseline in our Phase 3 program is typical

3   of what may be expected in complicated skin soft tissue

4   infections. Eighty percent of patients had

5   staphylococcus aureus infections which together with

6   streptococcus pyogenes accounted for towards 95 percent

7   of baseline isolettes.

8   Of those staphylococcus, 40 percent were MRSA,

9   a good enriched population. Of which 70 percent were

10   Panton-Valentine leukocidin-positive.

11   The susceptibility of baseline pathogens from

12   our Phase 3 studies is essentially the same as those

13   derived from the same species in our non-clinical

14   surveillance studies. The histogram showing

15   essentially overlapping MIC distributions between Phase

16   3 baseline pathogens in the orange and those from our

17   surveillance studies in blue demonstrating that staph

18   aureus from our Phase 3 study are representative.

19   No change in MICs to iclaprim were detected

20   for any strain of staph aureus in our clinical program.

21   Indeed for any other gram-positive baseline, no change

22   in baseline MIC to iclaprim was detected. Similarly,

1 for the MRSA subset of staph aureus, super imposable

2 MICs and the same for streptococcus pyogenes, the

3 second most common pathogen.

4   Iclaprim demonstrates a microbiological

5 profile that is clinically very useful. The baseline

6 microbiology from our Phase 3 study demonstrates

7 concordance with non-clinical studies, and suggests

8 that what is encountered is typical of what may be

9 encountered in day-to-day clinical practice in the

10 United States.

11   To further present the clinical efficacy and

12 safety of iclaprim we'll hand over to my colleague, Dr.

13 Wayne Dankner.

14   WAYNE DANKNER: Thank you, Dr. Jones. The

15 clinical -- the iclaprim clinical program was a

16 comprehensive program. It consisted of 14 Phase 1

17 trials that focused on pharmokinetics, ADME, formal ECG

18 and drug/drug interaction studies in normal volunteers.

19 And also included studies in special populations.

20   Overall these trials demonstrated that

21 iclaprim was well tolerated. When -- we then conducted

22 a Phase 2 dose finding study in patients with cSSSI,

1 comparing two doses of iclaprim to vancomycin, the

2 comparative discussed yesterday. This study

3 demonstrated that iclaprim was efficacious and well

4 tolerated in patients. And then we moved on to two

5 Phase 3 pivotal studies. In these trials we chose

6 linezolid as the approved comparator because unlike

7 vancomycin, linezolid is approved for both MRSA and

8 non-MRSA skin infections and considered by some to be

9 superior to vanco. These studies also showed high

10 clinical cure rates and a good safety profile.

11   Before we discuss the Phase 3 trials, it is

12 useful to review the pharmokinetic profile of iclaprim.

13 At a dose of 0.8 milligrams per kilogram infused over

14 30 minutes, which is a therapeutic dose chosen for the

15 Phase 3 development, iclaprim has a half life of 2.5 to

16 3 hours. It also has a large volume of distribution.

17   Over the full set of doses studies AUC and C-

18 Max were determined to be dose proportional. There was

19 no drug accumulation after multiple dose administration

20 for up to ten days. And there was rapid and extensive

21 tissue distribution.

22   Within the volunteers treated in the PK

1   studies, iclaprim was well tolerated with no drug

2   related SAEs, with exposure up to four times the

3   therapeutic dose.

4   The short half life helps us interpret the one

5   early phase finding of a QT effect.

6   In formal ECG studies iclaprim showed a small,

7   but rapidly reversible T-Max related QTc effect. The

8   white line represents the QTc measurements for the

9   placebo control. And the yellow line represents the

10 QTc measurements for the .8 milligram per kilogram

11 therapeutic dose infused for 30 minutes.

12   These trials show that the largest change in

13 QTc is at the end of the infusion period, T-Max when

14 then rapidly decreases back to its baseline within

15 about 30 to 45 minutes.

16   Once again, within the full set of ECG studies

17 iclaprim showed a dose dependant increase in QTc with a

18 mean maximal increase about ten milliseconds at the

19 therapeutic dose. Also, no difference in QTc change

20 was observed between males and females.

21   Additionally, this drug shows a low potential

22 for drug/drug interactions. Although iclaprim is

1 primarily metabolized by the cytochrome p450 enzymes,

2 3A4 and 2C19, there was no significant drug interaction

3 with strong inhibitors of 3A4, ketoconazole, or 2C19,

4 omeprazole. Additionally, two studies were conducted

5 with frequently used drugs in the hospital setting

6 warfarin and digoxin. Both of these have narrow

7 therapeutic windows. Once again there were no

8 clinically relevant interaction seen with either of

9 these drugs.

10   Finally, studies conducted in special

11 populations demonstrate that there's a limited need for

12 dose adjustments. No dose adjustment is necessary for

13 patients with any degree of renal insufficiency,

14 including those with end stage renal disease on

15 dialysis. Similarly, there was no dose adjustment

16 required for patients with mild hepatic insufficiency

17 or those with moderate obesity.

18   We will be recommending a dose adjustment for

19 patients with moderate hepatic insufficiency, those

20 with Child-Pugh Class B or with severe obesity, those

21 with BMIs greater than 40.

22   Following the PK safety tolerance studies, the

1 dose findings Phase 2 study was conducted in

2 hospitalized patients with complicated skin and skin

3 structure infections. This was a blinded randomized

4 study comparing two doses of iclaprim, .08 and 1.6

5 milligrams per kilogram to vancomycin, 1 gram. All

6 drugs were administered Q12 hours and for 10 days.

7 With the clinical cure at the test of cure of visit

8 being the primary end point of the trial.

9   A total of 92 patients were enrolled in the

10 study. No drug related SAEs were observed at either

11 the current therapeutic dose of .8 milligrams per

12 kilogram or twice the therapeutic dose at 1.6

13 milligrams per kilogram. And overall iclaprim was well

14 tolerated at both these doses.

15   The most frequent pathogen found in the study

16 by staphylococcus aureus for which iclaprim

17 demonstrated high clinical cure rates and

18 microbiological cure rates. Overall clinical cure

19 rates were above 90 percent for both iclaprim doses and

20 for vancomycin.

21   Based on the combination of the Phase 1 and

22 Phase 2 studies, the .8 milligram dose was chosen for

1   the Phase 3 trials. The Phase 3 trials were referred

2   to as the ASSIST Program. The ASSIST Program consisted

3   of two independent randomized, double blind, multi-

4   center studies in hospitalized patients with cSSSI.

5   These studies were essentially identical in all aspects

6   of study design.

7   Linezolid was chosen as the approved

8   comparator for these non-inferiority trials. The only

9   allowable concomitant antibiotics were aztreonam for

10   gram-negative coverage and metronidazole for anaerobic

11   coverage.

12   And independent monitoring committee was

13   established to monitor safety for both of these pivotal

14   studies.

15   As presented earlier in the course of this

16   three day meeting, the NI margins chosen for the

17   primary analysis in the ASSIST-1 and ASSIST-2 trials

18   had a pre-specified lower limit of the 95 percent

19   confidence interval for the treatment difference of

20   iclaprim to linezolid of -12.5 percent.

21   We had prospectively planned to combine data

22   from these two trials, which had essentially identical

1 study design and utilized the same approved comparator.

2 This was to allow additional powering for comparison of

3 efficacy and safety results. As with other trials in

4 this clinical indication the primary end point was

5 clinical cure at test of cure visit and the co-primary

6 populations were the intent to treat and for per

7 protocol populations which are subsequently referred to

8 as ITT and PP.

9   The next slide graphically depicts the study

10 design of the two ASSIST studies. Patients were

11 randomized to receive either IV iclaprim at .08 mg/kg

12 q12h or IV linezolid at 600 mg, q12h for 10 to 14 days.

13 Study visits were scheduled for the first four days

14 then every other day until the end of therapy. The

15 test of cure visit, which is the primary end point of

16 the trial, was to occur 7 to 14 days after the end of

17 therapy visit. And the late follow up visit to occur 7

18 to 14 days after the TOC visit.

19   Efficacy of the randomized treatment regiment

20 was assessed at both EOT and TOC. Microbiological

21 samples were taken at baseline then again at day three,

22 on day ten if the patient received more than ten days

1   of study medication and at both EOT and TOC of

2   clinically indicated.

3   Additionally, sparse PK sampling was performed

4   on days one and four for developing a population PK

5   model for iclaprim. Central laboratories were utilized

6   to confirm the bacterial isolettes obtained from the

7   primary cultures performed at these study sites and to

8   analyze the PK samples.

9   Overall there were 991 patients enrolled in

10 the two ASSIST studies. A high percentage of patients

11 completed their assigned treatment in both study arms.

12 Geographically the U.S. patients accounted for some 39

13 percent of the total population. The patient

14 demographics were comparable between these two trials.

15   There was a predominance of males and close to

16 15 percent of the patients were older than 65 years of

17 age. The observable difference between the two studies

18 relates to the ethnic distribution, with a higher

19 percentage of black and Hispanics noted in the ASSIST-2

20 trial. This difference is accounted for by the high

21 number of U.S. patients enrolled in the ASSIST-2 study,

22 283 patients, compared to the ASSIST-1 study, 101

1 patients. Although not shown on this slide, these

2 patient characteristics were well balanced between the

3 two study arms in both trials.

4   The cSSSI infection types were also well

5 balanced between regiments. The types of infections

6 encountered in this trial are typical of complicated

7 skin and skin structure infections that you find in a

8 hospitalized setting and have been discussed over the

9 last two days. More 90 percent of infections were

10 considered to be severe, based on protocol defined

11 criteria.

12   Deep and extensive cellulitis was the most

13 frequent infection type observed followed by wound

14 infections and major abscesses.

15   Per study entry criteria all patients had to

16 have a documented fever and/or an elevated white count

17 above 10,000 to be eligible for entry into the study.

18   Across these infection types iclaprim proved

19 itself to be non-inferior to linezolid.

20   These are the results from the ITT population

21 analysis. We defined the ITT population as all

22 patients randomized in the study and who received at

 1   least one dose of study drug. Iclaprim, shown in

 2   yellow in this and subsequent slides, demonstrates high

 3   clinical cure rates at the test of cure visit which are

 4   comparable to those of linezolid shown in green in this

 5   and subsequent slides.

 6   Each independent study met its pre-specified

 7   NI margin of -12.5 percent. Additionally,

 8   prospectively planned pooling of the data, shown in the

 9   combined results, demonstrates the lower confidence

10   bound as -7.7 percent.

11   In the next slide we show the efficacy results

12   for the co-primary population, the PP population. The

13   PP population is derived from the ITT except it

14   excluded all patients with predefined protocol

15   violations that could impact the physicians' assessment

16   of efficacy. Iclaprim demonstrated high clinical cure

17   rates in each individual trial as was the case with the

18   ITT population. Once again, each independent study met

19   its pre-specified NI margin of -12.5 percent.

20   Additionally, the combined results demonstrated the

21   lower confidence bound on this -8.7 percent.

22   Even though we met our primary end points in

1 this patient population, we noted a larger difference

2 between arms than anticipated. Consequently we looked

3 for a possible explanation to these results and

4 discovered an imbalance between the two regiments.

5   The marked imbalance found was between

6 treatment groups and the use of prohibited antibiotics

7 of high dose steroids. The effect of this imbalance is

8 that a disproportionate number of indeterminist

9 patients who normally would be considered failures are

10 removed from the linezolid arm. This in effect

11 artificially raises the cure rate in the PP population

12 by removing them from the denominator. No other

13 imbalances were found and all protocol violations were

14 defined in a blinded fashion prior to data lock and

15 unblinding of the database.

16   As a result of finding this imbalance we

17 conducted a sensitivity analysis according to ICHE-9

18 guidance and created a modified clinically evaluable

19 population. This population consists of the PP

20 population with the addition of the patients who had

21 received prohibited antibiotics of high dose steroids,

22 to be counted as clinical failures.

1   Subsequently, analysis of the MCE population

2   demonstrates that cure rates are comparable between the

3   two treatment arms when this imbalance is addressed.

4   This suggests the results previously noted in the PP

5   population can be explained by this imbalance.

6   To demonstrate that we've been paying

7   attention to proceedings over the last couple of days,

8   we've conducted a subgroup post hoc analysis of the

9   efficacy results, with the removal of patients with

10   major abscesses. Iclaprim again demonstrated high

11   clinical cure rates as compared to linezolid in this

12   population or patients with more severe infections.

13   Additionally, in the ITT population the lower bound of

14   the non-inferiority confidence interval was -10.8 for

15   ASSIST-1, -10.1 percent for ASSIST-2 and -8.3 percent

16   for the combined results even with the sample sizes

17   decreased by the removal of the patient with abscesses.

18   Another subgroup analysis, and one

19   specifically requested by the FDA was to evaluate the

20   efficacy results in the population of patients enrolled

21   in the U.S. For this analysis we combined the U.S.

22   patients enrolled in the two studies. As indicated

1 earlier U.S. patients accounted for nearly 40 percent

2 of the total patients enrolled in the two ASSIST

3 trials. The cure rates, once again, are high on all

4 populations, ITT, PP and the sensitivity analysis

5 population, MCE. And very comparable to linezolid.

6   Having demonstrated iclaprim's efficacy in

7 patients without abscesses and in the U.S. patients,

8 and as Dr. Jones alluded to earlier, iclaprim was also

9 effective against MRSA infections. In the MITT

10 population iclaprim demonstrated comparable cure rates

11 to linezolid. Although the cure rates appear somewhat

12 more disparitourous in ASSIST-1, the sample sizes are

13 small as opposed to ASSIST-2 where the sample sizes are

14 larger and the cure rates for iclaprim and linezolid

15 are very similar.

16   As indicated earlier by Dr. Islam, the FDA had

17 reclassified a handful of patients for the efficacy

18 analysis accounting for the differences you see between

19 our efficacy results and those published in the FDA

20 briefing document and in the slides released this

21 morning by the FDA.

22   These are the three cases from ASSIST-1 that

1 the FDA has reclassified from clinical cure to failure.

2 Based upon the FDA reclassification all three cases

3 would now be defined as clinical failures in both the

4 ITT and PP population analysis. I'd like to review

5 these cases one by one.

6   Patient 113-03 received a 12 day course of

7 iclaprim, was considered a clinical cure by the

8 investigator of that at both EOT and TOC, the primary

9 analysis end point for the trial. The patient

10 developed a new or recurrent infection 14 days after

11 TOC and 22 days after the last dose of study

12 medication.

13   Patient 302-12 received a 10 day course of

14 iclaprim and was considered a clinical cure by the

15 investigator at both EOT and TOC. This patient

16 developed a new or recurrent infection four days after

17 TOC and 11 days after the last dose of study

18 medication.

19   Patient 303-17 received a 13 day course of

20 iclaprim and was also considered a clinical cure by the

21 investigator at EOT and TOC. This patient developed a

22 new infection on the opposite buttock that was

 1 diagnosed and treated after the TOC visit. However the

 2 investigator felt the original infection site had been

 3 cured.

 4   Each patient grew different pathogens at the

 5 baseline visit, however follow up cultures at the time

 6 of the new or recurrent infection were not available

 7 for evaluation of the new or recurrent pathogens.

 8   These are the four cases from ASSIST-2.

 9 Patient 616-03 received a 14 day course of iclaprim,

10 was considered a clinical cure by the investigator at

11 both EOT and TOC. This patient developed a new or

12 recurrent infection two days after TOC and nine days

13 after the last dose of study medication.

14   Patient 649-02 received a 12 day course of

15 iclaprim and was considered a clinical cure again at

16 EOT and TOC. This patient developed a new or recurrent

17 infection 12 days after TOC and 28 days after the last

18 dose of study medication.

19   Patient 624-34 who received an 11 day course

20 of iclaprim was reclassified by the FDA review as

21 having an indeterminant outcome. This patient had

22 received 24 hours of prior treatment with oral

1 trimethoprim and a dose of cefazolin in an outside

2 emergency room from an abdominal wall infection due to

3 MRSA the day before study entry. The patient was

4 admitted the next day because of lack of therapeutic

5 effect and given a dose of IV clindamycin prior to

6 study enrollment.

7   Although this patient had received more than

8 24 hours of prior antibiotic therapy, they met study

9 entry criteria due to lack of clinical response to

10 prior treatment. This patient otherwise was considered

11 a clinical cure by the investigator of both EOT and

12 TOC.

13   Patient 616-14 who received a 14 day course of

14 linezolid was also reclassified as having indeterminate

15 outcome. This patient received a single dose of

16 cefazolin on study day two following an I&D procedure.

17 However, this patient's baseline pathogen was

18 documented to be MRSA and as such we did not consider

19 the receipt of cefazolin relevant to this patient's

20 clinical course. This patient otherwise was considered

21 a clinical cure by the investigator of both EOT and

22 TOC.

1   While we respect the questions raised by the

2   agency, we believe our original classifications are

3   correct and the efficacy profile of iclaprim is as

4   represented this morning.

5   In both our independent studies iclaprim

6   achieved predefined non-inferiority margin of -12.5

7   percent. The combined data of the non-inferiority

8   margins were -8 to -9 percent. Additionally, iclaprim

9   showed high clinical cure rates, especially in the

10   protocol population, which were comparable to the

11   approved comparator linezolid used in the Phase 3

12   studies. And as discussed earlier, iclaprim also

13   showed comparable cure rates in the Phase 2 study when

14   vancomycin was used as a comparator.

15   From a microbiological perspective iclaprim

16   was effective against staphylococcal infections

17   demonstrating high clinical cure rates, over 80 percent

18   against both methicillin sensitive and methicillin

19   resistant staph aureus infections with comparable

20   activity to linezolid. And as Dr. Jones showed

21   previously, there was no change in baseline iclaprim

22   MICs while on therapy.

1   And these efficacy results occurred in the

2   context of a safety profile consistent with what we

3   might expect from a drug in the DFHR class.

4   In evaluating the clinical safety results we

5   moved back to our study design slide. Incidents and

6   description of adverse events and use of concomitant

7   medications was assessed at each study visit. ECGs for

8   morphologic assessment and measurement of QTc were

9   obtained pre-dose baseline on day one, post-dose day

10 one and post-dose day four. All ECGs were done in

11 triplicate, with post-dose ECGs started within ten

12 minutes of the end of study drug infusion in order to

13 ensure the capture of the maximal QTc effect.

14   ECGs were transmitted to an ECG central

15 laboratory where they were reviewed and assessed by

16 blinded cardiologists and entered into the study

17 database.

18   Specimens for laboratory analysis were

19 obtained at baseline day three, day ten for those

20 patients receiving more than ten days of study drug,

21 EOT, TOC and late follow up. These specimens were also

22 analyzed by a central laboratory. Based on these

 1   assessments the AE profile of iclaprim was observed to

 2   be similar to linezolid.

 3   The adverse event profile shows two trends.

 4   First, the adverse event rate is similar between

 5   iclaprim and linezolid with iclaprim demonstrating a

 6   lower rate of related AEs as compared to linezolid in

 7   the two two trials. Next, the rates for severe AEs,

 8   AEs leading to permanent discontinuation of study

 9   medications, SAEs and deaths are low, and again,

10   comparable to linezolid. Expect for one serious

11   adverse event in the iclaprim group all other SAEs and

12   deaths were assessed by the investigators and also as

13   assisted by the blinded medical monitor, me, and safety

14   physicians from Arpida as unrelated to iclaprim or

15   linezolid.

16   In their briefing document the FDA reviewer

17   had to reassign four deaths, three in the iclaprim

18   treated patients and one non-fatal SAE as possibly

19   related to study medication. We reviewed these events

20   and will provide our rationale for why we consider

21   these events to be unrelated to study drug

22   administration.

1   Patient 306-27, with a history of alcoholic

2   cardio myopathy received a full course of study

3   medication, had no documented affect of iclaprim on QTc

4   at days one or day four and whose death occurred seven

5   days after the end of the treatment. Given the half

6   life of three hours for iclaprim the patient's death

7   occurred well beyond any pharmacologic affect of the

8   drug, most especially cardiac related.

9   The patient's anemia was noted to be pre-

10   existing with a value of 8.1 milligrams per deciliter

11   at study entry and was not impacted by the

12   administration of iclaprim, with the value of 8.4

13   milligrams per deciliter at end of therapy.

14   The autopsy confirmed the presence of the

15   alcoholic cardio myopathy.

16   Patient 306-34 developed evidence of acute

17   renal failure at the TOC visit and then had a sudden

18   death 12 days after the last dose of study drug. A

19   review of the patient's renal function test results

20   revealed no change in serum creatinine while on study

21   therapy similar to Patient 306-27, the patient's death

22   occurred well beyond any potential pharmacologic effect

1   of iclaprim.

2   Patient 306-33 had significant co-morbidities

3   related to alcohol related disease and was further

4   complicated by a very large wound that contributed to

5   severe metabolic abnormalities. This patient did

6   expire while receiving study money. And although noted

7   to have some affect on QTc at day one and day four the

8   affect was decreasing over time. Did I advance that by

9   mistake? Sorry. Thank you. Thank you.

10   A review of the timing of the patient's death

11   revealed that she had received her last dose of

12   iclaprim 11 hours prior to the time of her arrest.

13   Since the peak QTc effect of iclaprim occurs at T-Max

14   and dissipates quickly over the next 30 to 60 minutes,

15   it was felt unlikely that exposure to iclaprim

16   contributed to this patient's death.

17   The events of peripheral edema and swelling of

18   the face occurred in association with hypoalbunemia

19   seven days prior to her death. In the event of cardiac

20   failure, which directly associated with the death

21   itself. As such we did not feel these events were

22   consistent with a hyper sensitivity or anaphylactic

1   reaction.

2   The last patient death we reviewed, Patient

3   304-38 occurred in the linezolid arm. This patient,

4   like 306-34 developed acute renal failure associated

5   with a renal infection and expired due to a pulmonary

6   embolism. A review of the patient's renal function

7   test results revealed no change in serum creatinine

8   while on therapy. Additionally, this patient's death

9   occurred ten days after the last dose of linezolid,

10   also well beyond the likely pharmacologic effect of

11   this particular drug.

12   And now we'll go to the right slide. The one

13   non-fatal SAE of acute renal failure, patient with

14   acute tubal necrosis, documented on renal biopsy,

15   assessed by the FDA reviewer as possibly related to

16   study medication, occurred in Patient 133-01. This

17   patient had received iclaprim but had study drug

18   discontinued on day number two due to lack of

19   therapeutic effect. The patient was diagnosed with

20   acute renal failure three days after the last dose of

21   iclaprim had been administered and after the patient

22   had already received intravenous vancomycin at 1.5

1 grams per dose and multiple doses of oral and

2 parenteral non-steroidal anti-inflammatory agents.

3   A review of the patient's renal function test

4 revealed that leading up to the event of ARF normal

5 serum creatinine values were noted at baseline and

6 again at study day number three which was one day after

7 the study drug iclaprim had been discontinued. Based

8 on these data we continued to assess these events as

9 unrelated to study drug administration.

10   Additionally, the FDA reviewer has highlighted

11 the treatment emergency AE rate for renal and urinary

12 disorders for iclaprim as 2.8 percent. However, the AE

13 rate for this system organ class for linezolid is no

14 different at 2.7 percent. Additionally the agency

15 pointed out that there were no discontinuations due to

16 AEs in the system organ class.

17   The rest of the adverse event profile supports

18 that iclaprim is no different than linezolid in the

19 most frequent adverse events. While the differences

20 between iclaprim and linezolid are very modest,

21 iclaprim demonstrates a lower rate of related events in

22 all categories except headache and nausea. And no

1   related event occurred at a rate of more than four

2   percent in the iclaprim group.

3   Based on the preclinical and Phase 1 data,

4   iclaprim had a potential to prolong QT and as such we

5   studied the QT effect in our Phase 3 trials. The data

6   presented represented change in QTc from baseline at

7   day one and day four using either the Bazett or

8   Fridericia Corrections for both iclaprim and linezolid.

9   Since linezolid is known not to have a QT effect it

10   served as a good control in this clinical setting.

11   Iclaprim demonstrated in an absolute increase

12   of seven and four milliseconds by QTcB and 9 and 10

13   milliseconds by QTcF at study days one and four

14   respectively. However, the relative increases compared

15   to linezolid was quite consistent by either QT

16   correction factor of approximately six milliseconds on

17   day one and four milliseconds on day four.

18   Various subgroup analyses were performed on

19   this data and there was no differences associated with

20   gender, age, body mass index or previous cardiac

21   history. In our continued assessment of cardiac safety

22   we performed a categorical analysis looking at patients

 1   who had a change of greater than 30 milliseconds or 60

 2   milliseconds on both days and those with absolute QTc

 3   measurements above 500 milliseconds.

 4   While the change of greater than 30

 5   milliseconds was twice as high in the iclaprim treated

 6   patients as compared to those with linezolid, there was

 7   no difference between the two treatment groups and the

 8   more relevant QTc change of greater than 60

 9   milliseconds. Additionally, only one patient in the

10   iclaprim group had an absolute QTc measurement on

11   therapy that was translucently above 500 milliseconds.

12   Of interest, the one patient that met QTc

13   related study withdrawal criteria, absolute QTc greater

14   than 520 milliseconds associated with a QTc change from

15   baseline of greater than 60 milliseconds, was a patient

16   treated with linezolid. Overall no rhythmogenic events

17   were associated with QTc prolongation in either trial.

18   Taken together, the safety results generate a profile

19   suitable for an alternative in the treatment of cSSSI.

20   Our experience in the Phase 3 trials shows

21   that iclaprim, at the therapeutic dose of .8 milligrams

22   per kilogram, is well tolerated with a good safety

1 profile comparable to linezolid. Evaluation of the

2 effect of iclaprim on QTc demonstrated a relative

3 change from baseline of four to six milliseconds and

4 this change is similar to that observed for oral

5 moxifloxacin. Within the scope of QTc effect of

6 iclaprim no arrhythmogenic events were encountered.

7   Next I'd like to have Dr. Wei come up and

8 discuss the NI margin.

9   LJ WEI: Thank you very much, Wayne. I was

10 told this morning my job is (inaudible) Dr. Dankner's

11 seat and warm up the seat for Dr. Fowler. So I will

12 try my best. I don't want to be repetitive. Convenes

13 the members here 12.5 percent because Professor Charles

14 -- Chuck Davis did a great job on Tuesday. I just want

15 to share with you some -- a little new things we did in

16 the past two days after we heard the valuable comments

17 from the committee members on Tuesday, also yesterday.

18   Now forgive me just say take one minute of my

19 time, not Peter's time. We think about NI margin, Dr.

20 Rex asked the other day, give us a number, ten percent,

21 15 percent, 13 percent, whatever is good, because we

22 need some information. Now we ask ourself, is this

 1   reasonable to give us a number? The answer is yes and

 2   no. The part of yes, when you design a trial, when

 3   you're monitoring the trial, the NI margin is very

 4   important. And the company want to decide they're

 5   going to go in this game and what the cost, what's the

 6   benefit.

 7   And on the other hand, if a trial's over, like

 8   Dr. Hilton said the other day, you know, NI margin

 9   really doesn't matter anymore. Like the past two days

10   you're talking about safety and efficacy. So you need

11   to see the totality of evidence not only an NI margin

12   was set up in the beginning. And Peter did a great

13   job. First they went in the game, they said 12.5

14   percent, that's my goal, and they did it. And they

15   didn't say post-trial set up 12.5 percent.

16   Now I just want to use a few minutes to

17   demonstrate maybe we should think about NI margin when

18   you deliberate today. Should we always use ten percent

19   or something actually -- there's room to fluctuate?

20   Now Peter didn't use vanco as a comparator, instead he

21   uses a better one as comparator. And on Tuesday

22   Professor Davis actually show us this result based on

1 four studies. Actually we spent quite a bit time to do

2 the literate search a couple months ago and find out

3 how many and which one, actually it's randomized

4 controlled trials involving our active comparator.

5   So here is again the four trials. The

6 horizontal line is a percentage and zero in the middle,

7 middle means there's no difference between the

8 linezolid against the comparator. On the right hand

9 side in favor of our comparator. You notice these four

10 trials, the point estimators, they're all on the right

11 hand side in favor of our comparator.

12   The pooling is actually -- tell us the lower

13 bound of the cavernous interval is 2.0 roughly. Our

14 per pound is like almost seven percent, in the middle

15 it's roughly five percent to six percent.

16   Now because Dr. Follmann say, look have you

17 done meta-analysis? So we did meta-analysis with four

18 trials, it runs the cavernous interval is almost

19 identical to fixed effect. So that's a very good

20 sensitivity analysis. Then Dr. Fleming asked, look at

21 this Wilcox, the first trial, the cure rate is 93

22 percent, the rest of the guys not. But look at this,

1 very interestingly, even the Wilcox trial the cure rate

2 is 93. But when you think about a difference, the four

3 trials are pretty homogeneous.

4   But in any event, we followed Tom's idea. We

5 do another sensitivity analysis. By deleting this

6 ally, this so-called ally, a possible ally and luck

7 turns out again the cavernous interval is roughly

8 between two and seven.

9   So the next is the meta-analysis Dr. Charles

10 Davis talking about, published 2008. They got more

11 trials involved and look this auto (ph) ratio. Instead

12 of the use of risk difference they used auto ratio the

13 one is in the middle, there's no difference. Again,

14 every trial tended to in favor of our comparator.

15   So what's the conclusion from this contrast?

16 That indicate isolette actually is better at least by

17 two percent, that's most a conservative evaluation.

18   Now Dr. Hilton actually asked the other day,

19 say, when the trial's over can you actually compute

20 this so-called NI margin? So we follow also Dr.

21 Fleming's idea, instead of 50 percent we're going to

22 show you 60 percent efficacy retention at 70.

1   So let me go just very quickly. This is three

2   different severities. This is severe, serious and not

3   serious. And in our trial, with two trials combined,

4   you see the proportion of patients, 39, 33, 28. Now

5   using Ideas A position paper we have active minus a

6   placebo cure rate difference, 42 percent in this

7   category, 28 percent in this category, 14 percent in

8   this category.

9   Now those numbers are very conservative. That

10 means I take the best shot for placebo but the worst

11 show for the active control. If we take a 50 percent

12 retention efficacy, just divide it by two, 21, 14 and

13 7. So if you use this proportional (inaudible)

14 etcetera we figure out that the averaging NI margin

15 will be 15 percent. Now if we retain a 60 percent

16 efficacy instead of 50, we've got a margin that's 12

17 percent. And the retention, if it's 70 percent is nine

18 percent.

19   Now think about it, if we use vanco instead of

20 linezolid, we actually got a 15, 12 and 9 percent.

21 Then you plus two percent extra. It should be 17, 14

22 and 11.

1   Now, again based on Dr. Fleming's let's do the

2   sensitivity analysis. We delete this not a serious

3   case, now we're 39 and 33. We do the same argument.

4   You notice the retention 50 percent, NI margin becomes

5   18 percent, 60 percent retention becomes 14 percent, 70

6   percent becomes 11 percent. So if you notice Arpida's

7   result they're roughly 11 percent -- the worst case is

8   11 percent.

9   So my conclusion is that using a fixed number

10   for everybody may not be fair. And we should think

11   about which comparator. And in this trial Arpida used

12   the best comparators. So I hope my message got across.

13   Thank you very much. Dr. Fowler.

14   VANCE FOWLER: Thank you, Dr. Wei. Over the

15   next few minutes I'd like to make the argument that

16   there's a medical need for new antibiotics for

17   complicated skin and skin structure infections. And

18   that iclaprim represents an attractive alternative and

19   step in the right direction towards addressing that

20   unmet medical need. Oh there we are, thank you.

21   I'm going to build this argument on three

22   central pillars: Increasing clinical need, largely

1 based on the exponential increase in skin and soft

2 tissue infections; declining numbers of new and

3 effective agents based upon the rapid emergence of

4 resistance; and the decline in development of

5 investigational agents. And then what I refer to as

6 the Allen wrench analogy which basically can be

7 summarized by the clinical need for treatment

8 alternatives.

9   Okay, so let's talk about clinical need.

10 We've talked about this for the last several days and

11 there could certainly be little argument that the

12 frequency of soft tissue infections have increased.

13 These are data published a couple months ago from

14 national ambulatory care databases, demonstrating a 50

15 percent increase in the proportion -- cases of skin

16 soft tissue infections from 1997 until 2005. And over

17 95 percent of that increase was related to abscess and

18 cellulitis. So point one, increasing clinical need.

19   Point two, declining numbers of new and

20 effective agents. Well there's several means by which

21 the number of effective agents are declining. The

22 first is rapid resistance in the pathogens, in general,

1   in staph aureus in particular. So these are data

2   published from clinical infectious diseases last year

3   demonstrating the interval between the year of

4   introduction of a particular antibiotics and the year

5   that -- resistance to that agent was described.

6   And I'd simply like to bring your attention to

7   the rows involving linezolid and daptomycin with the

8   rapid introduction and description of resistance

9   subsequent to its use.

10   The second means by which the number of

11   antibiotics are declining is dwindling development.

12   These are data you all know, published earlier this

13   year, demonstrating a significant drop in the total

14   number of approved antibiotics from 1983 to 2007.

15   So point one, increased clinical need largely

16   due to increased skin and soft tissue infections.

17   Point two, declining numbers of new and effective

18   agents, due in part to rapid resistance and dwindling

19   development. So this leads me to my third pillar of

20   this argument, what I call the Allen wrench analogy.

21   And the key message here is the need for clinical

22   options.

1   Okay, so we all know what an Allen wrench is,

2   basically it's a specialized tool that allows you to

3   tighten or loosen specific types of nuts and bolts.

4   And the reality is you don't need an Allen wrench every

5   day. But having said that, when you actually need an

6   Allen wrench there's very little you can use in place

7   of that Allen wrench. So my point here is that

8   antibiotics, in many ways, are similar to these

9   specific tools and Allen wrenches in general.

10   We're not going to need a particular

11   antibiotic every day. There's no such thing, at least

12   to my knowledge, as the perfect antibiotic. However,

13   in a particular patient there will often be an

14   antibiotic that makes the most sense.

15   Let me give you an example. This afternoon,

16   after I finish this, I'm going to have to go back to

17   the hospital and round, because I'm on service now.

18   One of the patients I'm rounding on is a 50 year old

19   gentleman, healthy guy, fit, marathon runner, came in

20   with community acquired staph aureus bacteremia and

21   verci verlostu myelitis (ph). So for a variety of

22   reasons this patient is being treated with synercid,

1   quinupristin/dalfopristin.

2   Now let me make it real clear,

3   quinupristin/dalfopristin is not my first choice for

4   staph aureus bacteremia, nor is it my second, third or

5   fourth choice for staph aureus bacteremia, for that

6   matter. But in this particular patient this was an

7   option, it was a tool that we had to use. So my point

8   here is that we need alternatives.

9   There we are. So what's in our current tool

10   box for skin and soft tissue infections with regards to

11   staph aureus and MRSA? They're currently listed here.

12   And the point of this slide is to demonstrate that for

13   all of these agents there are characteristics that both

14   favor the use and favor the avoidance of a particular

15   antibiotic.

16   So for example, vancomycin, it's got a wealth

17   of clinical experience from which we as clinicians can

18   gain comfort in knowing what we're likely to get.

19   However recent discussions about regarding MIC creep

20   and treatment failure and things of that nature, have

21   dampened the enthusiasm of this particular agent. And

22   there are similar examples of characteristics favoring

1   the use and favoring the avoidance for each of the

2   other agents.

3   So how does iclaprim fit into this toolbox

4   model? Well like most arguments, there are -- it can

5   be viewed from the standpoint of benefits and risks.

6   From the standpoint of benefits, I believe that it's

7   safe. As a second generation trimethoprim class it

8   benefits from the safety and experience of that drug

9   class. Has a low potential for drug/drug interaction,

10 as we've heard. And no real requirements for dose

11 adjustment with regards to renal impairment.

12   It's efficacious with high cure rates in

13 complicated skin. And I should point out that the cure

14 rates in the intend to treat populations for the

15 ASSIST-1 and -2 trials were actually quite consistent

16 with those of similar registration trials for other

17 agents seeking this indication.

18   It's durable with regard to -- in terms of in

19 vitro selection of resistance, so-called resistance to

20 resistance, if you will. Good tissue and lung

21 penetration which leads to the prospect of future areas

22 of indication. For example, pneumonia and if I'm not

1 mistaken the recent pneumonia trial has just been

2 completed by a sponsor.

3   And finally, and candidly, most interesting to

4 me personally is the prospect of oral bio-availability

5 because what this offers is the possibility of an oral

6 alternative, in the future, an oral alternative to

7 trimethoprim/sulphamethoxazole and linezolid. So that

8 prospect seems particularly promising to me personally.

9   With regard to risk, QTc prolongation probably

10 is the major one that I have identified in terms of --

11 but I think it's manageable. For example, the QTc

12 prolongation tends to be small, in the four to six

13 range. By comparison this is fairly consistent with

14 that observed with moxifloxacin which is commercially

15 available. It's transient and rapidly reversible.

16   Okay then, so how would I see iclaprim fitting

17 into the tool box, if you will, to continue using that

18 analogy, in treatment? So I think the characteristics

19 that would favor its use would include the safety

20 profile, the fact that it appears to be durable with

21 regards to development of reduced susceptibility in

22 therapy, and from my personal prospective, the prospect

1 of an oral alternative in the future for

2 trimethoprim/sulphamethoxazole. And I think that it

3 was briefly mentioned that a recent IV to oral switch

4 trial has just been completed, testing that hypothesis.

5   Features that favor avoidance of -- favor its

6 avoidance would include QTc. I think it's also

7 relevant to mention probably the issue of streptococcus

8 pyogenes. But at the end of the day the unmet medical

9 need isn't due to streptococcus pyogenes, it's due to

10 staph aureus in general and MRSA in particular.

11   So in summary, I've tried to make two basic

12 arguments. First, that there's an unmet medical need

13 for additional antibiotics for the treatment of

14 complicated skin and skin structure infections. And

15 this is based on increased rates of the problem,

16 growing problem, more infections, dwindling arsenal due

17 both to resistance and declining treatment alternatives

18 and the clinical need for treatment options to do our

19 job. And the second argument that iclaprim presents an

20 attractive alternative therapy for the treatment of

21 complicated skin and skin structure infections.

22   Thank you very much for your attention.

1   KAHLID ISLAM: Thank you, Dr. Fowler. I know

2   that I'm going to try and do everything very quickly.

3   Our presentation this morning will conclude on touching

4   on some of the differences between our analysis and

5   those performed by the FDA review team.

6   As (inaudible) the blinded investigator, the

7   medical monitor and the Arpida physician as well as the

8   unblinded data monitoring committee, all considered

9   these deaths to be unrelated to the study drugs. Dr.

10   Dankner noticed that three of the four deaths with both

11   treatments occurred well past the period when the

12   pharmacological effect would be expected to be present,

13   based on the short half lives of both the treatment

14   arms.

15   One death, 306-33 occurred 12 hours after the

16   last dose. This is again several half lives away from

17   the maximal QT effect which is seen at the end of

18   infusion. This patient was also seen conscious in the

19   morning prior to expiration. While we cannot totally

20   exclude this death as drug related, it appears highly

21   unlikely.

22   Just very quickly going over the study design.

1 I'd just like to point out that our primary analysis

2 end point that was discussed and agreed with the agency

3 was test of cure.

4 Now regarding the FDA analysis, all of these

5 patients were judged to be cured by the blinded

6 investigator, the medical monitor and the Arpida

7 physician at the primary efficacy end point which was

8 the test of cure visit. The statistical analysis plan

9 specified this as the primary end point. And the test

10 of cure visit is actually some seven to 14 days after

11 the end of therapy.

12 In the majority of these cures the reinfection

13 or new infection was observed well over two to three

14 weeks after the end of therapy. Therefore it appears

15 reasonable that all these patients should be considered

16 cured and that Arpida's primary analysis is a correct

17 reflection of the clinical cure rates.

18 On the first day we heard a number of comments

19 on study design. Just very rapidly again, in the

20 ASSIST trials patients were followed on a daily basis

21 for the first four days and subsequently every second

22 day to the end of therapy and then at TOC visit.

1   Several parameters could be followed. For

2 example, time to defervescence. And you can see here

3 that these are very comparable between iclaprim and

4 linezolid, two to four days. We could also follow time

5 to resolution of signs and symptoms in cSSSI. And

6 again you can see that they're very comparable between

7 iclaprim and linezolid.

8   Clinical cure at the EOT once again shows you

9 that the margins here are around -8.5, -8.3 and -11.5

10 in the different populations. And this is actually

11 shown in the protocol population with respect to the

12 ITT population previously.

13   And just looking at the combined population,

14 looking at the non-inferiority margins, just point out

15 to you that in the combined population which is

16 obviously a larger number, all populations meet the

17 primary end point.

18   So overall iclaprim has shown to be

19 efficacious. Results non-inferior to linezolid, a

20 drug, which unlike vancomycin, is approved for the

21 treatment of both MRSA and non MRSA infections. While

22 vancomycin is generally acknowledged to be inferior to

 1 semi-synthetic penicillins, linezolid appears to be

 2 more efficacious, not only to semi-synthetic

 3 penicillins but also to vancomycin and other

 4 comparators.

 5   Finally, iclaprim has been demonstrated to be

 6 well tolerated in subjects in hospitalized patients.

 7 And with this it only remains for me to thank you for

 8 your kind attention. And we'll be delighted to answer

 9 any questions that you'll have. Thank you very much.

10   BARTH RELLER: The sponsor's presentation

11 having concluded we'll next move, before the questions

12 for and clarifications by sponsor and FDA that will

13 take place, after the FDA presentation by Dr. John

14 Alexander.

15   JOHN ALEXANDER: I want to welcome everybody

16 to about mile 24 of the FDA marathon advisory

17 committee. Hopefully nobody's hitting a wall at this

18 point and we can just push on through.

19   I'm here to present the FDA review for

20 iclaprim for injection. So as a brief overview of

21 iclaprim the drug is a dihydrofolate reductase

22 inhibitor, so it has a similar mechanism of action to

1 trimethoprim.

2   The product under consideration is a

3 concentrated solution that would be diluted in

4 intravenous fluids for delivery as an IV on product.

5 Although you've heard this morning that the product

6 also has oral bio-availability. But the product under

7 consideration in NDA-22269, which was submitted in

8 March of 2008, is the IV solution. And the indication

9 being sought is for complicated skin and skin structure

10 infections.

11   So about the cSSSI studies, the IND for this

12 product was submitted actually fairly recently, in

13 February of 2005. And that's because much of the Phase

14 1 and Phase 2 development of the product occurred

15 overseas, prior to the IND. So one of the first

16 studies that was part of the original IND application

17 was actually one of the Phase 2 studies, the ASSIST-1

18 trial.

19   But both of the Phase 3 ASSIST-1 and ASSIST-2

20 were conducted under the IND. They were similar in

21 design. Both of them involved treatment with iclaprim

22 at a dose of .8 milligrams per kilogram of iclaprim

1 base, every 12 hours. And the comparator was linezolid

2 at the approved dose, every 12 hours. The complicated

3 skin and skin structure infection studies you've heard

4 about already, they were designed to include patients

5 with these types of infections, cellulitis, major

6 abscesses, infected ulcers, wound infections and

7 infected burns.

8   The sponsor mentioned that 12.5 percent non-

9 inferiority margin was proposed by them for both

10 trials. When they came to discuss these trials at the

11 FDA we did recommend to them, at the time, that they

12 should use a 10 percent non-inferiority margin. And we

13 discussed the fact that if they had fairly

14 straightforward results that wouldn't be an issue. But

15 if we had any concerns about the results, either on the

16 efficacy or safety side, that we'd likely be discussing

17 this at an advisory committee. And here we are today.

18   So I'm going to move on to the efficacy

19 analyses. So this slide shows the primary outcome for

20 the analyses for the two studies. The primary outcome

21 was clinical cure at the test of cure visit, which was

22 7 to 14 days after completion of the 10 to 14 days of

1 treatment. The slide shows the results for the co-

2 primary and per protocol populations for both studies.

3 Now these numbers and the numbers on the

4 subsequent slides for efficacy differ from the sponsors

5 results and they also differ from what was provided in

6 our FDA's original briefly document. And I wanted to

7 explain that a little bit. These numbers are provided

8 in an addendum to the FDA briefing document which is

9 also available on our website along with the original

10 briefly document materials.

11 As we were preparing our briefly document we –

12 – the FDA statisticians identified 17 patients who were

13 considered cured in the sponsor's analyses, but had

14 received systemic antibiotics after starting study

15 treatment. As we were preparing our briefing document

16 what we did with those individuals was to assign them

17 with an outcome that was indeterminate. And so that's

18 what is represented in the numbers in the original

19 briefing document that was provided to you.

20 Subsequent to the briefing document

21 preparation, what we did was we conducted a case review

22 of each of the individual cases without knowledge of

1 the specific treatment that the patient was assigned

2 to, in order to evaluate whether assigning all of these

3 patients an indeterminate outcome was correct. There

4 were a total of 17 patients, as I mentioned. Out of

5 those we considered ten of them to be appropriate as

6 cures. These include patients who it was clear that

7 they received the antibiotic that had for an infection

8 at a site other than the original site to treatment.

9   So there was one patient who developed a UTI

10 after completing antibiotic treatment for the skin and

11 soft tissue infection. There was another patient who

12 developed an infection of the ear lobe at a separate

13 site from the original infection. There were five

14 other patients who were considered failures and two

15 patients who were considered to have an indeterminate

16 outcome.

17   In the case of the failures the concern was

18 that we were looking at patients who shortly after the

19 patient's test of cure development infections at what

20 appeared to be the same site that was described as the

21 original site of infection in the cSSSI protocol.

22   The indeterminate outcomes were described

1   already. The issue there is the idea that those were

2   some protocol violations and that was how the

3   indeterminate patients were described, as individuals

4   who potentially received other antimicrobials that

5   could account for some of the improvement that was

6   seen.

7   So I did want to go over these numbers then.

8   What you have there are the results for the ITT and per

9   protocol populations in ASSIST-1, in the top two lines

10   and then the ITT and per protocol populations in the

11   ASSIST-2. These are co-primary populations for the

12   evaluation of the primary outcome. And what you see in

13   terms of the results are results in ASSIST-1 where the

14   treatment difference in both populations is fairly

15   consistent, -6.8 in the ITT, -5.9 in the per protocol

16   population. And you have the 95 confidence interval

17   showing a lower band of -13 in the ITT and -10.2.

18   Also, in the ASSIST-2 trial what you have is

19   some difference in terms of the outcomes in the

20   treatment differences for the ITT and the per protocol

21   population. In the ITT the treatment difference is -

22   1.4 and the per protocol is much larger at -7.4. And

 1 then you have the corresponding lower bounds of the

 2 non-inferiority margins at -8.3 for the ITT population

 3 and -12.8 in the per protocol population.

 4   Also of interest to know though, in these

 5 trials are the upper bounds of the confidence intervals

 6 for three out of these four co-primary populations in

 7 the two studies where the upper bound in ASSIST-1 for

 8 the ITT population was -0.5. In the per protocol

 9 population was -2.2 percent. And then looking at

10 ASSIST-2 you had the -- in the ITT group an upper bound

11 of 5.2 and in the per protocol an upper bound of -2.1.

12 So in three of those populations there's a suggestion

13 of statistically significant difference between the

14 iclaprim and the comparator, linezolid, in terms of the

15 upper bound.

16   So moving on then, we're looking at secondary

17 outcomes by infection type. These are patients who are

18 in the ITT population and results for the Assist-1 and

19 the ASSIST-2 trials are listed separately. Of note, in

20 ASSIST-1 there are a larger number of patients in the

21 iclaprim and linezolid groups who have cellulitis as

22 compared to abscess or wound infection, whereas in

 1   ASSIST-2 the wound infection numbers are larger with

 2   smaller numbers of patients who had either cellulitis

 3   or abscess.

 4   Now as you remember, in the primary population

 5   there was a larger treatment difference in the ITT

 6   population in ASSIST-1 and the -- in the ITT

 7   population in ASSIST-2 the outcomes were roughly

 8   similar. And if you looked at the patients who had

 9   either abscess or wound infection, what you see are

10   results that are consistent with the overall primary

11   outcome results. So that in patients with abscess or

12   wound infection, the results between iclaprim and

13   linezolid are fairly comparable for ASSIST-1 -- or

14   ASSIST-2, excuse me. Whereas for ASSIST-1 there's a

15   larger treatment difference between the iclaprim and

16   the linezolid groups.

17   Curiously, for cellulitis in the ASSIST-1

18   trial there is a treatment difference of roughly nine

19   percent. In ASSIST-2 there's still some treatment

20   difference of about six percent between the iclaprim

21   group and the linezolid group.

22   So now we're moving on to secondary outcomes

1   by pathogen. This is the patients who are in the MITT

2   population. So that's defined as the patients who are

3   in the ITT population who had microbiologic isolette at

4   baseline. These results are broken down again by

5   ASSIST-1 and ASSIST-2. And what we're looking at here

6   are the results for patients with staph aureus, broken

7   down by those who had MRSA and those who had MSSA.

8   And again, remembering the difference seen in

9   the ITT populations between ASSIST-1 and ASSIST-2, you

10 have consistent results when comparing patients across

11 the two treatment arms. So in the iclaprim -- I'm

12 sorry in the ASSIST-2 trial, when looking at patients

13 with MSSA or MRSA, you have fairly comparable results

14 acrossed treatment arms in terms of the clinical cure

15 rates. When looking at ASSIST-1 you have somewhat

16 larger treatment differences, especially for MRSA in

17 the ASSIST-1 trial.

18   Again additional organisms. We're starting to

19 get to smaller numbers, but I think it's important to

20 note here, in particular for S. pyogenes, in both

21 trials that what you're seeing is something of

22 difference of outcomes. So for the ASSIST-2 trial you

1 had 75 percent clinical cure rate for patients who had

2 S. pyogenes at baseline versus 86 percent for

3 linezolid. And in ASSIST-1 you had 80 versus 88.2.

4   As you get to the other organisms here you

5 start to get to really much smaller numbers.

6   So moving on to the safety analysis. This

7 slide provides a summary of the adverse events for the

8 combined Phase 3 studies, and the overall numbers of

9 patients who were in the iclaprim or linezolid treated

10 groups. And what you have here are roughly comparable

11 numbers, in terms of patients with any treatment

12 emergent AE, any severe treatment emergent adverse

13 events, any serious AEs and any treatment emergent

14 adverse events that resulted in study drug withdrawal.

15   Deaths I'm going to go into a little bit more,

16 but you see six in the iclaprim group versus two in the

17 linezolid group.

18   So overall in the Phase 2 and 3 studies, there

19 were seven deaths that occurred in the ITT safety

20 population of 526 who received linezolid. So one death

21 occurred in the Phase 2 population and then the other

22 six were in the Phase 3 population, as described on the

 1   previous slides. There were three patients that, in

 2   the FDA analysis, were considered as possibly related

 3   to iclaprim. All three patients were found either

 4   deceased or unconscious in their hospital beds and had

 5   multiple pre-existing co-morbid conditions.

 6   It's not clear that we can assign the deaths

 7   as definitely related to iclaprim but this was one of

 8   the concerns that was raised. The associated treatment

 9   emergent adverse events were anemia in two patients,

10   hypoproteinema and acute renal failure.

11   Four deaths occurred before the completion of

12   therapy. Although only one of these was in a patient

13   who, I think, was considered possibly related to

14   iclaprim treatment. And there is a table that

15   describes a little bit more information about the

16   deaths in the FDA's briefing document.

17   Moving on to then serious adverse events.

18   What we're looking at here are serious adverse events

19   by system organ class. And what you see are fairly

20   comparable results in terms of the overall numbers of

21   serious adverse events with infections and

22   infestations, mainly infections accounting for the

 1   largest number of serious adverse events in either

 2   group.

 3   So then looking at these serious adverse

 4   events, most of the secondary infectious complications,

 5   such as pneumonia, septic arthritis, osteo -- or the

 6   development of an abscess appeared to have been related

 7   to underlying conditions or prolonged hospitalizations.

 8   And then with the exception of pneumonia which occurred

 9   in in three patients treated with iclaprim, there was

10   no specific serious adverse event preferred term that

11   was reported in a patient more than once in each

12   treatment group.

13   Moving on to study treatment withdrawals, this

14   table shows the results for the combined Phase 3

15   trials. Looking at reasons for early withdrawal and

16   what you see are fairly comparable results across the

17   two trials expect perhaps with the exception of

18   treatment failure, which was reported for five patients

19   in the iclaprim group versus one in the linezolid

20   group. Again there were three patients who died on

21   therapy in the Phase 3 trials in the iclaprim group.

22   Looking at treatment adverse -- any treatment

1 emergent adverse events as a whole, what we saw was

2 that reports of increased AST and ALT were the most

3 commonly reported adverse events among the iclaprim

4 group, at 7.2 percent with a comparable number, 6.9

5 percent in the linezolid group. These numbers are just

6 reports of the adverse event, without attribution.

7   There was an increased frequency in the

8 iclaprim group compared to linezolid group for Pyrexia,

9 reported in 5.2 percent of iclaprim treated person,

10 versus 2.2 percent of linezolid treated patients. We

11 did look into this a little bit to try and see if we

12 could sort out how much of this is related to the

13 underlying infection. And it appears to be that 13 out

14 of the 26 reported in the iclaprim group were likely

15 related to the infection compared to four out of 11

16 treated with linezolid.

17   Looking at other adverse events, these are

18 adverse events that occurred in greater than three

19 percent of the population that aren't discussed on some

20 of the other slides. Overall, in terms of nausea,

21 vomiting or dyspepsia as an adverse event, that was

22 reported for roughly 8.6 percent of the iclaprim group

1 versus 10.8 percent of the linezolid group. Headaches,

2 diarrhea or frequent bowel movements, constipation,

3 pruritis, abdominal distension, you can see the

4 numbers.

5   Interestingly, for rash it was 2.8 percent in

6 the iclaprim group versus 3.5 percent in the linezolid

7 group. So there isn't a high incidence of that

8 particular adverse event.

9   Going on then, looking at potential adverse

10 events of interest. There were two patients who has

11 serious renal AEs that were considered possibly related

12 to the use of iclaprim. Patient 306-34, a 70 year old

13 male who developed septic arthritis four days after the

14 EOT, went into acute renal failure 12 days after EOT

15 and found dead. That was again described previously as

16 one of the deaths that was considered possibly related.

17   Patient 133-01 was a 38 year old male who

18 received two days of therapy, did not respond to

19 treatment and then was described by the sponsor, had

20 received multiple other antibiotics and NSAIDS for

21 headache and had an increase in creatinine to 4.4

22 milligram per deciliter on day four. The renal biopsy

1   showed acute tubular necrosis and the patient

2   recovered.

3   Cardiac adverse events, there was a thorough

4   QT study that was conducted, concurrent with the Phase

5   3 studies. And I think it's important to note here

6   that this thorough QT study does establish a clear dose

7   response relationship in terms of treatment with

8   iclaprim and elevation in QT.

9   It's concentration dependent and therefore it

10 is also affected by infusion rate. So at a dose of 0.8

11 milligrams per kilogram given over a half an hour, the

12 Delta Delta QTcF is 12.4 milliseconds, with a 90

13 percent confidence interval around that rate, around

14 that increase in QT shown here. And at 1.6 milligrams

15 per kilogram given over an hour the Delta Delta QTcF

16 the site 21.6 milliseconds.

17   Now let me explain. There is a Delta Delta

18 QTcF so what is going on is that the QTcF is QT

19 measurement that's adjusted both for the patient's

20 baseline QT as well as being adjusted for the rate

21 change seen in the placebo group.

22   Looking at cardiac adverse events, in

 1   comparison with linezolid, treatment with iclaprim did

 2   demonstrate a higher mean change in QTc so this is just

 3   the change from baseline in QT. The incidents of QTc

 4   prolongation exceeding 30 milliseconds occurred at

 5   twice the rate seen with linezolid. So you can see

 6   that for the patients who had a change in QTc on day

 7   one, that was greater than 30 milliseconds, it was 3.2

 8   percent in the iclaprim group versus .8 in the

 9   linezolid group. And then at day four it was 12.1

10   percent for the iclaprim group versus 5 percent for the

11   linezolid treated group.

12   As you start to get to higher changes in QTc,

13   you have fewer patients, as expected, and roughly

14   comparable rates between the iclaprim and linezolid

15   groups.

16   The affects on Delta QTcF were similar in men

17   and women. Patients taking drugs known to prolong QT

18   accounted for two of the three patients in the iclaprim

19   group who had a Delta QTcF threshold on day four

20   greater than 60 milliseconds.

21   In the combined Phase 3 studies there were no

22   reported severe AEs such as torsades or ventricular

1 arrhythmias that were related to QT prolongation

2 associated with the use of iclaprim for up to 14 days.

3 No significant differences were noted in the incidents

4 of abnormal vital signs between the two treatment

5 groups.

6   There were two patients in each treatment

7 group who were withdrawn due to QTc prolongation. This

8 was part of the initial design of the Phase 3 trials,

9 because of the fact that we didn't have the thorough

10 QTc study done at the time that the study was started,

11 so that there was some discretion on the parts of

12 investigators who could decide to withdraw patients,

13 although specific instructions for doing that for

14 patients who had QT measurement of greater than 500

15 milliseconds or a change of greater than 60 were given.

16   So there were two patients in each treatment

17 group who were withdrawn due to QTc prolongation, as I

18 mentioned. In the iclaprim group there was Patient

19 802-02 who was an 81 year old female with a history of

20 hypertension and peripheral arterial disease. She

21 received only one study dose. Her post dose mean QTcF

22 increased to 413 from a baseline of 405. And the

1 investigator decided to withdraw this particular

2 patient.

3   Patient 619-23 received four days of iclaprim

4 and on the third and fourth day of treatment she had

5 elevations, from baseline, of greater than 60

6 milliseconds. At the time of the study she was 56

7 years of age, had a history of MI, cirrhosis and was on

8 an escalating dose of methadone.

9   Again, with regards to cardiac adverse events,

10 there were two patients. Patient 306-33 was found

11 unconscious. Had two preceding QTcF measurements that

12 were prolonged in post-dose measurements. But we're

13 talking about a change of 33.7 milliseconds on day one

14 and 16 milliseconds on day four.

15   Patient 306-34 also found unconscious,

16 prolonged QTcF measurements, compared to baseline of

17 7.3 milliseconds on day one and 44 milliseconds on day

18 two.

19   Moving on then to hepatic adverse events.

20 There was one patient, 455-07, how experienced a

21 serious hepatic AE, possibly related to the use of

22 iclaprim. Twenty-three year old, white male received

1 ten days of therapy with iclaprim and no other

2 concomitant medications. LFTs were normal from

3 baseline throughout EOT. And then at the test of cure,

4 13 days after his last dose of iclaprim, had an AST of

5 314, ALT of 1,007 and the bilirubin and alk. phos.

6 shown there. The abdominal ultrasound performed and

7 viral panel were negative. Laboratory values at late

8 follow up returned into the normal range. And he

9 ultimately recovered.

10   Looking at hepatic adverse events overall,

11 there were more patients treated with iclaprim who

12 experienced an elevation of ALT of greater than three

13 times the upper limit of normal, 3.9 percent versus 2.9

14 percent at test of cure and 5.3 percent versus 1.8

15 percent at follow up. Slightly more patients were

16 found to have elevations in AST of greater than three

17 times the upper limit of normal at the long term follow

18 up, 3.3 versus 2.3 percent.

19   There were no study drug discontinuations due

20 to the elevations in transaminases. There were no

21 cases that met Hy's Law. None of the deaths were

22 associated with abnormal liver function tests or

1   indications of hepatotoxicity.

2   Hematologic adverse events, anemia was

3   reported as a treatment emergent adverse event in 3.6

4   percent of patients treated iclaprim, and that's

5   comparable to the linezolid rate of 4.1 percent. There

6   were no reported hematologic AEs associated with

7   premature discontinuation. There was anemia that was

8   an AE associated with deaths in two patients, as

9   reported previously. There were no meaningful

10   differences seen between the two groups' hematologic

11   parameters, looking at either of those that are outside

12   of the normal range or looking at change in mean values

13   from baseline.

14   So the issues for discussion that we'd like

15   you to address. Did the data presented demonstrate the

16   safety and effectiveness of iclaprim at the -- for

17   treatment of complicated skin and skin structure

18   infections? And should there be any limitations for

19   the use of iclaprim?

20   In your response we'd like you to discuss the

21   following: The comparative outcomes for iclaprim and

22   linezolid from the Phase 3 trials; the specific

1 clinical situations where iclaprim should be used and

2 the basis for any specific restrictions.

3   With that I'd like to acknowledge the work of

4 the iclaprim review team which includes these

5 individuals who are members of the team and many others

6 who contribute to the development of these

7 presentations and the work on the NDAs. Thank you very

8 much.

9   BARTH RELLER: The panel will now have the

10 opportunity to have questions for and clarifications by

11 either the sponsor, Arpida AG or FDA. Dr. Bennett.

12   DR. BENNETT: I'm concerned about the margin

13 of safety when iclaprim would be used at higher doses

14 or for prolonged treatment. Though it would inevitably

15 be used in clinical practice in patients who are not

16 responding well, the dose would be increased or the

17 therapy prolonged. My concern mainly is about bone

18 marrow suppression that's been seen with all the

19 dihydrofolate reductase inhibitors.

20   And perhaps the most destructive example is

21 our use of pyrimethamine in treating toxoplasmosis

22 which is given for a duration typically of six weeks or

1 more. If used 25 milligrams you see virtually no

2 leukopenia or occasionally thrombocytopenia. But among

3 the recommended doses is 50 milligrams and with that,

4 after two weeks, seeing leukopenia is extremely common.

5   So the iclaprim study I think the duration was

6 so short and the dosage was such that even linezolid,

7 which is known to cause bone marrow suppression, was

8 not seen. I'm reminded that when linezolid came before

9 a committee of the FDA it was not appreciated that

10 linezolid actually caused bone marrow suppression,

11 although if you read the transcript, which is available

12 online, you notice that one committee member pointed

13 out that thrombocytopenia and leukopenia tended to be

14 occurring in patients who were given more prolonged

15 therapy. And now we know that that's one of the major

16 limitations of using linezolid.

17   So another concern I have is higher doses that

18 might be used in clinical practices, QT prolongation,

19 which is clearly dose related.

20   BARTH RELLER: Dr. Septimus.

21   DR. SEPTIMUS: A couple of quick questions.

22 On slide 11 of the sponsor's presentation, you looked

 1 at some killing curves and if I recall that it was sort

 2 of slower killing with the VRSA. And I was curious as

 3 to whether or not you had any H-VISAs or other

 4 vancomycin strains with MIC of two to see how it might

 5 compare on that regard.

 6   Second, is there a post antibiotic effect

 7 that's seen with this particular drug? Third, any

 8 incidents of clostridium difficle disease associated

 9 with the drug? And also sort of similar to what we see

10 with prolonged therapy with certain other drugs, are

11 the rashes that were described, were any of them severe

12 or approach either erythema multiforme (inaudible) or

13 toxic epidermal necrolysis and what's that potential?

14   BARTH RELLER: Yes, Dr. Islam.

15   KHALID ISLAM: Thank you. I will first reply

16 back to you regarding the sital action, perhaps there's

17 a little bit of confusion. The two lines that are

18 drawn in yellow and light orange both represent

19 iclaprim and they are at two different concentrations

20 with respect to DMIC. The kill rate for VRSA is

21 actually identical to this graph.

22   I will also ask Dr. Jones to perhaps go

1 through the other questions that you posed, and Dr.

2 Dankner to go through the safety.

3   MARK JONES: May I also add that perhaps the

4 panel member was referring to the blue line which is a

5 control utilizing vancomycin which demonstrates

6 typically slow sital activity over a 24 hour period.

7 Slide up, please.

8   With regards to the panel member's question

9 concerning a PAE, typically as you can see in the third

10 column, the PIE -- PAE in this case to staph aureus and

11 at the bottom to Group A streptococci is around one and

12 a half to two hours. However, I think of particular

13 interest, if you look on the far right, these are PAEs

14 when organisms have been exposed to sub MIC levels of

15 drug, much more typical of the clinical situation where

16 you see PAEs extending over three to four hours or

17 greater.

18   KHALID ISLAM: Thank you. Maybe Dr. Dankner

19 can touch the questions regarding C. difficile and

20 rash.

21   WAYNE DANKNER: So there were no cases of C.

22 diff. related disease in the safety database.

1   Additionally, we would not expect much in the way of,

2   with this particular drug, one has targeted against

3   gram-positives. It has little anaerobic coverage. And

4   the history with trimethoprim sulfur suggests it's not

5   a common drug causes C. diff. related disease.

6   In terms of the cutaneous safety, there were

7   no cases of SJS or Tens noted in the trial. They are

8   uncommon events, I'm not sure we'd expect to see one in

9   the database of that size. But I think it's important

10   to point out that the common rash that have been seen

11   with trimethoprim-sulfur are primarily due to the

12   sulfur component. And what we'll be dealing with is

13   iclaprim and the rash rate associated with trimethoprim

14   alone, based upon European data where the drug is used

15   by itself, is much lower than would be seen with TMP-

16   SMX.

17   MARK JONES: Thanks for the clarification.

18   I'll let the statisticians talk about the rest of the

19   superiority -- inferiority data.

20   BARTH RELLER: Dr. Alston.

21   KEMPER ALSTON: If you could bring up slide 66

22   of the sponsor. I was just wondering if Dr. Fowler

1 could put trimethoprim on this table. Or, how would

2 you do it?

3   (Off microphone comment)

4   VANCE FOWLER: Not generally -- not

5 specifically, no. I think in general the resistance to

6 trimethoprim sulfamethoxazole in terms of clinical

7 isolettes from U.S.A. 100 clones and U.S.A. 300 clones,

8 for example, is still relatively low. I guess that's

9 probably the extent of the -- to address that question.

10   KEMPER ALSTON: I guess trimethoprim's been

11 around for a long time and I think resistance has been

12 around for a long time. And I would just caution that

13 when we're using a modified drug with a same target, to

14 say that there's a low propensity for resistance and

15 that it's going to be quite durable, you just have to

16 be a little bit careful based on three weeks of in

17 vitro data, especially without the addition of a sulfa

18 component.

19   KHALID ISLAM: If I can just add one comment.

20 As you correctly pointed out, trimethoprim's been used

21 for about four decades plus. And in fact the

22 resistance rates in staph aureus epidemiological

 1 studies show that they're about one percent in MSSA

 2 resistance and about four to five percent in terms of

 3 MRSA, after quite a long use with trimethoprim.

 4   BARTH RELLER: Dr. Goetz.

 5   MATTHEW GOETZ: I'll just follow up on the

 6 MRSA. I think many of us observed, in the late 1980's

 7 that our MRSA -- hospital associated MRSA isolettes had

 8 much higher rates of resistance to trimethoprim

 9 sulfamethoxazole, although I acknowledge the data for

10 MSSA are largely correct.

11   But I would like to come to the data shown on

12 slide six and eight by the FDA. And maybe the sponsor

13 can comment. On the cellulitis in Group A

14 streptococcal activity of the iclaprim, the cellulitis

15 data we see, both in ASSIST-1 and ASSIST-2 -- granted,

16 this could be called again a data safari, I suppose, as

17 we commented yesterday. But the success rates in both

18 cellulitis in both studies are lesser. If I calculate

19 this right there are about 75 percent successes, if we

20 pool ASSIST-1 and ASSIST-2 for iclaprim versus 84.4

21 percent for linezolid.

22   And for the Group A streptococci shown on

1 slide eight, the numbers are relatively small, but

2 again we see that there is a lesser effect of the

3 iclaprim versus linezolid in the MITT population. Does

4 this relate in any way to the MICs of iclaprim against

5 streptococcus pyogenes or is there another perhaps

6 explanation for this observation?

7   (Off microphone comment)

8   KHALID ISLAM: I don't know if the FDA wanted

9 to comment, but we'll --

10   MATTHEW GOETZ: I'm just commenting on their

11 data.

12   KHALID ISLAM: Sure.

13   JOHN ALEXANDER: I think there is a table that

14 looks at outcomes by MIC, in the microbiology section

15 of the FDA's briefing package. I don't think that we

16 could see that there was a specific relationship

17 between the outcome by MIC for patients with S.

18 pyogenes.

19   MATTHEW GOETZ: Right. Because the concern

20 arises because the Group A streptococcus is common --

21 is perhaps a more common cause of cellulitis, raising

22 some concern about the activity of the iclaprim against

1   -- for the treatment of cellulitis.

2   BARTH RELLER: Doctor --

3   KHALID ISLAM: Can you put the slide up,

4   please?

5   BARTH RELLER: We have additional comment from

6   Dr. Islam or Dr. --

7   KHALID ISLAM: Yes. My apologies. This is

8   actually the strep pyogenes with respect to MIC data

9   and with respect to surveillance data. And I think you

10   also want to see the rates on the cellulitis patients?

11   Right, if you can give me the slide on the different

12   infection types, please. I'll come by -- I'll come by

13   strep pyogenes actually.

14   BARTH RELLER: While that slide is -- here we

15   are.

16   KHALID ISLAM: Thank you. So basically if you

17   look, and you're right, there is a slightly lower cure

18   rate for strep pyogenes that we note in the ASSIST

19   studies, with respect to linezolid. But the cure rates

20   are around 80 percent, which is quite different from

21   trimethoprim.

22   BARTH RELLER: Dr. Gutierrez.

1   KATHLEEN GUTIERREZ: My question was the same

2   as Dr. Goetz's. But I also -- I think I remember

3   reading in the sponsor's brochure that there were, you

4   know, more patients in the strep pyogenes group who had

5   gotten iclaprim who had failed. And I was wondering if

6   we could have some clarification on who the -- on what

7   the situations in those patients were. Because I too

8   am concerned about the lower cure rate.

9   And I actually have another question that sort

10   of relates to adverse effects. And there was no

11   mention of teratogenicity studies with this drug. But

12   I think I read in one of the brochures that it was

13   going to possibly be classified as a Category C. And I

14   just wondered what the data was on the teratogenicity.

15   KHALID ISLAM: Your first question was

16   regarding the lower cure rates. Yes, as I just pointed

17   out there is a lower cure rate with strep pyogenes, for

18   iclaprim with respect to linezolid. Could you put the

19   slide up, please. Thank you.

20   And these are actually, if you look at the

21   numbers, in ulcers, burns, abscesses and cellulitis,

22   cellulitis has the highest numbers of strep pyogenes

1 isolated baseline. You can see that there is a

2 difference from 74 percent to 86 percent. In the other

3 infection types the numbers are rather small, so you

4 can't really look at much more than that. But there is

5 a slightly lower cure rate that we could see in

6 cellulitis.

7   It's also important to just point out that

8 strep pyogenes was found in a number of infection

9 types. It was not just in cellulitis.

10   And the second question is related to adverse

11 rates and teratogenicity. So the adverse rates with

12 respect to the comparator adverse rates in general.

13   KATHLEEN GUTIERREZ: The question was about

14 any teratogenicity studies in animal models when --

15   KHALID ISLAM: Right. I was trying to see if

16 my colleagues could find the data.

17   KATHLEEN GUTIERREZ: Okay, thank you.

18   BARTH RELLER: We'll come back to that point.

19 Meanwhile, Dr. Leggett.

20   JAMES LEGGETT: Two questions. Slide 39 you

21 attempted to address Dr. Fleming's question with the

22 removal of the abscesses. You looked at the ITT

1   population? Did you also look at the protocol

2   population and was that about the same or do you have a

3   slide to show us, is the first question.

4   KHALID ISLAM: I'm sorry, I couldn't hear

5   property. The ITT population with respect to --

6   JAMES LEGGETT: Yes, CC-39 looks at the ITT.

7   What about the PP?

8   KHALID ISLAM: Could you put me CC-39, please.

9   Okay, the slide up please. Okay, this is what you're

10 referring to, this refers to the ITT population, you'd

11 like to see the same result on the PP population. Can

12 you locate me this PP population on the -- slide up,

13 please.

14   So this is actually looking at the PP

15 population with respect to the ITT.

16   JAMES LEGGETT: And my second question is to

17 the FDA. In the brochure we were given, in tables 6-4

18 and 6-5, you discussed North American versus the rest

19 of the world, Eastern Europe, those kind of things.

20 And then you made, in the presentation today, some

21 comments about differences between ASSIST-1 and ASSIST-

22 2. And we know that there are different population

1   flavors to those mixtures. Would you care to comment?

2   Or can you comment at all?

3   I guess my question being can some of the

4   differences not be attributed to those center's

5   evaluations? I was struck by, for instance, 100

6   percent cure rates. That always gets my attention.

7   JOHN ALEXANDER: That was part of the issue

8   with looking at the results that we were seeing by

9   trial, is that we did see some sites, particularly

10   European sites, I think, in the linezolid group where

11   you did have what were reported as fairly high cure

12   rates. And that does lead to some of the issues with

13   sort of trying to interpret the overall results of the

14   trial.

15   Because if you have really higher cure rates,

16   and the statisticians I think can comment on this, then

17   that does affect what you see in terms of the bounds

18   around the non-inferiority margins. But I can't really

19   give you a good explanation of why people following

20   sort of the same protocol have what appear to be much

21   different cure rates for linezolid, and much higher

22   cure rates.

 1   BARTH RELLER: Yes, Dr. Valappil.

 2   THAMBAN VALAPPIL: Thank you, Dr. Reller.

 3   That also point to the fact that there is lack of

 4   internal consistency in the treatment effect

 5   across regions. If I may, just a couple of other

 6   issues if -- is that okay?

 7   BARTH RELLER: Please.

 8   THAMBAN VALAPPIL: This is on a slightly

 9   different topic on the non-inferiority margin evidence

10   presented by Dr. Wei. If I could bring the slide

11   number 56, please. 56, from Dr. Wei's presentation.

12   KHALID ISLAM: Slide up, please.

13   THAMBAN VALAPPIL: And the concern here is

14   that three out of the four trials listed here are open

15   label studies with the potential to introduce bias and

16   uncertainties in the treatment effect. Only two studies

17   actually compared to vancomycin. For example, the Weigelt

18   study and the Stevens study. Wilcox study was compared to

19   teicoplanin and the second Jauregui was dalbavancin

20   versus linezolid comparison. So there are concerns on

21   the control effect of linezolid.

22   If you could go to the next slide, please, 57.

1   KHALID ISLAM: 57, please.

2   THAMBAN VALAPPIL: 58, I'm sorry. Slide 58,

3 please. Thank you. As you can see in this slide, you

4 can see the wide confidence intervals around these

5 estimates for most of the studies and it includes the

6 odds ratio one. Of course, it's partly due to the small

7 sample size. And so in a sense I think there's a lot

8 of uncertainty in these estimates.

9   BARTH RELLER: Thank you. Dr. Nelson.

10   LEWIS NELSON: Thanks. I have a couple of

11 questions. I'm not sure how many, I guess we'll find

12 out as I keep talking. But not surprising to

13 everything, I have to ask a QT question. And actually

14 it might relate back to a question -- and actually all

15 of these questions might relate back to a question

16 about metabolites. In the briefing document it talks

17 about there being upwards of 20 metabolites. And I

18 don't know if you have any information on the

19 metabolites, because certainly historically metabolites

20 have been a cause for concern, both in terms of QT and

21 in terms of hepatotoxicity and potentially in terms of,

22 you know, other problems we're not even discussing

1 here.

2   So because the QT prolongation on day four, on

3 slide 52 percentage-wise, and on slide 51 in terms of

4 absolute measurement in the mean change using the

5 Fridericia formula, because it's delayed and increased

6 over time and the person hasn't changed, presumably,

7 very much during that time, could this be a factor

8 related to a metabolite that's cardio toxic? And could

9 the delayed onset of hepatotoxicity, the rise in LFTs

10 up to above three times the upper limit of normal, but

11 also related to a metabolite? What is known about

12 those?

13   KHALID ISLAM: Would you give me the slide

14 with the formal ECG study, please. And I'll come back

15 to the question. From the colored slides, please.

16 Slide up, please. So first I'd just like to quickly

17 point out we did a formal ECG study. And this actually

18 shows you the change and the time of the change. The

19 time of the actual maximal QT change is actually the

20 time of the end of infusion. So this is the peak value

21 that we can capture. It rapidly goes down thereafter.

22   And we have done this at different dose

 1   levels, going upwards from therapeutic dose. And in

 2   fact, as Dr. Alexander commented, we did a dose

 3   dependent study.

 4   Also, I'd just like to correct one thing that

 5   Dr. Alexander said earlier. I think there was a little

 6   bit of confusion between whether we gave the formal ECG

 7   studies to the USFDA, to the agency or not. In fact we

 8   had set up on the ASSIST program two stages, stage one

 9   and stage two. So maybe there was a little bit of

10   confusion we'd just like to correct.

11   Stage A looked at excluding patients for

12   enrollment who had a baseline QT of greater than 470

13   milliseconds. And we had arranged that the DMC look at

14   the first 200 patients after which the DMC could decide

15   to recommend to the company whether the exclusion

16   criteria needed to be kept or needed to be removed.

17   The DMC did look at the first 200 patients in the

18   ASSIST program and actually opined that there was no

19   requirement for the baseline inclusion criteria. So

20   that baseline inclusion criteria was -- exclusion

21   criteria was actually excluded. So that was just a

22   small correction so that it's clear.

1   In terms of the curity of facts, I think the

2   FDA presented the slide showing that it was dose

3   dependent and showed what the levels were at .8 and 1.6

4   milligram per kilogram. So when we look at the QT

5   effect and after (inaudible) we have not seen

6   accumulation effect. You referred to the changes that

7   we saw on day one and on day four. Indeed we see more

8   changes, both as QTcB and QTcF in terms of over 30

9   milliseconds. We do not see more changes with respect

10   to over 60 milliseconds, nor do we see differences

11   between the two treatment groups in the number of

12   patients that go over 500 milliseconds and those that

13   show over 500 milliseconds at over 60 milliseconds.

14   So coming back to your question about

15   metabolites, based on the type of profile that you're

16   seeing, we don't think that the metabolites would be

17   actually implicated in a QT effect. And the changes

18   that you're seeing are not accumulative changes.

19   If you can take me back to the course slide

20   that we were just looking at. Thank you. So when you

21   look at the changes you can see, for example, on day

22   four also for linezolid, the actual QT change is about

1   six milliseconds. So, you know, if you take -- if you

2   realize that linezolid is not a QT prolonging drug, or

3   at least not labeled as such, you can see that those

4   changes are actually very coherent and consistent

5   between day one and day four.

6   LEWIS NELSON: Yeah, so if I could just follow

7   this up. I mean I can't disagree with that. I'm still

8   troubled by the degree and the number -- the degree of

9   elevation prolongation and the number of patients. And

10 again with hepatotoxicity and with QT prolongation

11 there is presumably, as it appears to be, a uniquely

12 susceptible population which you're not going to find

13 with 500 patients or even 1,000 patients in many cases.

14 So this is something that just concerns me because we

15 all, you know, historically overlook this time and time

16 again only to later on come back and say, how could we

17 have overlooked this, when the signal is here

18 potentially.

19   And just one other issue that could equally as

20 well be overlooked, is the fact -- it says in the

21 briefly documents at least that 3A4 is inhibited by

22 this drug. And that wasn't really touched upon.

1 Admittedly it has multiple metabolic pathways so other

2 drugs may not inhibit its metabolism very easily. But

3 its ability to inhibit other drug's metabolism, and

4 since most of these patients are probably going to get

5 multiple medications, something that we have to be very

6 careful of as we move forward is to look and warn

7 against potential drug interactions.

8   And I don't know if you've studied this or if

9 there's any more data.

10   KHALID ISLAM: We have not done a drug/drug

11 interaction study. And I think the FDA briefing did

12 point that out. We have not done a drug/drug

13 interaction study with iclaprim as an inhibitor and

14 looking at the metabolism for a substrate of

15 (inaudible). We have though done the studies looking

16 at ketoconazole and omeprazole as to SIP inhibitors and

17 looking at the affect on the pharmokinetics and those

18 do not really change.

19   I'm just wondering if Dr. Peter Kowey might

20 want to make some comment regarding the QT aspects of

21 this drug. And perhaps also regarding the liver and

22 LTST elevations. Perhaps I'll turn to Dr. Lewis.