Trends-in-Medicine

December 2008

by Lynne Peterson

SUMMARY

♦ The FDA plans to issue new guidance for development of anti-infective drugs for cSSSI and uSSSI, based on the guidance of a recently convened Advisory Committee. It is likely that guidance will better define what types of infections should be included, set a 10% non-inferiority margin standard, and more.

♦ An FDA Advisory Committee recommended approval of Theravance/ Astellas' telavancin for cSSSI, but most members believe it should have a Pregnancy Category X warning.

♦ The panel recommended against two other anti-infectives – Targanta's Nuvocid (oritavancin) and Arpida's iclaprim – saying they are promising but just haven't shown sufficient efficacy, especially against MRSA. The panel recommended each company do another trial. Targanta is continuing with its drug, but iclaprim's future is uncertain.

Trends-in-Medicine
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FDA TO CLARIFY REGULATIONS FOR ANTI-INFECTIVE DRUG DEVELOPMENT

Advisory Panel Recommends Approval of One New Agent, Turns Down Two Others

College Park, MD
November 18-20, 2008

On Tuesday, November 18, 2008, the FDA's Anti-Infective Drugs Advisory Committee met to discuss non-inferiority margins for anti-infective drugs to treat complicated skin and skin structure infections (cSSSI), such as infected ulcers, burns, and major abscesses and infections of deeper soft tissues. Then, over the next two days the panel considered applications for three new anti-infective drugs to treat Gram-positive infections, recommending approval of one and turning down the other two.

- **THERAVANCE/ASTELLAS' telavancin** – powder for reconstitution (10 mg/kg) and IV administration Q24H for 7-14 days for the treatment of complicated skin and skin structure infection. **Thumbs up.** The panel voted 21 to 5 that the data demonstrate the safety and effectiveness of telavancin. They determined that telavancin is at least equivalent to vancomycin in efficacy, but they had serious concerns about renal safety and birth defects. Panel members generally recommended a strong risk management program and a Pregnancy Category X classification. No FDA decision (PDUFA) date has been set.

- **TARGANTA THERAPEUTICS' Nuvocid (oritavancin)** – 200 mg QD (300 mg QD for patients weighing >110 kg) daily for 3 to 7 days for the treatment of complicated skin and skin structure infection. **Thumbs down.** The panel voted 10 to 8 that the data were insufficient on efficacy, particularly against methicillin-resistant *Staphylococcus aureus* (MRSA), though the drug was generally viewed as safe. The panel suggested that one additional trial would be sufficient. The FDA PDUFA date is December 8, 2008.

- **ARPIDA's iclaprim** – ampoules of concentrated solution that are diluted to a dose of 0.8 mg/kg infused over 30-45 minutes BID for 8-14 days. **Thumbs down.** The panel voted 17 to 2 that the Phase III trials failed to show safety and efficacy for iclaprim. Should the FDA decide to approve iclaprim, the panel voted overwhelmingly that use be restricted to patients refractory to or unable to take other approved antibiotics. The panel suggested another trial be done before approval – this time using the FDA-recommended non-inferiority margin of 10% and vancomycin as the comparator. The FDA PDUFA date is January 16, 2009.

The panel's message to industry was clear: Despite an urgent need for new antimicrobials for cSSSI or uncomplicated SSSI (uSSSI), a sponsor has to show clear and convincing efficacy for its agent, and that must include efficacy against MRSA. The panel was not inclined to let companies cut any corners. Once efficacy is shown, safety will dictate labeling and use.

The panel's overall message to the FDA also was clear: Industry needs to have the rules – the regulatory requirements – clarified or new drugs will not be developed, and new drugs are definitely needed. The advisory committee offered the FDA this guidance in drafting those rules:

- Non-inferiority trials are appropriate in cSSSI, but they should focus on cellulitis and wound infections.
- A non-inferiority (NI) margin of 10% is acceptable.
- cSSSI trials should have a clearly understood clinical endpoint that is measured at two time periods – at 2 days and again at the end of treatment (7-14 days).
- Major abscesses should be studied separately, not included in a cSSSI trial with cellulitis, wound infections, and erysipelas (an acute streptococcus bacterial skin infection). Likewise, diabetic foot infections should be studied in separate, placebo-controlled, superiority trials.
- uSSSI studies should include impetigo, erysipelas, folliculitis, furuncles, etc., but probably not abscesses, which should be studied separately in a superiority trial.

FDA officials indicated they got the message, and new guidance will be issued. Dr. Edward Cox, director of the FDA's Office of Antimicrobial Products in the Center for Drug Evaluation and Research (CDER), said, "What we heard helped us to get a better understanding of the committee's advice on the treatment effect in skin infections…They voted pretty clearly – 20 to 0 – in favor of using a non-inferiority margin, and they defined some types of infections to include. They also gave advice on uncomplicated skin infections, where they defined patients with less deep infections and without systemic symptoms, voting in favor of superiority studies. That was helpful advice."

Dr. Cox said the FDA guidance is likely to be updated after this panel meeting, "That is interesting…It gets to the point of understanding what the margin is or the treatment effect is in the study. You need to understand who is in your trial. It is something that bears further looking into in how that might be utilized. Depending on who is enrolled, your study may affect your treatment effect – the idea that it is the endpoint and the clinical setting that will impact on treatment effect…The (panel) advice is something that is helpful, and we can go back and look at our guidance documents and the information that we give…I do expect we can use this (information from the panel) to update our guidance documents."

Asked how the panel's recommendations will change what the FDA is doing, Dr. Cox said, "This is not so much a change as defining the reasons behind what we are doing. We had never spent the time to (explain) what the (FDA) recommendations were based on. This was more a definition, a background behind what we are doing…We heard from the committee that (we need to) clarify our definitions of what is complicated SSSI and what is uncomplicated SSSI…(Our) older guidance document was based in part on anatomic consideration and the need for surgical intervention. The committee helped to put in focus the severity of disease as being an important distinguishing factor."

Will there be a major shift in sponsor requirements if the FDA takes the panel's advice? Dr. Cox said, no, "The requirements are the same…It is more the (definitions and explanations)."

Asked how the FDA views the panel's advice on major abscesses, Dr. Cox said, "We were advised to look at that further, look at the definition and get a better understanding of what the treatment effect might be in that patient population. More work is probably needed to understand the treatment effect in that group."

Asked if the panel was recommending that major abscesses be taken out of cSSSI, Dr. Cox indicated that was the message. Dr. Wiley Chambers, deputy director of the FDA's Division of Anti-Infective and Ophthalmology Products, CDER, added, "What I heard was go back to studies of abscesses and look at the definitions in those studies. Where an effect was not demonstrated, there is no reason to include them in the NI studies, and they should be in a superiority study (instead)."

Currently Approved Treatments for cSSSI

Company	Brand name	Generic name	FDA review date	Non-inferiority margin
Wyeth	Tygacil	Tigecycline	2005	15%
AstraZeneca	Merrem	Meropenem	2005	10%
Cubist Pharmaceuticals	Cubicin	Daptomycin	2002	10%
Merck	Invanz	Ertepenem	2001	10%
Johnson & Johnson/Ortho-McNeil	Levaquin	Levofloxacin	2000	15% (inferred from results)
Pfizer	Zyvox	Linezolid	2000	10%
King Pharmaceuticals	Synercid	Quinupristin/dalfopristin	1998	10% (cure rates >90%) 15% (cure rates 80% to <90%) 20% (cure rates <80%)

NON-INFERIORITY (NI) MARGINS

Before considering any of the three drug applications, the panel met for a full day to talk about the design of trials for anti-infectives. The panel heard from FDA staff, officials of the three companies whose drugs they were going to consider later, and one public witness. Then they debated the issue among themselves.

The FDA believe there is "an urgent need to re-invigorate antimicrobial development" and developing non-inferiority margins for cSSSI trials may help with that. Clarification of NI margins is considered by industry to be critical to enable continued antimicrobial development.

Over the last several decades, rising antimicrobial resistance has created a critical need for new antimicrobial agents. While resistance decreases the efficacy of available agents, it also increases the difficulty of superiority testing of new antimicrobial agents because patients infected with bacteria resistant to the approved comparator drug used in a clinical trial are excluded from enrollment in that trial. These excluded patients are the very patients for whom a new antimicrobial agent is likely to be superior to the approved comparator drug, so antimicrobial clinical trials are inherently biased against finding superiority of the new agent. Thus, non-inferiority trials have become the standard method by which investigational antimicrobial agents are tested for efficacy.

Critical to the design of an NI trial is the selection of the acceptable NI margin of efficacy. For example, a 10% margin of NI means that the investigational drug will be considered non-inferior if it is no worse than 10% less efficacious than the standard comparator drug – most often vancomycin or linezolid. In general, the wider the NI margin, the smaller the required patient sample size to demonstrate NI, but the less precise the estimate of relative efficacy. Therefore, selecting an appropriate margin of NI requires a balance between the practicality of conducting the study and the need for clinicians and the FDA to ensure that the new drug is not unacceptably worse than the comparator drug.

The four key issues the FDA wanted the panel to discuss were:

1. Acceptability of non-inferiority trials.
2. Appropriate margins and endpoints.
3. Timing of assessments.
4. Infection type for inclusion in new trials.

BACKGROUND INFORMATION ON NON-INFERIORITY MARGINS

In briefing documents prepared for the panel, the FDA laid out the history of the problem very nicely. Historically, the majority of skin infections were caused by Gram-positive organisms such as *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus agalactiae*, and that remains true today. All recent pivotal trials for the indication of cSSSI have been non-inferiority trials with a non-inferiority margin of 10%-15%. Treatment guidelines recommend antibacterial agents for the treatment of skin and soft-tissue infections, with the choice of antibacterials based on the nature and severity of infection and susceptibility patterns.

However, there are differences in the microbiological characteristics of organisms when comparing studies from the earlier part of the 20th century to the present, especially with regard to antimicrobial susceptibility. There has been an increasing prevalence of MRSA, especially community-acquired MRSA in skin and soft-tissue infections in recent years. While patients today tend to have more comorbidities, they also generally get better ancillary and supportive care.

A variety of trial approaches have been used to determine efficacy in the treatment of cSSSI.

- There are no **placebo-controlled trials** in cSSSI.
- Two **studies** have been done comparing sulfonamides to ultraviolet (UV) light. Those studies and a meta-analysis of those studies found a statistically significant advantage to sulfonamides. The treatment effect of sulfonamides in the treatment of erysipelas over UV light at 48 hours for cessation of lesion spread was 24.1% and for resolution of pyrexia was 27.8%. However, there was a treatment effect for UV light over other local therapies, so the effect of sulfonamides over placebo is likely to be higher.
- Several other **historical studies** of topical therapies vs. UV light have been conducted. Most showed that UV light had better outcomes, but placebo cure rate estimated from UV light treatment is believed to be an overestimate of the true placebo effect.
- **Natural history studies** are not directly relevant to or reflective of present day clinical trials, but they do indicate that antibacterial therapy, primarily sulfonamides or penicillins, has a "remarkable effect" on the resolution of signs and symptoms of skin infections.
- Several studies have evaluated **other antibacterials**.
- **Dose-ranging studies** in cSSSI did not yield reliable estimates of placebo-cure rates.

Efficacy in Recent Clinical Trials

Drug (Study)	Comparator	Drug efficacy	Comparator efficacy
Tigecycline (Study 300)	Vancomycin + aztreonam	73.6%	75.4%
Tigecycline (Study 305)	Vancomycin + aztreonam	84.0%	86.7%
Daptomycin (Study 9801)	Vancomycin or semi-synthetic penicillin (SSP)	62.5%	60.9%
Daptomycin (Study 9901)	Vancomycin or SSP	80.4%	80.5%
Linezolid (Study 55)	SSP	65.5%	65.4%
Meropenem (Study 35911L/009)	Imipenem / cilastatin	57.8%	60.9%
Moxifloxacin (Study 100273)	Piperacillin / taxobactam	54.2%	57.3%
Moxifloxacin (Study 100279)	Amoxicillin / clavulanate	72.6%	74.8%

- **Uncontrolled studies** of surgical infections looked at skin and soft-tissue infections treated with penicillins or sulfonamides. The results indicate that patients treated with antibacterials appear to have a quicker resolution of pus and a faster return to normal function.
- **Prophylactic administration** of antimicrobial therapy reduces some infections, but the magnitude of the treatment effect has not been able to be quantified.
- **Contemporary cSSSI trials** generally have entry criteria involving deeper soft tissue or requiring surgical intervention. Severity is often defined based on the presence of fever, purulent drainage, localized warmth, tenderness, elevated white blood cell count, etc. Patients in these studies often have comorbidities, such as diabetes or peripheral vascular disease. Most studies have been done with parenteral antibacterial therapy in an inpatient setting, though some have involved outpatients. All recent registration trials have had a non-inferiority design, with a margin of 10%-15%. The active comparators have included vancomycin, linezolid, and semi-synthetic penicillins (SSPs).

One of the strategies employed in choosing a treatment effect (M1) for an NI trial is through "discounting" or reducing the effect of the active control to account for uncertainties. An M1 of antibacterial drugs in cSSSI of 18% should be considered.

A 10% NI margin can be justified for a clinical response endpoint in cSSSI trials, provided appropriate patient populations are enrolled and appropriate endpoints are evaluated. It will also be important that confounders such as surgical interventions be minimized and balanced across treatment arms.

However, in a uSSSI study, there are more uncertainties in the treatment effect especially if patients with infections such as minor skin abscesses, folliculitis, and furunculosis are enrolled. Thus, it is important to enroll patients in an uSSSI study with conditions such as erysipelas or impetigo and to exclude patients with minor skin abscesses where there is no demonstrable treatment effect for antibacterials beyond that achieved by the incision and drainage procedure alone.

In October 2007, the FDA issued draft guidance on non-inferiority in antimicrobial clinical trials. However, the guidance did not explicitly describe how the effect size of a standard comparator should be determined, particularly for diseases lacking placebo-controlled trials. Selection of an appropriate NI margin is problematic for clinical trials in cSSSI because antimicrobials became available before randomized, placebo-controlled trials were conducted. Complicated SSSI are very common in the U.S. and throughout the world, and the spread of community-acquired MRSA has made it increasingly difficult to treat cSSSI with currently available antimicrobials, providing a major impetus to develop new antimicrobial agents for these infections.

A comprehensive review of the historical literature of cSSSI, found penicillin (PCN) more efficacious than sulfonamides, making PCN the "clear gold-standard antimicrobial agent." Preservation of 50% of the "gold-standard" comparator (PCN) is considered reasonable, and the FDA found the lower limit of efficacy of PCN vs. no antimicrobial treatment was 28%. Thus, the NI margin should be:

- 14% for cellulitis/erysipelas.
- 21% for wound/ulcer infections.
- 7% for major abscess.

In practice, cSSSI studies typically enroll mixtures of these patient populations, so the NI margin for a specific cSSSI trial should be weighted for the proportion of enrolled patients with cellulitis/erysipelas, wound or ulcer infections, and abscesses. The FDA wrote in the draft guidance: "We considered our suggestion to preserve 50% of the 'gold-standard' comparator's efficacy to be conservative…A case for preserving a smaller amount of the 'gold-standard' comparator's clinical cure efficacy, resulting in wider NI margins, could be made for individual studies, especially if the new agent offered other clinical benefits, such as enhanced activity against antimicrobial-resistant bacteria, enhanced safety profile, etc., compared to currently available agents."

FDA Presentation to the Advisory Committee on NI Margins

In opening remarks Dr. Katherine Laessig, deputy director of the FDA's Division of Anti-Infective and Ophthalmology Products, CDER, noted that the panel has three days of detailed discussions ahead, comparing it to a marathon and suggesting it be broken down into smaller parts to make it less daunting, "The goal today is to establish a treatment effect (M1) for anti-infective drugs for the skin…and deriving an NI margin (M2), based on acceptable loss of efficacy…as well as a discussion of trial design elements."

Among the introductory points she made were:

- uSSSI are simple abscesses, impetiginous lesions, furuncles, and cellulitis.
- cSSSI are infection ulcers, burns, major abscesses, and infections of deeper soft tissues.
- The majority of SSSI are caused by Gram-positive organisms, but some are associated with Gram-negative organisms and anaerobes.
- MRSA has been isolated from 59% of adults presenting to emergency rooms in 11 U.S. cities. 85% of invasive MRSA infections are healthcare-associated and 14% community-associated.
- The FDA is interested in adequate and well-controlled studies, but many anti-infective agent trials do not include a placebo control (only an active control), so the treatment effect compared to placebo is needed.

Thamban Valappil PhD, statistical team leader in the FDA's Division of Biometrics IV, Office of Biostatistics, CDER, laid out the issues and considerations relating to non-inferiority margins for cSSSI studies. He noted that superiority trials provide direct evidence of a treatment effect, but non-inferiority trials provide indirect evidence of a treatment effect. Statistical uncertainties in non-inferiority studies include:

- Lack of reliability, uncertainty in magnitude, and lack of precision of the active control treatment effect.
- Validity of constancy assumption that the active control effect in the NI trial and historical studies is similar.
- Poor trial design and conduct.
- Non-compliance, misclassification of outcomes, and missing values.
- Confounding factors, such as use of concomitant medications or adjunctive therapies.

Dr. Sumati Nambiar, deputy director for safety in the FDA's Division of Anti-Infective and Ophthalmology Products, CDER, offered a history of the regulatory background on non-inferiority margins. She noted that in contemporary cSSSI trials:

- Disease definition includes infections involving soft tissue or requiring significant surgical intervention, such as infected ulcers, burns, and major abscesses, but excludes necrotizing fasciitis, secondarily infected dermatoses, and infections involving prosthetic materials.
- Active comparators have been vancomycin, linezolid, semi-synthetic penicillins, imipenem, piperacillin-taxobactam, amoxicillin/clavulanate
- Surgical interventions and local therapies allowed in the protocols have varied across studies.
- Treatment duration has been 7-14 days.
- Primary endpoint: clinical response of cure or failure based on resolution or improvement of signs and symptoms and the need for further antibacterial therapy as assessed by the investigator.
- Timing of assessment has been 7-14 days after end of therapy.

Dr. Nambiar cited a number of uncertainties in the estimate of treatment effect (M1):

- **Endpoints** have varied.
  - In erysipelas studies, treatment effect was assessed at 48 hours.
  - In impetigo studies, it was assessed at the end of therapy (7-9 days after start of therapy).
  - In patients with hand infections, by 1 week most penicillin-treated patients were cured, while the control group remained symptomatic much longer.
- **Patient populations** are different in contemporary trials – with more comorbidities but better ancillary care.
- **Treatment effect** could be either underestimated or overestimated.
  - The effect is likely to be higher with present-day antibacterials. The treatment effect of sulfonamides over placebo could be greater than that seen over UV light.
  - Improved supportive and wound care can make the treatment effect with antibacterials difficult to discern.
- **Case definition** varies because cSSSI is a spectrum of diseases, not one clinical condition. Cure rates, for example, are higher in cellulitis and lower in those with wound infections or ulcers.

Dr. Nambiar concluded:

- In erysipelas, there is a treatment effect for the clinical endpoints of cessation of spread of lesion and resolution of fever assessed at 48 hours.
- In impetigo, there is a treatment effect for the clinical endpoint of cure based on resolution/improvement in signs and symptoms at the end of therapy (7-9 days after starting therapy).
- In superficial skin abscesses, there is no treatment effect with antibacterials beyond that achieved with incision and drainage alone.
- Natural history studies and case series provide supportive evidence for antibacterial treatment effect in cSSSI.

However, Dr. Nambiar also posed three questions for the panel to consider:

1. Can we assume that the treatment effect of cSSSI is at least as large as seen in erysipelas/uSSSI studies?
2. Can we conclude that the historical treatment effect (M1) of antibacterial drugs in cSSSI is quantifiable based on the historical data presented, given its limitations?
3. If the treatment effect is quantifiable, how much of it should be discounted and how much should be preserved?

Panel questions for the FDA on NI margins

The panel had a number of mostly technical questions for the FDA presenters. Thomas Fleming PhD, a biostatistician from the University of Washington, pointed out that a non-inferiority margin depends on: the endpoint, the timing of the endpoint, and the patient population studied. He noted, for instance, that cellulitis might be either complicated or uncomplicated SSSI.

Dr. John Rex, infection clinical vice president at AstraZeneca and the industry representative on the panel, argued that time is incorporated in every study, "You don't see a patient on

Day 1 and not see her for 2 weeks. And the patient is only in the study as long as she is improving; if the patient doesn't respond, she is out of the study. So, we do wash people out early. You can't succeed on Day 2, but you can be a failure." Dr. Fleming argued with this, saying it would change the endpoint.

Industry Perspective on NI Margins

All three companies – Targanta, Theravance, and Arpida – addressed the advisory committee on the general topic of NI margins.

Theravance's presentation on NI margins

Alan Hopkins PhD of Theravance made several points in addressing the advisory committee, including:

- The vancomycin cure rates from the telavancin studies: 74.8% in Study 0017, 75.7% in Study 0018, 75.3% in the pooled analysis, and 75.6% in a meta-analysis.
- The placebo cure rates for uSSSI (impetigo) in randomized clinical trials has been shown by meta-analysis to be 35.7%.
- The estimated difference between the placebo cure rate and the vancomycin cure rate is 39.9%, so a conservative estimate of the vancomycin advantage over placebo is 32.8%.
- 10% is a conservative prospective NI margin for cSSSI and preserves >50% of the active treatment effect.

Dr. G. Ralph Corey, Duke Clinical Research Institute, emphasized how modern antibiotics have changed the treatment and outcome of cSSSI, which in the pre-antibiotic era often meant serious local damage and death. But *S. aureus* cSSSI remains "a daily and deadly adversary…Our patients need options and antibiotics are essential and provide a large benefit…Are non-inferiority trials acceptable in patients with cSSSI? Absolutely. Is a 10% margin acceptable? Yes."

Targanta's presentation on NI margins

In briefing documents, Targanta Therapeutics explained to panel members why it chose specific non-inferiority margins for its two Phase III studies of oritavancin. The company insisted that the NI margins it used were "clinically relevant and statistically sound and robust."

Targanta argued that the severity of illness – such as severity and complications – plays a role in the selection of an acceptable NI margin in cSSSI studies. The company explained how a variety of patient population characteristics were used in its studies as indicators of cSSSI disease severity.

An FDA guidance document in 1998 suggested that for any product with an expected cure rate between 80%-90%, a 15% NI margin was an appropriate choice. Additionally, NI margins of 20% or 10% would be appropriate for products with cure rates <80% or >90%, respectively. In line with this, a Phase II/III study (ARRD) initiated in 1999 and completed in 2001 found that oritavancin met the primary endpoint of non-inferiority (a 15% NI margin) to vancomycin/cephalexin.

However, Targanta chose a different NI for its next Phase III trial (ARRI). In 2001 – after the ARRD trial was completed but before the ARRI trial began – the FDA proposed that sponsors change how they selected an NI, recommending they choose an NI based on clinical and statistical rationale in accordance with the ICH Guidance Documents E9 and E10.

With this in mind, Targanta started the ARRI trial in June 2001 and completed it in November 2002, using an NI margin of 10%. The trial met the primary endpoint: NI ≤10%.

Targanta argued that its 10% NI choice in ARRI was appropriate under ICH guidance because:

- Study **design** characteristics – ARRI adhered closely to historical studies and was in line with the design of other approved antimicrobials, such as daptomycin.
  - Vancomycin/cephalexin was chosen as the comparator because it has a proven track record from clinical studies and in clinical practice, it is highly effective, and it has a sufficient sensitivity-to-drug effect.
  - The patients enrolled in this ARRI trial were well-defined, exhibited a range of severity, had substantial morbidity, and were reflective of the severity of patients in earlier vancomycin studies.
- Defining an acceptable **non-inferiority margin** – the 10% NI choice was based on acceptable clinical ***and*** statistical criteria. Targanta also pointed out that efficacy is "not the exclusive consideration when evaluating benefit:risk. A larger NI margin may be considered ***clinically*** acceptable if a new therapy provides advantages of safety and/or tolerability over existing therapies." Vancomycin is associated with several adverse events, including nephrotoxicity, and Targanta claims oritavancin may be an effective ***and safe*** alternative to vancomycin.
- Study **oversight** – the study closely adhered to relevant historical studies and was high quality, utilizing both randomization and double-blinding.

Results of Oritavancin Studies

Measurement	Results
ARRD (NI ≤15%)	
Patients enrolled	417
Evaluable patients	384 (74%)
Clinical response rate	75.6% 1.5 mg/kg oritavancin 75.6% 3.0 mg/kg oritavancin 80.2% vancomycin/cephalexin
ARRI (NI ≤10%)	
Patients enrolled	1,246
Evaluable patients	1,000
Cure rate	78.6% oritavancin 72.6% vancomycin/cephalexin

- Historical evidence of **sensitivity-to-drug effect** – vancomycin produced an effect superior to that of placebo. From the literature, it is unlikely the placebo response would be >35%.

In Targanta's formal presentation to the panel, Dr. Alan Forrest, senior scientist, pharmacometrics, Ordway Research Institute, and a consultant to Targanta, reviewed the oritavancin Phase III trial design and non-inferiority results and a rather lengthy review of how the company chose the non-inferiority margins for those trials.

He also emphasized, "The literature suggests a placebo response rate of no more than 20%-50% in severe cSSSI infections, including cellulitis, wound, and abscess. A typical vancomycin response rate of ~80% is a very conservative estimate. In pharmacodynamic studies in evaluable patients, the upper asymptote is 90%-100%."

Dr. Forrest concluded that both trials "adhered to the major NI margin considerations as well as the contemporary regulatory guidance principles and good clinical practice standards. The NI margins…are clinically relevant and statistically sound… The oritavancin cSSSI population was inclusive of patients with severe infections that were complicated by substantial underlying comorbidities…An NI margin of 15% is very conservative."

Arpida presentation on NI margins

Khalid Islam PhD, former Arpida CEO, pointed out that Arpida used linezolid as a comparator in its trials of iclaprim instead of vancomycin, which the other companies (before the panel) used in their trials.

Charles Davis PhD, a statistical consultant to Arpida, noted that the NI margin is generally identified based on past experience in placebo-controlled trials of adequate design under conditions similar to those planned for a new trial – and the lack of an ability to do that with anti-infectives is the problem in front of the panel.

He emphasized that Arpida followed the ICH E9 and E10 guidelines in selecting its NI margin, with the recognition that an NI of 10%-15% has been used in other registration trials. Linezolid was chosen as the comparator because it "was thought to be the superior comparator…Although difficult to quantify, the placebo cure rate in cSSSI is likely less than 50%. The linezolid cure rate is at least 75%...In a recent meta-analysis published in ***The Lancet***, the pooled cure rate for linezolid was 90.3%."

Is there evidence to support a different NI margin if linezolid is the comparator? Dr. Davis said:

- Vancomycin is an appropriate choice for MRSA infections. However, for the treatment of infections due to methicillin-sensitive *Staphylococcus aureus* (MSSA), semi-synthetic penicillins are superior compared to vancomycin.
- Linezolid is approved for infections caused by MRSA, MSSA, and streptococci.
- In randomized trials in cSSSI, linezolid was shown more efficacious than teicoplanin by 4%, dalbavancin by 6%, semi-synthetic penicillins by 4%.

Dr. Davis concluded:

- An NI margin of at least 12.5% is reasonable, especially in populations with significant MRSA.
- A larger NI margin is reasonable when choosing linezolid, rather than vancomycin, as the active control.

J.J. Wei PhD, biostatistician from Harvard, offered a proposal for future NI trials in cSSSI. He said Harvard started a quantitative science in pharmaceutical medicine program two years ago. The intent was a dialog between FDA, industry, and academia on how to speed up approval of safe drugs. Dr. Wei recommended using the contrast between placebo and the active control to set the NI margin. Then, use the weighted average NI margin to plan the sample size via a one-sided confidence interval estimate. He recommended:

- Closely matching the planned proportions of subjects in each severity category.
- If the proportion cannot be attained, determine the possible change in weighted NI margin, and potentially adjust the sample size.
- Use the "prediction" idea to assess the feasibility/futility of demonstrating non-inferiority at the end of the trial.
- Use the observed proportions of patients before unblinding to adjust the NI margin for the final analysis.

Weighted Average NI Margin

Degree of severity of infection	Patient proportion (planned)	Placebo rate (liberal)	Active control rate (conservative)	NI margin
Severe	0.33	0.40	0.80	0.20
Serious	0.33	0.55	0.85	0.15
Not serious	0.33	0.80	0.90	0.05
Weighted average NI margin	---	---	---	0.13

NI Margin Example Based on Weighted Average

Infection type	Linezolid	Daptomycin	Tigecycline	Iclaprim
Wounds and ulcers	2.4	13.3	1.9	8.2
Cellulitis	6.3	---	8.3	4.6
Abscesses and others	3.1	2.6	3.3	2.0
Weighted NI margin	12%	16%	12%	15%

Infectious Disease Society of America (IDSA) Perspective

Dr. Brad Spellberg, an infectious disease expert from UCLA, presented a review that was conducted – with no outside financial support – by the Antimicrobial Availability Task Force of IDSA, and many panel members were very impressed with his presentation.

The task force conducted a systemic literature review from 1900-1950, covering 90 peer-reviewed publications. Of these 37 reported quantitative results. Among the points Dr. Spellberg made were:

- Cure is defined as alive and no septic complications, no worsening of infection after treatment was initiated, no persistence of infection after completion of treatment, no persistence of infection for ≥28 days on treatment, no relapse/recurrence, no failure to heal wounds/dehiscence, no failure of skin grafts, and no amputation.
- There was no difference in cure with "no antibiotic therapies – creams/ointments, UV treatment, x-ray treatment, "vaccination," anti-toxin serum, bacteriophage, or autologous blood.
- Sulfa monotherapy was not discussed because "it is irrelevant in the modern era," and it was inferior to penicillins in all the task force's analyses.
- The review found "unambiguous, robust evidence" of a large antibiotic treatment effect in cSSSI. Time-to-cure studies all showed a marked superiority of antibiotic therapy vs. non-antibiotic therapy. Topical therapies were less effective than systemic antibiotics.
- Mortality is not a viable endpoint for cSSSI because mortality rates are very low with antibiotics. But he reminded the panel, "We've forgotten how deadly cSSSI were in the pre-antibiotic era."
- The cure rates with systemic penicillins were estimated at:
  - 28% for cellulitis/erysipelas.
  - 42% for wound/ulcer.
  - 14% for major abscess.
- The implications of findings for NI studies are:
  - A 28% effect size translates to a 14% NI margin – if the goal is to preserve 50% effect size, but Dr. Spellberg said he is not advocating that.
  - Overall effect size in a study depends on the proportion of patients with cellulitis/erysipelas, wound/ulcer, or abscess.

Dr. Spellberg concluded, "The data are imperfect data…but we are not going to get other/better data…We need new antibiotics. So we must weigh the limitations vs. the need… We really are in a crisis mode…Antibiotics are truly unique drugs. This means there is a unique public health need for antibiotics that is different than for any other class of drugs… We believe the data sufficient for NI margin justification for antibiotic treatment for cSSSI should be based on: the magnitude of the efficacy, the robustness of the data, conservative calculations, compliance with critical features of ICH and FDA guidance, and the critical need for a new antibiotic."

In response to a panel question, Dr. Spellberg stressed that the composition of a trial's patient population has to be carefully analyzed. He suggested that cellulitis should generally be considered a complicated, not uncomplicated, SSSI.

Dr. Fleming, a panel member and a biostatistician, challenged some of Dr. Spellberg's conclusions: "You commented that you are overly conservative, but it may not be conservative at all…You are making assumptions that…the nature of the treatment effect is the same across different definitions of the endpoint, and that is patently wrong as well…It appears (the treatment effect) is dramatic in cellulitis and wound infections – much less clear in major abscess. The endpoint has to be objective…but the course needs to be highly predictable, and there is considerable heterogeneity in cSSSI…The things not taken into account are differences in the quality of supportive care between control and the penicillin group used historically and between penicillin historically and what patients get today …There appears to be substantial risk that there are imbalances in very predictable factors and modifiers."

Asked by another panel member if he is implying that approval standards have dried up the pipeline of new drugs, Dr. Spellberg said, "I'm sorry if I gave that impression…It is not an issue of relaxing approval standards but clarifying them. The standard used to be 15% NI…but if a company doesn't know the regulatory standard, it won't take the risk of investing in R&D only to find the standard changed when the studies are done...We are seeking clarification. Tell us what the studies need to be. We are not saying 10% is better; just tell us what they are so companies know what they need to shoot for when developing a drug."

The industry representative, Dr. Rex of AstraZeneca, added, "On behalf of industry, we are desperate for table rules…You have to know where you are going when you start, or business will not invest the prodigious sums involved…The data (with an NI trial instead of a superiority trial) are not satisfactory, but if we combine statistics with medical knowledge, we can get to a reasonable spot."

Public Witness on NI Trials

Susan Nicholson, therapeutic area lead, anti-infective franchise, Johnson & Johnson/Ortho-McNeil, told the panel, "We agree that for Phase III studies an NI margin of 10% is adequate." But she argued that the various conditions that fall into cSSSI should be included, that trials don't need to be done in a single subgroup of patients, "We cannot think of an example where an antibiotic is effective in treating cellulitis but not effective in treating abscess or a wound infected with that same pathogen…So, it is important to include wound

infections, cellulitis, and abscesses in the same trial…cSSSI is a continuum of disease…but you could stratify the subgroups by severity differences."

She asked the FDA for guidance, "If efficacy is proven in one subgroup, is efficacy implied for all cSSSI? If yes, which subgroup is appropriate? We need guidance on this…And how do diabetic foot infections fit into this paradigm?"

Panel Consideration of FDA Questions on NI Margins and Trials

The advisory committee voted unanimously that non-inferiority trials are acceptable for the indication of cSSSI, but they qualified this by adding that this applies to cellulitis and wound infections only, not abscesses. They agreed a 10% non-inferiority margin is acceptable, and they recommended clinical endpoints be used that are measured at least at two time points – at about 2 days and then at the end of therapy (7-14 days). They also asked the FDA to provide better, clearer definitions of cSSSI, uSSSI, and major abscess.

Question 1a. Are non-inferiority trials *ever* acceptable for the indication of cSSSI?

Vote: Unanimously YES

Question 1b. If yes, please discuss the following points and provide your rationale:

- ***What margin is acceptable?*** The panel agreed overwhelmingly that a **10% NI margin** is sufficient.
- ***What is the appropriate primary endpoint?*** The panel agreed that a **clinical endpoint**, as is currently used, is appropriate.
- ***What is the appropriate timing of assessment of the primary endpoint (e.g., on therapy, at the end of therapy, or at a fixed time point after completion of therapy)?*** The panel offered a range of suggestions, but most seemed to want **2 time periods** measured – at 2 days and again at end-of-treatment (7-14 days).

Panel member comments on these questions included:

- *Panel chair Dr. L. Barth Reller, a pathologist from Duke University:* "I think 10% is a reasonable balance…From a clinical standpoint improving therapy is important. So, an endpoint somewhere out 2-4 days, where decisions are being made to continue or not continue therapy – and some reasonable timeframe afterward to pick up the relapses – (would be good)…One of the things the newer organisms do more than in the past is they come back… So, assessment at multiple time points is important."
- *Dr. W. Kemper Alston, an associate professor of medicine from the University of Vermont:* "I think safety is important because of the nature of the condition, and…for these infections we can still give vancomycin and linezolid…I would argue, as a clinician, that we have to take safety issues more seriously than for some other infectious diseases."
- *Dr. Fleming, biostatistician:* "I do believe there are settings in which non-inferiority can be done...and I think a 10% margin is defensible in settings where you clearly established benefit…Outcomes should be clinically relevant – what patients care about. Signs and symptoms are fully appropriate – worsening of symptoms. But if you change the endpoint, you change the margin…Timing is a tough issue…My sense is the optimal timing is 10-14 days after initiation of therapy to have a fairly comprehensive assessment and yet to still capture the essence of treatment vs. natural history. There are not data to base a margin on if you choose a later time period, but I do support the interest in looking later in time for a supportive measure. Or, if you want to do a superiority trial, I am comfortable with a later point in time."
- *Dr. Matthew Goetz, director of the VA Greater Los Angeles Healthcare System:* "I've come to the clear conclusion that there is difference in treatment effect across the different domains, depending on what primary endpoint is defined, and certainly depending on the timing of the assessment…(A) 10% margin is likely to be correct …End-of-treatment at 7-10 days should be the endpoint… It is also critically important to look at any antimicrobial advantages of a new agent."
- *Dr. Kathleen Gutierrez, a pediatric infectious disease specialist from Stanford:* "On endpoints, I'm a little conflicted. I like to know at 48-72 hours if there is an effect to see if I need to add or change therapy, so I would argue for an earlier endpoint as well as an end-of-treatment endpoint."
- *Joan Hilton ScD, a biostatistician from the University of California, San Francisco:* "Two time points might be sensible."
- *Dr. James Leggett, an infectious disease specialist from Oregon Health Sciences University (OHSU):* "I can't reliably tell the difference between (an NI margin of) 10% and 12.5% in terms of saying yes or no to a drug…We need to make this as generalizable to the public as possible…I think end-of-treatment makes the most sense to me…It has to be a clinical endpoint, and we probably can't factor in relapses."
- *Dr. Lewis Nelson, medical toxicologist and emergency room doctor from New York University School of Medicine:* "When you take a drug from the setting of a clinical trial and bring it to an emergency room or medical ward where you are treating on a presumed diagnosis, not an expert opinion, that changes the nature of the safety and efficacy of the drug…Somehow, when we look at the risk and benefits of drugs, we have to realize the situation we will use them in is different from how they are used in clinical trials…The concept of the margin has to be figured in light of other issues involving the drug, in

particular safety issues and other therapies. The drugs we are looking at here are not to replace existing drugs…If it covers the infection in a subgroup or a different group, perhaps having an inferior profile is not ideal but not necessarily an unacceptable factor. Clearly, I want a drug to be as effective as it could be…I think the margin has to be relative to a lot of the issues like safety, other drugs out there, and how the drug will be used in practice. As someone who sees a lot of infectious disease, though I'm not a specialist…48 hours is nice, but ultimately a longer-term outcome is more important."

- *Dr. Edward Septimus, an infectious disease specialist from Houston:* "A three-day assessment of response to therapy seems reasonable…The other endpoints should be at end-of-treatment or two days after that – perhaps on response to therapy. How fast a patient responds and gets back to work could be another parameter with some of the new drugs."
- *Jeanine Thomas from the MRSA Survivors Network, the panel's patient representative:* "I'm very concerned about the irritability in regard to vancomycin…I was on vancomycin once. I know how painful it is…I'm very concerned about the painful administration of antibiotics …As we know, if you are colonized with MRSA, you have a 10-fold chance of getting an infection from it…A 10% margin is acceptable…The timing of assessment should be within 72 hours."
- *Dr. Melvin Weinstein, an infectious disease expert from Robert Wood Johnson Medical School:* "I'm comfortable with a 10% (non-inferiority) margin…and I would like to see more than one time endpoint measurement, maybe at 48-72 hours and then at end-of-treatment."

QUESTION 1c. Qualifications in which non-inferiority trials are not acceptable in cSSSI?

The panel overwhelming recommended that **abscesses not be included** in cSSSI trials, that abscesses be studied separately in a randomized clinical trial vs. placebo. If abscesses are included, there was a suggestion that this group be limited to <25% of enrolled patients. Panel chair Dr. Reller summed up the sentiment: "The sense of the committee is that subcutaneous abscesses are palpable, visible, and drainable and should not dilute the rigor of a non-inferiority trial, with regard to the more serious complicated infections that would fall in the category of cellulitis, erysipelas, and wound infections.

There was a great deal of debate over what the placebo cure rate is and what the vancomycin or linezolid cure rate is. One reason for the confusion is the difference in patient populations in the various trials, and the nature of the patients and the organism has been changing, with the number of MRSA cases rising.

Panel comments included:

- *Dr. Alan Cross, an infectious disease specialist from the University of Maryland:* "I think it is possible to separate out the different groups and perhaps abscesses would be separate."
- *Dr. Fleming, a biostatistician:* "I feel we need to do a non-inferiority trial, based on what is currently evidence-based, in cellulitis and wounds but not currently for major abscesses…One approach to abscesses would be randomized clinical trials, and this is happening. In addition, there are four major trials ongoing or about to start – by NIH, Baylor, and St. Louis University. Academia is already launching placebo-controlled trials looking at… complicated abscesses. I could see justification, in spite of all the uncertainties we have, saying in cSSSI – if it is a wound infection, cellulitis, or erysipelas, I could defend a 10% non-inferiority margin…but if you put major abscesses in there, I see no basis except superiority. (But) theoretically, you could put (abscesses) in and do a weighted average."
- *Dean Follman PhD, a biostatistician from the National Institute of Allergy and Infectious Diseases (NIAID):* "I thought we should break abscesses out from cellulitis and wound infections…Abscesses could be done in a superiority trial."
- *Dr. Goetz:* "Minor abscesses need to be in a different category, and you need to give different consideration to the non-inferiority margin for major abscesses."
- *Dr. Gutierrez:* "I'd separate simple abscesses from major abscesses."
- *Dr. Carol Kaufmann, chief of infectious diseases for the Veterans Administration Healthcare System in Ann Arbor MI:* "As a clinician, I am going through the patients I've seen in the last few months to see if I could put them in little buckets (categories), and I can't. They don't necessarily fall into categories. For instance, a diabetic bumps his shin and has a wound and then gets cellulitis…I think they really merge. It is a question of designing (the trial) right up front where to categorize the patient."
- *Dr. Septimus:* "I hear a clear consensus around this table on classifying these conditions by severity, trying to see if there are differences by pathogens (MRSA), differences in subcategory types. And there are some differences in timing, fever, drainage, site of erythema, etc. One thing I'm grappling with is trying to interpret a trial when we have such heterogeneous groups…The virulence of the organism has changed, the hosts have changed – people are living longer, there's more diabetes, etc…So, the pathophysiology may have commonality, but there are lot of things changing. What is the bar we want to set for determining the efficacy of new drugs in this arena – to say this drug clearly is efficacious?...I would prefer superiority (to non-inferiority) on abscesses."

- *Dr. James Steckelberg, chairman of the Division of Infectious Diseases at the Mayo Clinic:* "I have established treatments to give patients, and I want a reasonable certainty that a new treatment (is as effective)…To me 10% less efficacy would probably be unacceptable, but a 10% margin (of non-inferiority) doesn't mean 10% less effective. To me 10% (NI margin) is a reasonable compromise that is reasonably doable."
- *Ms. Thomas, the patient advocate:* "Abscesses should be separated."
- *Dr. Weinstein:* "I agree on abscesses…I have less confidence in the issue of abscesses because I think the pathology is different, and the treatment is often difficult because abscesses often get drained."
- *Dr. Corey of Duke, Theravance's expert:* "Smaller abscesses I would agree we don't need antibiotics for…and I would like the FDA to somewhat arbitrarily make decisions on what they consider a complicated infection."

QUESTION 2a. Please discuss if it is acceptable to justify an NI margin for cSSSI as a group or should it be justified by specific infection type (i.e., cellulitis, wound infections, or abscesses).

This was answered with the discussion in Question 1 – that **abscesses should be excluded** (or at a minimum should be limited to <25% of patients).

QUESTION 2b. If it is acceptable to study cSSSI as one group, should the number of infections of any one type be limited?

Again, the panel answered this in Question 1 – **exclude abscesses** or limit them to <25% of enrolled patients.

QUESTION 2c. Should patients with diabetic foot infections be studied in a separate clinical trial or should they be included in cSSSI trials?

The panel agreed that **diabetic foot infections should be excluded** and should be studied in a placebo-controlled, randomized, superiority trial. Panel member comments included:

- *Dr. Cross:* "That perhaps may be true, but from a practical point of view…if we add in diabetic foot infections, we enter into a more difficult realm…In practical terms, it would be difficult to include them overall…I think there is more than enough patients with diabetic foot ulcers that we could do a separate study in them."
- *Dr. Peter Katona, an infectious disease specialist from UCLA:* "I agree…They have a totally different (situation) …and compliance comes into it…as well as accessibility to good wound care."
- *Dr. Kaufmann:* "It is a different beast and would require expensive imaging studies to be sure there isn't underlying osteomyelitis…I think it should be (studied) separately."
- *Dr. Leggett:* "I'll play devil's advocate. How do we define diabetic foot infections? We don't have (just) a diabetic; we have a patient with diabetes and a wound or ulcer…And if we want this (treatment) to be generalizable, I would like diabetics in the group to see how they really (do)."
- *Chair Dr. Reller:* "I think there is a consensus that we may need more precision on definitions…but there are diabetics with sufficient vascular impairment and neuropathy, particularly associated with plantar ulcers that are frequently complicated with osteomyelitis, that those patients should be excluded. But diabetes in and of itself is not an exclusion in patients with acute cellulitis or acute other problems like post-operative wound infections."

QUESTION 3. Given that the data evaluated for determining treatment effect in skin infections includes data from various types of skin infections, are non-inferiority trials acceptable for the indication of uSSSI? If no, please provide your rationale and advice you may have on alternative trial designs.

Vote: 19 NO, 1 YES

The panel generally agreed that a **superiority** trial would be more appropriate in uSSSI.

Panel comments included:

- *Dr. Alston:* "I wonder if patients with uSSSI will be admitted and available to us for these trials?... If there is any chance of a superiority trial, you should (do it) because the non-inferiority design is so flawed."
- *Biostatistician Dr. Fleming:* "It would be a whole lot easier to assess efficacy in a superiority trial…If I were a sponsor…it would be easier to do a placebo-controlled superiority trial…Impetigo is not a major morbidity, so why not do a superiority trial?...You are in a far more interpretable mode to do a superiority trial…And patients join trials for altruistic purposes as well as their own benefit."
- *Biostatistician Hilton:* "I voted ***yes***, and I'm standing by my vote. I was moved by a comment – 'Why don't we leave that open, allowing them if they prefer to do non-inferiority trials?'"
- *Dr. Katona:* "Any time you can justify placebo over non-inferiority, you should go for it, and I think that is the case here…You can probably get this through the human subjects committees."
- *Dr. Weiderman:* "I think the magnitude of the benefit of treatment is low enough that maybe I wouldn't get

ethically concerned about a placebo-controlled trial…but if I put myself in the investigator's role trying to explain this to the family. I could explain in good conscience, but I don't think I will get a lot of takers."

QUESTION 4. What types of infections would you include in uSSSI studies in a superiority trial?

Originally, this question was: Should uSSSI studies only enroll patients with infections such as impetigo, erysipelas, and cellulitis and exclude those with abscesses? But, with the agreement of the FDA, it was changed to a non-voting clarifying question.

The panel recommended **including impetigo, erysipelas, folliculitis, furuncles, etc., but probably not abscesses** in a uSSSI superiority trial. The chair summarized: "This question is more complicated than what meets the eye…It seems there are entities that clinicians feel are caused by bacteria that may respond to therapy…but the appropriate method of studying them would be a superiority trial where you want to show effectiveness but currently, for these clinical entities, it is not sufficiently certain there is a therapeutic effect over and above placebo or surgical drainage. If they were not infected at all, why do a trial? So, there has to be infection. Antibiotics may make a difference, but we are not sure, and those are the ones we want to enroll in a trial."

Panel comments included:

- *Dr. Goetz:* "I'm troubled by inclusion of erysipelas with a 10% mortality rate."
- *FDA's Dr. Cox:* "I think we are talking about milder manifestations."
- *Biostatistician Dr. Fleming:* "There is a wide spectrum of potential cases you could allow if you meet the definition of uncomplicated SSSI and use a superiority trial. Then, how broad a setting is it likely that your product would have a meaningful effect? It is really a question for clinical colleagues…Once we focus on uSSSI with a superiority trial, is it reasonable to anticipate you would have comparable benefit in minor skin abscess, furuncles, impetigo, and some definition of uncomplicated cellulitis, or are there groups that would benefit more?"

ADVISORY COMMITTEE CONSIDERATION OF SPECIFIC DRUGS

After a day of discussing clinical trial design for anti-microbials, the advisory committee took up, one at a time, three new drug applications. One (telavancin) got a positive nod, and two (oritavancin and iclaprim) got negative recommendations.

After all the drugs had been considered, FDA officials spoke with reporters. The FDA appears to have changed the rules in the middle of the game for oritavancin – approving the trial design for an SPA, the company meeting those requirements, and then deciding it wants more or different data. Asked about this, the FDA's Dr. Cox said, "We are in a situation where science advanced, and we have a greater understanding of trial design. If we know something now we didn't know then, we have to look at the trial based on the current understanding…We give the best advice we can at the time, but if something changes, we need to consider that."

Asked what the take-away is for other companies with drugs in the pipeline, Dr. Cox said, "The committee gave helpful advice on clinical trial design for folks thinking about cSSSI studies."

Asked if the message in the difference between the committee's reactions to telavancin and oritavancin means efficacy is more important than safety, Dr. Cox said you have to have efficacy before you can consider safety: "We look at studies on what they tell us about efficacy, and then also on safety, and weighing them. I think you have to have both safety and efficacy…The committee was looking at the (telavancin) trial and their vote was for efficacy, and then they counterbalanced that with safety. (With oritavancin), there was discussion of efficacy. Once you have that you can do risk:benefit (analysis)."

Anti-Infective Drugs Advisory Committee Issues

November 19, 2008		November 20, 2008
Theravance's telavancin	**Targanta's oritavancin**	**Arpida's iclaprim**
Evidence of safety and efficacy	Evidence of safety and efficacy considering primary endpoint and confidence intervals	Evidence of safety and efficacy
Implications of animal reproductive/toxicology data for use in pregnant women and women of childbearing age	Outcomes in patients with MRSA	Any limitations on the use, considering comparative outcomes of iclaprim and linezolid
Need for a REMS	Weight-based dosing regimen used in ARRD trial	Any clinical situation where it might be used

THERAVANCE/ASTELLAS' Telavancin

Theravance submitted telavancin – which will be co-marketed in the U.S. by Astellas – to the FDA on December 19, 2006, and the FDA issued an approvable letter on October 18, 2007. In the approvable letter, the FDA asked Theravance to provide information about manufacturing issues and analyses to better delineate the overall risk:benefit profile. More specifically, Theravance said the letter cited: contract manufacturing facility issues, outstanding financial disclosure forms for three investigators, several points impacting the risk:benefit assessment of the product, a request for information regarding isolates with differential sensitivity to telavancin and vancomycin, and a request for comment on the appropriate use of telavancin in pregnant women.

Theravance submitted its response on January 21, 2008. In the resubmission, the safety update and additional analyses the FDA had requested were provided.

The FDA had scheduled an advisory committee meeting on telavancin in February 2008, but the Agency said that just before the meeting it received information from site inspections that called into question the reliability of some of the data contained in the application, causing the meeting to be cancelled.

The FDA perspective on telavancin

Among the FDA's concerns with telavancin are:

Potential nephrotoxicity. The FDA expressed concern with the apparent decrease in clinical response rates for patients with baseline renal impairment treated with telavancin, saying that "was not explained and may be of clinical concern." The FDA staff reported that small increases in BUN (blood urea nitrogen) and creatinine along with renal tubular degeneration were found in rat and dog studies. FDA reviewers reported:

- 2 patients died from drug-related renal insufficiency vs. none with vancomycin.
- 19 patients had renal serious adverse events: 15 with telavancin, 4 with vancomycin. Three of the telavancin patients required hemodialysis; 2 refused dialysis and died. Three patients treated with telavancin showed incomplete resolution of creatinine with values still twice baseline level.
- 13 telavancin patients discontinued study medication prematurely due to renal serious adverse events vs. 1 vancomycin patient.

Teratogenicity. The presence of limb malformations across three species led the FDA to conclude that the findings are drug-related. Although the incidence rates were low, they occurred in a dose-dependent manner and at rates significantly higher than in the historical control databases. Of greatest concern to the FDA is that these malformations occurred at clinically relevant maternal exposures based on area under the curve (AUC). The FDA concluded that telavancin is a multi-species teratogen with skeletal (limb) malformations being the primary terata.

Dr. Zhou Chen, a medial reviewer from the FDA's Division of Anti-Infective and Ophthalmology Products, CDER, reviewed the teratogenicity of telavancin. He told the panel that the FDA believes telavancin is associated with limb malformations which occurred with a low incidence across all three species studied – rats, rabbits, and minipigs. He said there is no safety margin in the doses studied in animals, and the proposed human dose based on plasma AUC. The limb malformations are drug-related and a safety concern, he said.

Dr. Chen said a panel of CDER expert consultants found, "It was the consensus of the committee that the limb defects observed in those studies were related to the drug. While the evidence of drug-induced limb malformations in each species is weak, the weight of evidence across all three species strongly supports the findings are drug-related."

Thus, Dr. Chen concluded that the potential for serious complications in pregnancy should be considered when determining the risk:benefit profile and in labeling.

The FDA's Maternal Health Team (MHT) recommended that telavancin be classified as a pregnancy category X "based on lack of perceived benefit over existing therapy with an increase in risk based on teratogenicity potential." They also recommended a boxed warning, restricted distribution at the pharmacy level to include documentation of age, gender, and evidence of non-childbearing potential for females, and a risk evaluation and mitigation strategy (REMS) program that includes a pregnancy surveillance registry.

Dr. Karen Feibus, medical team leader, Maternal Health Team, in the FDA's Office of New Drugs, CDER, reviewed the pregnancy category options for telavancin, concluding there are two choices: Category C and Category X. However, the FDA staff clearly believe that it belongs in Pregnancy Category X, but they presented both options to the panel.

Dr. Feibus said, "If you have a pregnant woman with cSSSI, there is benefit in treating her effectively, but in situations where there are safer drugs available…that is a reason for

FDA Pregnancy Category Options for Telavancin

Category C	Category X
Animal reproduction studies have shown an adverse effect on the fetus.	Studies in animals or humans have demonstrated fetal abnormalities.
AND	**OR**
There are no adequate and well-controlled studies in humans.	There is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both.
AND	**AND**
The benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.	The risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (e.g., safer drugs or other forms of therapy are available).

listing a drug as Category X if it meets the other criteria… There are 8 other approved drugs for treatment of cSSSI, and telavancin is a highly suspected human teratogen based on animal reproductive and development toxicity study data."

There are ways to demonstrate relative benefit that would allow a Pregnancy Category C instead of X – superior efficacy or a better safety profile than other therapies. However, Dr. Feibus suggested that telavancin doesn't meet either of these criteria. She said telavancin "does not offer clinical benefit above and beyond that offered by vancomycin. Teratogenic findings…make telavancin a highly suspected human teratogen. Based on available data, the 8 FDA-approved treatments for cSSSI have a lower teratogenic risk. Thus, for a pregnant woman with cSSSI, telavancin does not offer enough clinical benefit (over current therapies) to justify the additional fetal risk (with a Category C rating)."

FDA Arguments For and Against Pregnancy Category C for Telavancin

For	Against
The unknown relative efficacy of telavancin vs. other approved anti-infectives for cSSSI and MRSA.	Healthcare practitioners may not see the risk for telavancin as different from other Category C drugs indicated for cSSSI.
Under an IND, isolated patients were treated successfully with telavancin who failed vancomycin therapy.	Category C designation would likely increase the likelihood of fetal exposures to a suspected human teratogen.

QT prolongation. Due to preclinical safety results, Theravance was required to do a "thorough QT study." At both the 7.5 mg/kg and 10 mg/kg doses, QT prolongation was >10 msec (the threshold for regulatory concern). QT prolongation was confirmed in Phase II studies. The FDA concluded that the adverse events "might be indicative of a problem with QT prolongation and/or ventricular arrhythmia, such as Torsades de pointes."

Data integrity and evaluation. The FDA's Division of Scientific Investigations performed 13 inspections relating to this NDA, conducted in two cycles.

- **Cycle 1.** The FDA told the panel, "The inspectional findings at two of these inspections raised serious concerns about data integrity."
  - Contract Research Organization (CRO) – the monitor for most of the clinical investigators in Studies 0017 and 0018. The FDA inspection showed that the CRO had identified all major GCP violations that the FDA identified at this site, but study monitoring was inadequate because the CRO failed to implement appropriate corrective actions as required. The CRO's monitoring of the remaining 3 clinical sites was adequate.
  - A clinical investigator, a clinical site with 51 enrolled subjects – the second largest site in Study 0018 and the fourth largest overall site for the two pivotal studies. The FDA found major deficiencies in good clinical practice, including retrospective alteration of efficacy data and losing or discarding critical source documents. The inspection also suggested inadequate study monitoring, which resulted in an inspection of the CRO responsible for study monitoring.
- **Cycle 2.** Additional clinical sites were selected for inspection based on: (1) large enrollment size, (2) efficacy data favoring telavancin over control (vancomycin), and (3) study monitoring by the CRO that had deficiencies in Cycle 1. At all 7 sites, the observed level of GCP compliance supported the integrity of the data reported from these sites. Major violations with the potential to affect data integrity consisted of electrocardiographic safety data from two sites, which were not obtained according to the timeframe specified in the study protocols. Study monitoring by the CRO routinely included the effective implementation of corrective actions when necessary. The results of FDA's inspections were also consistent with the results of Theravance's own internal audit.

Theravance's audit. The company inspected 31 sites (24%) and audited the records for 683 subjects (36%). Theravance concluded that there was no systematic pattern or incidence of GCP violations that could affect interpretation of the reported safety and efficacy data. The audit, however, identified two clinical sites at which study monitoring was not adequate.

Evaluation of data integrity. The FDA concluded that the results of its audits and the Theravance inspections support the Agency's current view that the data reported in the NDA ***are reliable***, with these exceptions:

1. Efficacy data from three sites.
2. Electrocardiographic (ECG) safety data from two sites.

Thus, efficacy and ECG data from the sites in question were excluded from the FDA's final analysis and will be excluded from the company's analysis and from presentations to the advisory committee.

Overview. Among the other points the FDA made about telavancin were:

- It has a low potential for development of resistance.
- It is not metabolized by the cytochrome P450 pathway.
- A dose adjustment is recommended for patients with moderate or severe renal impairment.
- QT prolongation was ~12-15 msec (vs. 24 msec for moxifloxacin).

Efficacy. In both Phase III studies, telavancin was demonstrated to be non-inferior to vancomycin on the primary endpoint of clinical response, using a 10% non-inferiority margin. However, telavancin failed to demonstrate superiority in a polled efficacy analysis.

Results of Telavancin Phase III Studies

Measurement	Study 0017		Study 0018	
	Telavancin n=426	Vancomycin n=429	Telavancin n=448	Vancomycin n=481
Primary endpoint: Clinical response (all treated patients)	72.5%	71.6%	74.7%	74.0%
Clinical response (clinically evaluable patients)	84.3%	82.8%	83.9%	87.7%
Pooled analysis of clinical response	Telavancin: 75.4% (Nss, p=0.18)		Vancomycin: 74.9%	
Renal and urinary disorders	11 patients (1%)		2 patients (<1%)	
Acute renal failure	4 patients (0.5%)		0	

Risk management. Suzanne Berkman, PharmD, a senior risk management analyst in the FDA's Division of Risk Management, Office of Surveillance and Epidemiology, CDER, reviewed the risk management programs rather generally, not specifically telavancin strategies. She suggested some practical challenges:

- Assuring inpatient access is linked to negative pregnancy test results. Current programs have independent verification of test results by pharmacies prior to dispensing.
- Inpatient education tools, such as Medical Guides, not generally provided to hospitalized patients.
- Should contraception be required for outpatient use?
- Should repeat pregnancy testing be required for longer outpatient therapy?
- Who will be responsible for patients after hospital discharge?

Berkman said that inpatient risk management requires education for all prescribers and support staff in hospitals. Hospital-specific programs could also help by educating providers, creating a standard order set for telavancin, creating computer order entry stops, and limiting prescribing to infectious disease consults. In the outpatient setting, she said prescribers, home health nurses, and pharmacists would all have to be educated – and this setting would require further discussion.

FDA conclusions. Dr. Janice Pohlman, acting medical team leader in the FDA's Division of Anti-Infective and Ophthalmology Products, CDER, summarized the FDA's view of efficacy and safety of telavancin. While the FDA used different definitions than Theravance for treated patients, the FDA staff concluded telavancin was non-inferior vs. vancomycin in each of the two Phase III studies, regardless of which definition was used (the company's or the FDA's).

Baseline Type of Infection in FDA-Defined All Treated Population

Infection	Study 0017		Study 0018	
	Telavancin n=426	Vancomycin n=429	Telavancin n=458	Vancomycin n=481
Major abscess	42%	45%	43%	42%
Cellulitis	37%	38%	33%	37%
Wound infection	17%	14%	15%	13%
Other (ulcers and burns)	4%	4%	9%	9%

In summary, the FDA staff found:

- Telavancin is non-inferior to vancomycin for the treatment of cSSSI.
- Serious adverse events, discontinuations, and predefined definitions of renal impairment were higher with telavancin than vancomycin.
- Telavancin prolongs the QT interval.
- Telavancin did not demonstrate superiority in the treatment of MRSA.
- GI adverse events were the most common adverse events with telavancin.

Theravance's perspective on telavancin

The company emphasized in briefing documents for the panel that telavancin demonstrated non-inferiority to vancomycin in two identical, randomized, multinational, double-blind Phase III trials. Although telavancin did not meet the criteria for superiority over vancomycin, Theravance pointed out that "the clinical, microbiologic, and overall therapeutic response rates were consistently numerically higher in the telavancin group in both analysis populations."

Two additional Phase III trials – identical, randomized, multinational, multicenter, double-blind, active-controlled studies – of telavancin vs. vancomycin were conducted in patients with hospital-acquired pneumonia, and preliminary data were submitted to the FDA. Both of these trials demonstrated non-inferiority to vancomycin.

Theravance also addressed the FDA concerns headon:

➢ ***Nephrotoxicity*** **– agreed it occurs and should be monitored.** In the briefing documents the company wrote, "Like vancomycin, telavancin is associated with renal adverse events. While renal adverse events were infrequent in the cSSSI studies, they occurred in more patients receiving telavancin (3.4%) than vancomycin (1.2%) and were associated with the presence of baseline comorbidities (e.g., heart failure, abnormal blood pressure, kidney disease, etc.) that increase the risk for renal impairment. Renal function should be monitored in all patients receiving telavancin. In considering the use of telavancin in

patients with moderate or severe renal impairment or with underlying conditions predisposing to kidney dysfunction, the possible risks of telavancin should be weighed against the potential benefits."

However, the company also noted that renal adverse events "were readily detectable and manageable." The company told the panel that a review of telavancin patients with renal serious adverse events found that nearly all of them had multiple reasons for developing renal impairment "that are deemed more likely than the use of study drug." Furthermore, in most of these patients, "the reviewing nephrologists indicated that they would not recommend discontinuation of study drug therapy since other underlying conditions and the infection would take precedence."

The bottom line was:

- **Risk.** Renal adverse events were more with telavancin than vancomycin (3.4% vs. 1.2%) but occur in patients with other risk factors and the majority of patients improved or recovered.
- **Monitoring.** Serum creatinine monitoring is recommended in all patients, with the dosage adjusted on the basis of estimated creatinine clearance.

➢ ***QT prolongation*** **– agreed it occurs but claimed it is less than with other anti-infectives.** The company wrote in the briefing documents, "Telavancin also causes a QT prolongation, but the prolongation is half of that observed in a controlled comparison with another drug (moxifloxacin) that is indicated for cSSSI and for other, less serious infections." At the panel meeting, company experts offered additional arguments about the cardiac safety of telavancin:

- **Study 104.** The effect on QT prolongation was extensively studied, and the result was a mean change of <5 msec and a maximum change of 11.6-15.1 msec. The results were similar to moxifloxacin, a drug generally considered of minimal risk for Torsades de pointes.
- **Studies 0017, 0018, and 202b.** In these studies comparing telavancin to vancomycin, the mean QT prolongation was 9.6 msec, with a maximum change of 16.2 msec, vs. a 2.7 msec mean and 8.4 msec maximum change for vancomycin. But cardiac serious adverse events were similar between telavancin and vancomycin, and there was no increase in cardiac death with telavancin vs. vancomycin.
- **Labeling.** There is a low arrhythmic risk, but there is proposed education and labeling on cardiac risk.

➢ ***Teratogenicity*** **– argued for pregnancy warning not complete contraindication.** "In non-clinical developmental studies there were minor fetal effects. After reviewing the data from all developmental studies, an independent expert concluded that the primary evidence of an adverse developmental effect was a reduction in litter weight in a study in rats and that there was no clear evidence of teratogenicity in any of the developmental studies. After evaluating the few observed limb defects, he noted that there was no embryologically coherent mechanism by which a common malformation syndrome could be postulated to have been caused by telavancin. Proposed labeling for the product advises that there are no adequate and well-controlled studies in pregnant women and that telavancin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

Telavancin has been made available for compassionate use (emergency IND) in clinical situations where other available therapies are inactive *in vitro*, have failed clinically, or the patient cannot tolerate other available therapies. To date, three patients have received telavancin under this program.

1. A female with complicated chronic sinusitis due to MRSA that had been unresponsive to several courses of different antibiotics. She was given telavancin for a period of approximately 2 weeks prior to a surgical procedure to drain and debride the sinuses. Following surgery, she received several more weeks of telavancin and has done well with resolution of the infection. No more information is currently available about this patient.
2. A 25-year-old female with persistent MRSA septicemia and bacteremia following perineal soft tissue infection. She remained ill despite therapy with vancomycin, linezolid, and intravenous clindamycin. Additionally, she had decreased hearing unilaterally beginning after the first dose of vancomycin. Multiple septic pulmonary emboli and pulmonary infiltrates precluded the use of daptomycin. She received telavancin and had a rapid clinical and microbiologic cure. She completed a 28-day course of therapy and tolerated the therapy well with the only adverse events reported being foamy urine and taste disturbance. She became pregnant shortly after treatment with telavancin was discontinued and delivered a healthy baby. She has remained well.
3. A 51-year-old female with end-stage renal disease on dialysis who developed MRSA sepsis due to an infected implantable cardioverter defibrillator (ICD). The ICD was removed, she developed back pain, and an MRI showed discitis with vertebral osteomyelitis of L4-5. Her blood cultures remained positive. MICs (minimum inhibitory concentrations) for the MRSA in her blood were determined – daptomycin, tigecycline, vancomycin, linezolid. Believing that this was an endovascular infection due to a VISA strain of *S. aureus*, treatment was switched to telavancin. Her blood cultures became sterile. Telavancin was initiated and continued for about 7 days, at which time she developed a new fever. She experienced no adverse effects related to the use of telavancin. The fever was likely due to peritonitis with necrosis of the rectosigmoid colon with *Klebsiella* in the blood. She underwent a sigmoid colectomy and proctectomy but failed to improve and died.

Dr. Anthony Scialli, an OB-GYN from George Washington University who runs a non-profit reproductive toxicology center, spoke on behalf of Theravance, reviewing non-clinical developmental (reproductive) studies. He said an independent expert panel directly challenged the FDA findings, concluding there is no teratogenic or developmental risk with telavancin. However, Theravance still is proposing a risk management program to minimize the exposure of pregnant women to the drug, with the drug categorized as Pregnancy Class C and controlled distribution via wholesalers and distributors to hospitals, inpatient hospital pharmacies, and home healthcare pharmacies.

Dr. Scialli went into detail on the reproductive issues with telavancin. He said toxicity was studied in two species and independently reviewed by an expert panel. The conclusion of that panel challenge the findings of the FDA. Dr. Scialli said:

- The only effect with telavancin was a small decrease in fetal weight at 100 mg/kg/day and at 150 mg/kg/day in rats, with statistical significance only at the higher dose.
- In contrast to our colleagues at the FDA, we did not find a teratogenic signal for telavancin (or vancomycin). Limb findings were mechanistically dissimilar, not reproducible in rats, and not attributable to telavancin.

Dr. Scialli particularly cited a rat study, which he said cleared telavancin of excess risk. He noted, "Micromelia is seen spontaneously in rat fetuses from time to time. So I'm not sure there were any true incidences of limb shortening in (the telavancin rat) study, but if there were, they were not reproducible…There were no incidences of limb shortening in the several hundred fetuses treated with any doses of telavancin, including the 100 mg/kg and 150 mg/kg doses used in the prenatal studies. There was one rat pup with transient limited use of a forelimb, but that resolved. It can't be a birth defect if it goes away."

Dr. Scialli argued that telavancin is not less safe in reproductive terms than vancomycin, "Although my FDA colleagues may tell you vancomycin doesn't produce malformations in these animals, that is not quite correct. There were 2 fetuses in rats with abnormalities of the eye and one multiple malformed fetus, including one abnormal rabbit in the telavancin study with vancomycin…So abnormalities such as this happen, but with the sporadic abnormalities and one fetus here and there, the general conclusion is we don't have a teratogenic signal. The FDA has made comments that telavancin is of concern (reproductively) because telavancin affects (occurred in) the same location (limbs). We did not reach that conclusion…and in vancomycin we have the same situation…Our conclusion is there is a lack of a teratogenic signal (with telavancin)."

Dr. Scialli also said the benefit of telavancin may outweigh a potential risk, "The presence of developmental toxicity ***studies*** that show abnormalities does not preclude the clinician and patient from the opportunity – the responsibility – to make a risk:benefit decision when it comes to therapy during pregnancy."

He posed the question: Is there any benefit to telavancin use during pregnancy? His answer: "Pregnant women get cSSSI just like all of us. And when they get an infection requiring an antibiotic, the presumption that not treating it is in the best interests of the fetus, assumes the infection won't affect the fetus, and that is highly unlikely...Keep in mind the telavancin non-inferiority study was done in people who had demonstrably vancomycin-sensitive organisms, not vancomycin-resistant or intermediate organisms."

Dr. Scialli's overall conclusion: "The developmental toxicity profile of telavancin is similar to that of commonly used drugs like vancomycin, that the decision to use telavancin is appropriately left to the patient and her clinician, and use in pregnancy will be addressed in a risk management program."

➢ ***Overall risk:benefit.*** Dr. Louis Saravolatz of Wayne State University School of Medicine, reviewed the risk:benefit of telavancin for Theravance. He said the benefits of telavancin were:

- Effectiveness in treatment of cSSSI – statistically non-inferior to vancomycin.
- No emergence of resistance seen to date.
- Fewer infusion reactions than vancomycin.
- Potentially effective in strains not susceptible or resistant to existing therapies, potentially reduced the rate of treatment failure, and potentially reduced days of hospitalization and IV antibiotics.

Dr. Saravolatz summed up the company's response to the demonstrated risks:

- Renal events – more than vancomycin but detectable, manageable, and reversible.
- QT prolongation – less than moxifloxacin, with incidence of cardiac serious adverse events and deaths similar to vancomycin.
- Potential effects on animal fetus – reduced litter weight in animals, but no human pregnancy data. It should be avoided during pregnancy unless the benefit to the patient outweighs the potential risks to the fetus.

Risk management program **(REMS).** Theravance is proposing a REMS, which includes:

- ➢ Product Label/Prescribing Information.
- ➢ Risk minimization strategy for cardiac events associated with QTc prolongation, nephrotoxicity, and adverse fetal development effects.
- ➢ Targeted data collection for events of interest.

- Targeted data collection forms to be developed to collect additional information regarding all adverse cardiac events associated with QT prolongation and nephrotoxicity that are reported post-approval. These events will be reported to the FDA every 3 months for the first 2 years post-launch via special reporting.
- The objective of the REMS will be to:
  - Educate prescribers about risk factors predisposing to nephrotoxicity, the need for renal function monitoring for patients while receiving telavancin, and the requirement for dose adjustment for patients with creatinine clearance ≤50 mL/min.
  - Educate prescribers about the potential for QTc prolongation.
  - To educate prescribers and patients about the potential risk of adverse effects on fetal development for women exposed to telavancin during pregnancy.
  - To ensure safe use of telavancin by recommending that telavancin is initiated in a controlled healthcare setting where the patient can be adequately monitored.
  - To ensure the safe transition to the outpatient setting in patients taking telavancin.

The proposed REMS would include:

- Prescribing information and patient package insert.
- Communication plan with educational materials distributed to healthcare professionals, including emergency room physicians, hospital pharmacists, surgeons, etc.
- Specific information to be included in the Formulary Kit provided to hospital pharmacies and pharmacy & therapeutics (P&T) committees on the appropriate use of telavancin.
- Introductory Dear Healthcare Provider letter at product launch.
- Additional materials available via sales and/or clinical representatives, on the telavancin website, and through a toll-free medical information line.
- An assessment strategy to evaluate physician and pharmacist compliance, knowledge, attitude, and behavior.
- Monitoring of the postmarket environment for any pregnancies exposed to telavancin, including a toll-free number for patients and/or prescribers to report pregnancies.

Panel questions for the FDA and Theravance on telavancin

The key questions the panel had for the FDA and the company generally dealt with fine points relating to:

- **Nausea and vomiting –** which the company estimated is twice as common with telavancin as with vancomycin, but transient and <1% of patients discontinued for each.
- **Renal toxicity –** serum creatinine, use in CKD patients, etc. A company speaker said, "Overall, acute kidney injury was, if anything, on the low side…the majority of the renal adverse events with telavancin…are not likely due to drug-effects…and are concordant with the literature…I believe telavancin exhibits a modest and reversible renal effect. Putting it in context. It is slightly more than vancomycin – which is considered to have a low acute kidney risk but increasing case reports with higher doses and may rise above telavancin at some point – but below β-lactams and trimethoprim-sulfamethoxazole and way below aminioglycosides and amphotericin B deoxycholate."
- **Risk management programs with multiple warnings –** which the FDA said is ~20% of risk management programs, citing the example of Actelian's Tracleer (bosentan) which has both a liver and a teratogenic warning.
- **Dysgeusia (metallic taste) –** which the company characterized as a generally transient side effect, occurring most often during infusion.
- **Pregnancy category –** Panel members wanted additional details on the animal toxicity studies and appeared to lean toward Category X rather than Category C.
- **Comparison to vancomycin –** Panel members tried to find advantages of telavancin over vancomycin to justify increased toxicity.

Panel discussion/comments on telavancin

Some of the interesting comments during discussion periods are presented below.

Efficacy/safety.

- *Dr. Henry Black of New York University School of Medicine:* "One thing that has been bothering me most of the morning is the concern – is there really going to be more vancomycin resistance? We would be approving a drug should that happen. If there isn't going to be more (vancomycin resistance), then I think the safety signal is bothersome (with telavancin)."
- *Dr. Goetz:* "There is no question vancomycin resistance is increasing…We also have concerns about the alternative antimicrobials…Daptomycin may be an imperfect drug for patients with vancomycin resistance."
- *Dr. Septimus:* "I think we are seeing (resistance) creep… I think the potential is out there (for increased vancomycin resistance)."

- *Dr. Fleming, biostatistician:* "Yesterday, we were explicit on how the non-inferiority margin is specific to the setting, and one aspect it is sensitive to is safety…We had significant discussions on nephrotoxicity, QT prolongation, and safety in pregnant women. In many studies it is not easy to characterize where the risk resides – what types of patients you can categorize where the risk resides. When you can't, it becomes especially problematic."
- *Arthur Levin, director of the Center for Medical Consumers, the panel's consumer representative:* "We have a lot of safety signals for a lot of directions. We don't have overwhelming evidence, but we have a lot of signals. So we are in a tough spot."
- *Dr. Nelson:* "I think it comes down in my mind to where we can make it clear enough in the labeling that QT prolongation is a real risk – because it is going to happen rarely but when it happens it could be very consequential."

Pregnancy.

- *Philip Mirkes PhD, a toxicology expert from Vancouver WA:* "We have conflicting opinions by the FDA and the company on reproductive toxicity…I don't know what to make of (the rabbit study with one fetus with a limb defect)…There is dose response, so one fetus, though not in historical controls, is meaningless to me…The rat study had two malformations, but it turns out the one thought to have a shortened limb…I don't know what that says. The minipig study to me is totally uninterpretable because there is something going on in the study based on the fact that the pregnancy rates were so low, and a fairly high percentage of pregnancies were terminated early for reasons I don't understand...I don't think there is as strong developmental toxicology evidence as the FDA indicated."
- *Dr. Fleming:* "It is really whether there are clinical situations where the established benefits of telavancin use exceed other options in a pregnant woman to outweigh the risk. The Category X wording is safer drugs or other forms of treatment are available. If one says there are safety issues of concern, there is efficacy but if efficacy can be provided by alternative therapies, that is the exact wording of Category X."
- *FDA's Dr. Cox:* "We are trying to understand if there are situations where people would turn to this drug (for pregnant women)…Are there situations today where you would consider it appropriate or inappropriate to give this drug based on what we know – and give us a feel for the frequency with regard to that situation arising."

Panel Consideration of FDA questions on telavancin

QUESTION 1. Do the data presented demonstrate the safety and effectiveness of telavancin for the treatment of cSSSI?

Vote: 21 YES, 5 NO

The panel generally agreed the renal toxicity and QT prolongation are manageable, but they were concerned about the potential teratogenicity of telavancin. Panelists offered the following explanations for and comments about their votes.

21 YES vote comments included:

- *Dr. Alston:* "Vancomycin is a dying drug, and I see vancomycin failures all the time, and if this is son of vancomycin with manageable toxicity…and nephrotoxicity we can easily detect. Hopefully, we can keep it away from pregnant women."
- *Dr. John Bennett, section chief of clinical mycology at NIAID:* "Telavancin has enough to offer with manageable toxicity that we should approve it."
- *Dr. Janet Cragan, medical officer, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (CDC):* "With increasing resistance, it appears to perhaps fill a clinical niche that could be critical to patient survival in certain situations…I agree the risk is manageable."
- *Dr. Cross:* "It is important that future physicians have some options…I do think the risks are manageable."
- *Dr. Fleming:* "I voted yes, but there are major issues. The strength is the two trials…It is a suboptimal (primary) endpoint and suboptimal timing…(But) we can characterize the risks and manage the adverse events…It seemed to me, then, the risk:benefit could be judged favorable… We definitely do need postmarket studies that allow us to more clearly understand the rate of serious adverse events and linkage to mortality."
- *Dr. Goetz:* "The renal risk is manageable. We can give a warning on QT prolongation and pregnancy."
- *Dr. Jeffery Kopp, staff clinician, Kidney Disease Branch, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH):* "Overall, the efficacy, if anything, seemed greater than vancomycin."
- *Dr. Leggett:* "I voted yes because the efficacy was established and across a wide enough range that I'm satisfied that it existed. The toxicity is manageable. Addressing the renal toxicity: neither of the other Gram-positive drugs are without their own problems."
- *Dr. Emil Paganini, a critical care nephrologist from Chesterland OH:* "I voted yes, and the label should warn about potential AKI (acute kidney injury)."

- *Michael Shelby PhD of the National Institute of Environmental Health Sciences:* "I voted yes a little reluctantly. The efficacy is similar to vancomycin, and it has separate problems…but I think the risks can be managed."
- *Mary Alice Smith PhD, a developmental reproductive toxicology expert from the University of Georgia:* "I voted yes. The growing problem with resistance is really important and played a part in my decision...As to toxicity, there are no completely safe drugs, but the risk can be managed."

5 NO vote comments:

- *Chair Dr. Reller:* "I was a no vote. The basis for that was safety concerns in multiple systems, not just one, that I think complicate risk management…I'd be much more enamored of an alternative or supplemental drug with a fundamentally different mechanism of action to address emerging resistance…I don't know how much difference this will make in adding to the armamentarium against resistance, that is why I fell on the seesaw to the no side."
- *Dr. Katona:* "I am not giving it an emphatic no vote...but I would have liked to see superiority over other things… Looking at the risk:benefit ratio, that (no) is my conclusion."
- *Consumer rep Levin:* "I'm not as sanguine about the ability to manage (telavancin) without an aggressive risk management program…I recognize the need for new drugs in the face of galloping resistance, but I am concerned about the number of safety signals."
- *Dr. Septimus:* "I was concerned with decreased efficacy in the sicker patients…I really could have gone either way …I do think the toxicity can be managed."
- *Ms. Thomas, the patient advocate:* "I know how toxic vancomycin is…I wouldn't want a drug more toxic than vancomycin. More trials are needed in renal impairment and…women who are or could be pregnant…and a study on the long-term effects of the drug."

QUESTION 2. Are there clinical situations when the benefits of telavancin use in a pregnant woman would outweigh the risks?

Vote: 18 YES, 5 NO, 3 Abstentions

However, overwhelmingly the panel said telavancin should be reserved for relatively rare, life-threatening situations in pregnant women, and most would give it a Pregnancy Category X classification.

18 YES vote comments included:

- *Dr. Bennett:* "Though I voted yes to use, I don't like the teratogenicity data we have. I don't know why they didn't use a higher multiple of the human dose…So, I'm concerned enough to think of Category X."
- *Dr. Cross:* "I can think of a situation albeit rare where there are no alternatives…But I think we do need more data on risk."
- *Dr. Fleming, biostatistician:* "The teratogenicity issues are very significant. They are not established, but the evidence suggests this risk is sufficient…My sense is the wording in Category X applies…With the concerns on safety, I voted yes with the idea that we would be protective against these safety issues that could tip the scale to an unfavorable risk:benefit."
- *Dr. Follman, biostatistician:* "I can see a situation where this is the only alternative…so I voted yes."
- *Dr. Katona:* "You can't just look at it as a drug of last resort."
- *Dr. Leggett:* "I can think of several infrequent but plausible scenarios where the benefit would outweigh the risks…You have to be concerned not only with known but also unknown pregnant women…Whatever the FDA decides about this, it should keep in mind what is currently around and in use right now. On teratogenicity, I agree that this could be a Pregnancy Class C drug…In Category X we (currently) have quinine and ribavirin, which are very different from this."
- *Dr. Nelson:* "It seems unrealistic to sentence pregnant women to death because of some potential to have a teratogenic event."
- *Dr. Paganini:* "Yes, because it should be used if there are no alternatives and it is a life-saving situation…I would place it in Category X."
- *Dr. Septimus:* "I can conceive situations where it might be used…but it has to be done very carefully with a risk management program in place and a registry to monitor for potential low level toxicity."
- *Dr. Steckelberg:* "Yes, because I can conceive of a situation where this might be true though I haven't seen such a situation…I would have said Pregnancy Category X if asked…My main concern is protection of the safety of the patient and without further data, I come down on the side of avoiding inadvertent use. My experience with physicians is if something is in Category C, it is more likely to be used without hard discussions and thought."
- *Patient advocate Thomas:* "I voted yes because it should be used when a patient has resistance to all other antibiotics – as a last resort."
- *Dr. Weinstein:* "I think there could be a situation where the benefit outweighs the risk – like a daptomycin-resistant patient."

5 NO vote comments included (also voting no was Dr. Fleming and Dr. Gutierrez):

- *Dr. Levin:* "I voted no not because I can't conceive of a situation where it could be used, but I think I would vote yes and then for the category I'm interested in (Category X)."
- *Dr. Mirkes:* "I was confused by the question, and I should have voted yes. I tried to convey we don't know the risks on teratogenicity…so I don't distinguish this from vancomycin. I'm in favor of Category C."
- *Chair Dr. Reller:* "I recognize that in a life-saving situation, no one would hesitate to use this drug based on efficacy. On the other hand, we are anticipating a greater need at the same time that we have such sparse experience on the development of resistance to this drug…I don't think it should be given to pregnant women unless one has exhausted other options."

3 Abstentions:

- *Biostatistician Hilton:* "I abstained because the teratogenicity data are inadequate to make this assessment. No amount of limb malformations is acceptable. One of my first research projects was DES (diethylstilbestrol) effects …I just couldn't think our society would accept that."
- *Dr. Kopp:* "I abstained because I don't have enough personal knowledge of the infectious disease side or on the teratogenicity side."
- *Dr. Shelby:* "I don't have enough knowledge to reach a conclusion."

QUESTION 3. Is a risk management strategy needed to prevent unintended use in pregnant women or women of child-bearing potential? (NOTE: *This is in addition to whatever pregnancy category it is given.*)

Vote: 25 YES, 1 NO

TARGANTA THERAPEUTICS' Nuvocid (oritavancin)

After the relatively positive vote on telavancin, the advisory committee's negativity about oritavancin was a surprise. The panel voted 10 to 8 that the data were insufficient on efficacy, particularly against MRSA, though the drug was generally viewed as safe. The panel recommended another trial. However, company officials insisted that they are not giving up on oritavancin.

The company's perspective on oritavancin

The emergence of vancomycin-resistance spurred chemists at Lilly to modify chloroeremomycin (a naturally occurring glycopeptide antibiotic that had been earlier discovered by Lilly) in an effort to create a new antibiotic agent with potent activity against both MRSA and VRE (vancomycin-resistant enterococci). The result was oritavancin. Lilly submitted an IND for oritavancin in August 1996 and conducted 6 Phase I, 3 Phase II, and 2 Phase III cSSSI studies. After the first Phase III study (ARRD), Lilly made a business decision to end its infectious disease drug development program and to focus on other therapeutic areas. Lilly then transferred the oritavancin IND to InterMune in January 2002.

InterMune completed the second Phase III cSSSI study (ARRI), a Phase II bacteremia study, and 5 additional Phase I studies. In two of those Phase I studies, injection site phlebitis was observed in numbers that caused InterMune to voluntarily discontinue the trials prior to completion. InterMune decided to focus on therapies for pulmonary and hepatic diseases, effectively placing oritavancin on voluntary clinical hold.

In February 2006 Targanta acquired the oritavancin IND from InterMune. After reviewing the available data and meeting with the FDA to discuss the phlebitis issue, Targanta demonstrated that the injection site phlebitis encountered was due to a combination of high infusion rates and high drug concentrations administered to healthy subjects – a finding common to vancomycin and other glycopeptide antibiotics. The company also showed that the incidence of injection site phlebitis after oritavancin administration was comparable to that of equipotent therapeutic doses of vancomycin, and that the events were not due to the causes suggested by InterMune. After review, the FDA agreed to lift the voluntary clinical hold imposed by InterMune.

In February 2008, Targanta submitted oritavancin to the FDA. The submission was based in large part on two randomized, double-blind, comparator-controlled, Phase III trials of oritavancin QD in cSSSI that showed both efficacy and safety vs. vancomycin/cephalexin BID. In addition, oritavancin required less frequent dosing, had statistically fewer treatment-emergent adverse events, and did not require special laboratory monitoring. Both studies met the primary endpoint of clinical response at first follow-up visit, demonstrating non-

Pooled Analysis of Oritavancin Safety

Adverse event	Oritavancin n=1,173	Vancomycin n=590	p-value
≥1 treatment-emergent adverse event	53.5%	62.4%	<0.001
≥1 drug-related treatment-emergent adverse event	18.0%	25.3%	<0.001
≥1 serious adverse event	9.1%	11.4%	Nss, 0.150
≥1 drug-related serious adverse event	0.9%	1.2%	Nss, 0.606
Fatal SAE	1.6%	2.0%	Nss, 0.566
Discontinued study drug due to an adverse event	3.0%	5.8%	0.006
Insomnia	4.9%	7.6%	<0.05
Dizziness	3.0%	1.4%	<0.05
Pruritis	2.4%	6.6%	<0.05
Rash	2.2%	4.1%	<0.05

inferiority. Oritavancin showed consistent efficacy across subpopulations (including patients with preexisting and/or concurrent comorbidities) and across disease categories (wound, major abscess, and cellulitis) in both of the individual Phase III studies as well as in a pooled analysis.

Thomas Parr PhD, chief scientific officer at Targanta, presented oritavancin as "a new option for gram-positive treatment" of cSSSI. He emphasized that it was studied in two positive Phase III trials and has been studied since 1977 in 1,617 patients. Unlike Theravance's telavancin which has a mechanism of action similar to vancomycin, he said oritavancin's multiple mechanisms of action reduce the probability of resistance. He also noted that oritavancin has a wide spectrum of activity, a short course of dosing, a strong safety profile, and fewer side effects and treatment issues than vancomycin.

Efficacy. Dr. Pierre Etienne, chief development officer for Targanta, reviewed oritavancin's clinical efficacy. He emphasized that oritavancin has shown:

- Efficacy in treating serious Gram-positive cSSSI with a low rate of relapse.
- Non-inferiority to vancomycin in 2 Phase III studies.
- Consistent efficacy across different patient populations.
- Consistent efficacy across different disease categories.
- Efficacy in patients with underlying diseases.
- Microbiological efficacy.

Safety. The key safety issues addressed by the company included:

➢ ***Phlebitis.*** Targanta conducted a comprehensive review and analysis of safety data relating to injection site phlebitis, including 1,962 patients and 243 healthy subjects. The company concluded:

- The incidence of injection site phlebitis was comparable to equipotent doses of vancomycin.
- No association was observed between drug substance lot or drug product lot or date of manufacture and the incidence of injection site phlebitis.
- Oritavancin was well tolerated in patients with bacteremia at doses up to 10 mg/kg/day for up to 14 days (maximum dose administered 1220 mg/day for 14 days), with an incidence of injection site phlebitis comparable with that of vancomycin.
- Oritavancin can be administered safely to patients in single doses up to at least 800 mg/day with a low incidence of injection site phlebitis (0.4% on first day of dosing in multiple-dose studies).
- In clinical studies of healthy subjects receiving multiple daily doses of oritavancin, injection site phlebitis was observed on the first day of dosing in 4.4% of subjects. Little or no associated injection site phlebitis was observed in healthy subjects receiving single doses of oritavancin.
- The drug administration parameters most clearly related to the incidence and severity of injection site phlebitis were: the drug delivery rate (mg/min) x concentration of the infusate (mg/mL), expressed as $mg^2/mL \cdot min$); the delivery rate of oritavancin to the vein in mg/min; and, to a lesser extent, the concentration of oritavancin infusate in mg/mL.

Results of Oritavancin Weight-Based ARRD Phase II/III Trial (NI ≤15%)

Measurement	Oritavancin 1.5 mg/kg n=173	Oritavancin 3.0 mg/kg n=169	Vancomycin 15 mg/kg n=175
Baseline demographics			
Wound infections	20.2%	20.1%	21.7%
Major abscesses	38.2%	36.1%	36.6%
Cellulitis	41.6%	43.8%	41.7%
Efficacy by primary outcome (clinical response) in specific patient populations			
Efficacy in IDCO patients *	75.8%	75.4%	80.0%
Efficacy in SDCO patients **	72.1%	73.4%	75.4%
Patient level microbiological outcome	65.8%	72.7%	74.7%
Efficacy in ARRD trial by disease category			
Wound infections	75%	77%	67%
Major abscesses	74%	77%	79%
Cellulitis	69%	69%	77%

* Investigator-defined clinical outcome ** Sponsor-defined clinical outcome

Results of Oritavancin Fixed-Dose ARRI Phase III Trial (NI ≤10%)

Measurement	Oritavancin n=831	Vancomycin n=415
Baseline demographics		
Wound infections	31.9%	33.5%
Major abscesses	44.0%	42.7%
Cellulitis	24.1%	23.9%
Sponsor-defined clinical outcome in ARRI		
Efficacy in IDCO patients	80.4%	81.8%
Efficacy in SDCO patients	76.9%	85.8%
Patient level microbiological outcome	72.8%	72.5%

Pooled Results of Oritavancin in ARRI and ARRD Trials

Measurement	Oritavancin	Vancomycin
Clinical efficacy in special patient populations		
Age ≥65	72.0%	69.0%
Age ≥75	68.3%	61.3%
Creatinine clearance >80 mL/min	78.1%	77.2%
Creatinine clearance >30 to ≤80 mL/min	75.7%	71.1%
Creatinine clearance >10 to ≤30 mL/min	60.0%	0
Hepatic insufficiency	62.2%	62.9%
HIV/AIDS	73.7%	66.7%
Diabetes	62.2%	62.9%
Relapse rate at late follow-up visit		
ITT	2.3%	2.0%
Clinically-evaluable	2.4%	1.9%

➢ ***Histamine-like infusion reactions***, sometimes called "Red man syndrome" or described as anaphylactoid reactions. These have also been observed with vancomycin, where they might present as flushing, erythema, wheezing, dyspnea, angioedema, urticaria, pruritis, pain, or muscle spasm. However, the company noted that among the 101 Phase III patients who had at least one possible histamine-like infusion reaction (HLIR), fewer oritavancin patients (25.0%) received medication for HLIR than vancomycin/cephalexin patients (44.6%), and fewer patients discontinued therapy due to HLIR with oritavancin (8.3%) than vancomycin/cephalexin (16.9%).

➢ ***QT prolongation*.** In a Phase I study, mean QTc changes with oritavancin were below a 90% upper confidence limit of 10 msec at all time points, and there was no evidence of a dose-response relationship. Because of preclinical findings, Targanta completed an extensive evaluation of cardiovascular safety with ECGs. No clinically relevant effect of oritavancin was observed on QT/QTc interval in any of these analyses.

Risk:benefit. Dr. Susan Moriarty, senior director of medical affairs for Targanta, explained that oritavancin is well tolerated with a favorable risk:benefit profile in cSSSI patients, that no dose adjustments are required in special populations, and no special laboratory monitoring is indicated.

The adverse events considered most likely to be treatment-related occurred in 12 categories, but in 7 of these the incidence was significantly lower with oritavancin than with vancomycin: pruritis, erythema, generalized pruritis, flushing, Red man syndrome, urticaria, and infusion site pruritis. Infusion site pain and infusion site phlebitis were comparable to vancomycin. Rash was less with oritavancin but not significantly. She added, "We see no initiation of late onset of adverse events with oritavancin…The time to adverse event resolution was similar to vancomycin…There were no clinically relevant safety findings in…any patient treatment group."

She also emphasized that there is no evidence of renal or hepatic toxicity and no QT prolongation. Animal data suggested a potential cardiac safety signal, primarily at higher doses, but subsequent dog studies did not show any QT prolongation or arrhythmia. A thorough QT/QTc study found no QT/QTc effect with the clinical (200 mg) dose or a supra-therapeutic (800 mg) dose.

Risk:Benefit Profile of Oritavancin

Benefits	Risks
Demonstrated efficacy	Injection site phlebitis
Favorable safety profile	Histamine-like infusion reactions
No special laboratory monitoring	Rare adverse events
Once-daily 3-7 day course	Development of resistance
Single dose adjustment	
Multiple mechanisms of action	
Potent *in vitro* activity	

The FDA perspective on oritavancin

The FDA staff found:

- No significant PK issues.
- A half-life of ~31 hours.
- No metabolism by the cytochrome P450 system.
- Dose adjustments are not needed for renal or hepatic impairment patients.
- The outcomes for oritavancin and vancomycin/cephalexin patients with cSSSI were comparable in subgroup analyses for age, gender, ethnic group, region, and disease category.
- Treatment-emergent adverse events include: injection site phlebitis, histamine-like infusion reactions, and gout.

In addition to concern about injection site phlebitis and histamine-like infusions, the FDA staff raised questions about:

- QT prolongation – which staffers said could be an issue in clinical use.
- Persistent histocytosis in multiple organs, including the liver, kidney, spleen, and lymph nodes, as well as at the injection site – which staffers called "troubling." The persistence at the injection site may be responsible for the phlebitis seen in clinical trials.
- Two interim analyses were planned in the ARRD trial, but no adjustment to the p=0.05 value was made in the final analysis. The company justified not adjusting the p-value because the trial was not to be stopped at either interim analysis for superior performance of either oritavancin treatment group.

Dr. Nasim Moledina, an FDA medical reviewer, said she was going to offer a "different perspective" on a few things. She declined to do a pooled analysis because the dosing regimens used in ARRD and ARRI trials "were not at all similar." On average, she estimated that oritavancin patients in ARRD 3.0 mg/kg received a higher dose and had a higher exposure vs. patients in ARRI…She added, "Any differences in efficacy for oritavancin between the ARRD 3.0 mg/kg group and the ARRI fixed dose group are not due to patients in the ARRD 3.0 mg/kg group receiving a lower dose."

FDA Comparison of Doses in Oritavancin Phase III Trials

Mean dose	Oritavancin dose	
	ARRI trial n=762	ARRD trial n=143
Patients 49-110 kg	200 mg (n=734)	224 mg (n=139)
Patients 111-122 kg	300 mg (n=28)	349 mg (n=4)

Safety – It was very evident that there were some adverse events that occurred more with oritavancin than vancomycin. More infection adverse events with oritavancin than vancomycin – particularly more osteomyelitis (0.4% vs. 0), limb

abscess (0.5% vs. 0.2%), septic shock (0.3% vs. 0) – but they were mostly patients who developed the infection due to their underlying disease.

Deaths – A total of 74 deaths occurred (8 of those during the post-study period) in both arms of the Phase III trials. Overall, "the vast majority of death were found to be related to the underlying medical condition of the patients."

Injection site vein toleration – An additional Phase I study was done, and she described it as "very well-done," but she said it gave no new information.

FDA View of Results of Oritavancin Studies

Measurement	Oritavancin		Vancomycin
ARRD Phase II/III trial (NI ≤15%)			
	Oritavancin 1.5 mg/kg	**Oritavancin 3.0 mg/kg**	**Vancomycin**
Patients enrolled	173	169	175
Discontinued	27.2%	31.4%	27.4%
Discontinued for lack of efficacy	4.6%	7.1%	3.4%
Discontinued for adverse events	3.5%	7.7%	7.4%
Primary endpoint: Sponsor-defined clinical outcome	56.6%	56.2%	57.7%
Cure rate	- 2.2% vs. vancomycin	- 3.2% vs. vancomycin	---
Serious adverse events	42.2%		50.0%
Sponsor-defined clinical outcome in ARRD			
Staphylococcus aureus	52.9%	54.0%	56.9%
MSSA	59.5%	51.2%	55.3%
MRSA	40.0%	62.5%	57.1%
Streptococcus pyogenes	35.7%	64.3%	55.0%
Streptococcus agalactiae	40.0%	75.0%	87.5%
Streptococcus anginosus group	50.0%	86.7%	47.8%
Streptococcus dysgalactiae	43.8%	75.0%	57.1%
Other *Streptococcus* spp	53.8%	75.0%	57.1%
Enterococcus faecalis	66.7%	60.0%	66.7%
Other *Enterococcus* spp	50.0%	33.3%	50.0%
ARRI Phase III trial (NI ≤10%)			
Patients enrolled	831		415
Discontinued	11.4%		12.5%
Discontinued for lack of efficacy	3.9%		2.9%
Discontinued for adverse events	5.7%		4.6%
Primary endpoint #1: Sponsor-defined clinical outcome	71.5%		68.4%
Primary endpoint #2: Cure rate	78.5%		75.9%
Sponsor-defined clinical outcome in ARRI			
Staphylococcus aureus	70.6%		71.2%
MSSA	76.6%		74.4%
MRSA	55.9%		67.9%
Streptococcus pyogenes	77.1%		58.1%
Streptococcus agalactiae	57.1%		75.0%
Streptococcus anginosus group	65.8%		68.4%
Streptococcus dysgalactiae	66.7%		40.0%
Other *Streptococcus* spp	75.0%		57.1%
Enterococcus faecalis	67.6%		66.7%
Other *Enterococcus* spp	50.0%		42.9%

Treatment-emergence events of special interest:

- IV infusion site phlebitis in 1.6% of patients vs. 1.5% with vancomycin.
- Infusion site pain reported in 1.7% of patients vs. 1.9% with vancomycin.
- Pruritis in 1.6% of patients vs. 5.4% with vancomycin.

Panel questions/discussion of oritavancin

- *Dr. Fleming, biostatistician:* "I don't know how to take it, but it seems that vancomycin is trending better (than oritavancin in MRSA)…To me it is a proof-of-concept measure. It (the primary endpoint) gives me a sense but no way measures directly the resolution of the clinical condition…I don't know how to justify a non-inferiority margin using this endpoint."
- *Dr. Kaufmann:* "My concern is it looks like this drug lives forever and has a long half-life…And you described granules which ultimately disappeared…Is that drug accumulation? And what is long-term toxicity of stuffing macrophages with something that is not metabolized away? Are there enough data to say this is safe?"
- *Chair Dr. Reller:* "I'm glad Dr. Kaufmann asked that because if it got to me, I had the same question …Is there any (other) drug like this…staying there seemingly almost in perpetuity? What are the precedents and the implications with what is a short follow-up time after therapy?"
- *Dr. Guy Paulus, a Targanta toxicology consultant:* "I should emphasize we are talking about a very short course of treatment with oritavancin…In the dogs, we actually give a daily dose for 90 days…so there is a big difference when you compare cumulative doses (~20 mg/kg in man vs. ~4000 mg/kg in dogs)…Given the compound's tissue penetration and long life in the body, we looked very carefully for any toxicity associated with that, and we found no evidence it had any adverse effect on the safety profile of the drug."

Panel consideration of FDA questions on oritavancin

QUESTION 1. Does study ARRI independently provide evidence of the effectiveness of oritavancin for cSSSI? In your response, discuss the primary outcome and 95% confidence interval (CI) for the study and discuss the outcomes for patients with known baseline pathogens, particularly MRSA.

Vote: 11 YES, 6 NO, 1 Abstention

11 YES vote comments included:

- *Dr. Bennett:* "I voted yes because the weight of the evidence is that the drug is effective."

- *Dr. Follman:* "The overall cure rate reliably showed it is non-inferior to the comparator. I have concerns though that the endpoint was suboptimal…I view this as one study, not having the weight of two studies. MRSA was murky and hypothesis-generating."
- *Biostatistician Hilton:* "I voted yes because the question did not focus on MRSA, or I would have voted no…I'm curious about pregnant women…and I'm hoping the sponsor is alert to what we heard (about telavancin and pregnancy)."
- *Dr. Leggett:* "The confidence intervals were well in the limits…and I thought it was safe."
- *Dr. Nelson:* "I think the main reason was the question actually asked about the overall efficacy of the drug not the MRSA effectiveness. If it asked that, I would be much less comfortable…I would go back and look for more proof on MRSA…In the overall picture, I think for cSSSI it is effective."
- *Dr. Septimus:* "This is actually a very attractive drug for dosing and toxicity except for the toxicities that I don't think are all due to the drug…I'm still a little concerned about the (efficacy in) streptococcus. On MRSA, it would be nice to go back and start today with MRSA and do an in-depth evaluation of this drug."
- *Patient advocate Thomas:* "I would have liked a larger study. I was a little perplexed by the (poor) MRSA results, but I understand this was done years ago. Osteomyelitis is a concern."
- *Dr. Weinstein:* "I based my yes vote on the overall issue of efficacy for the infections, but had it come to MRSA, I would have voted ***no***. The data presented, perhaps because of the study design, simply don't convince me there is non-inferiority, and I think we need data from contemporary isolates and contemporary studies."

6 NO vote comments included (also voting no were Dr. Alston and Dr. Katona):

- *Dr. Cross:* "It is an attractive drug, and overall showed efficacy for cSSSI…but in my case I am bugged by the MRSA (lack of efficacy) and the fact that, if anything, the MRSA has become more resistant to vancomycin."
- *Dr. Fleming:* "The MRSA results are obviously complicated to interpret…I would call the entire trial hypothesis-generating. The safety profile looks quite favorable. I do have concern about infection adverse events…But I do believe you could have a result that is compelling statistically but it also has to be highly compelling clinically, and the results can't be ignored from the (ARRD) trial which looks less favorable than this (ARRI) trial…So, there are many issues of concern in interpreting this trial…I could be persuaded that it is a supportive trial with a second high quality trial."
- *Dr. Goetz:* "I'm concerned that the wide confidence limits do not support use of this drug today in our current patient population."
- *Dr. Gutierrez:* "This is a very attractive drug, and I liked the safety profile, but in this day of MRSA, I couldn't be convinced it was not inferior to vancomycin. I really hope the sponsor pursues other studies, particularly in MRSA because I think it is a very attractive drug."

1 Abstention. The only abstention was consumer representative Levin, who said, "I found myself more and more confused. My vote probably should be a no vote because I was not convinced."

QUESTION 2. Does study ARRD independently provide evidence of the effectiveness of oritavancin for cSSSI? In your response, discuss the primary outcome and 97.5% CI for the study and weight-based dosing regimen used in study ARRD.

Vote: 10 NO, 8 YES

10 NO vote comments included:

- *Dr. Fleming:* "The results were underpowered and less relatable…Using a 10% non-inferiority margin this trial fails. You don't even meet the 15% margin (in some analyses)…It is a result from a Phase II screening trial…And the trend is slightly in the wrong way in this trial…So, for multiple reasons this is not one of two adequate well-controlled, positive trials."
- *Dr. Follman:* "I had questions about the endpoint, and the trial was too small. I think they inherited an underpowered study. It is not like you did a large study…I don't think it changes anything; it is just an underpowered study. On the 97.5% confidence interval issue, that is a more technical point, and I would be okay with a 95% confidence interval. I would focus on the 3 mg dose."
- *Dr. Gutierrez:* "The numbers were small, and they really only looked at the 3 mg dose."
- *Dr. Kaufmann:* "I think you inherited a dose-finding study, and the numbers were too small. I don't think it proved the point."
- *Dr. Weinstein:* "There was an inadequate number of observations."

8 YES vote comments included (Dr. Septimus also voted yes):

- *Biostatistician Hilton:* "It was the 15% non-inferiority that bothered me…It was basically an underpowered study but with good results."
- *Dr. Cross:* "I voted yes, with reservations – but I feel it was underpowered."

- *Patient advocate Thomas:* "It was small and the margins may be problematic, but it was a fairly good-designed study."
- *Dr. Nelson:* "I was not feeling strong about my decision, and I have concerns…They did find what they set out to find…They had higher statistical probability than 95%... so I think they did find what they were looking for. Small numbers are fine as long as it is statistically reasonable, and it seems to be."
- *Dr. Katona:* "The study really met the criteria…I have no problem with the 15% non-inferiority margin. Overall, I think it accomplished what it was supposed to accomplish."
- *Timothy Lesar, PharmD, director of pharmacy at Albany Medical Center:* "I voted yes – but with reservations."
- *Chair Dr. Reller:* "I was influenced by our discussions (on non-inferiority margins), but at the time it was done, the 15% margin was approved."

QUESTION 3. Do the data presented demonstrate the safety and effectiveness of oritavancin for the treatment of cSSSI? If no, what additional data/studies are needed?

Vote: 10 NO, 8 YES

10 NO vote comments included:

- *Dr. Cross:* "Even though it technically fulfilled the non-inferiority margin, I think you need something that covers MRSA better."
- *Dr. Fleming:* "I would think one additional trial would give us a reliable answer – with an endpoint more clearly aligned to addressing clinical conditions patients are seeking to address and giving us more insight on MRSA …I would recommend one additional quality study be completed."
- *Dr. Follman:* "I don't think the ARRD trial adds enough."
- *Dr. Goetz:* "I don't see how I could personally approve this drug for treatment of MRSA infections."
- *Dr. Kaufmann:* "It may be a wonderful drug, but we need more information."
- *Dr. Nelson:* "In the first two studies, there was a question about the studies, not the big picture. In the big picture, I don't think the study does what it is purported to do… And there are some lingering issues…It demonstrates it is not unsafe, but not necessarily that it is safe."
- *Chair Dr. Reller:* "To me, it (my no vote) sends a very strong signal that people want an effective drug, but we just haven't seen enough evidence with what the contemporary problem is, and I do not necessarily see an inconsistency in that. It is a consistent message that we need more information to be perfectly comfortable on questions of toxicity and, most important, on efficacy on this drug that (would be) used empirically in serious situations that require a drug of demonstrated effectiveness against MRSA. I think a follow-up study that would provide that assurance should be done with a single, appropriate dose, so we have the numbers for adequate comparison."

8 YES vote comments included (Dr. Katona, patient advocate Thomas, and Dr. Weinstein also voted yes):

- *Dr. Bennett:* "I'm very unenthusiastic. The problem is it is extraordinarily expensive to do these studies. It is not a wonderful drug, but on balance do we think this is worth another $7 million (trial)? I thought probably not."
- *Biostatistician Hilton:* "I voted yes because MRSA wasn't the stated goal."
- *Dr. Leggett:* "I think, on balance, the answer is satisfactory."
- *Dr. Lesar:* "I voted yes with great reservation, but the safety profile looks very good…But I have tremendous concern about (efficacy in) MRSA."
- *Dr. Septimus:* "A soft yes…I think it is attractive because of the safety and dosing issues. If I were asked about MRSA, I would vote no…It would be nice to have the study updated with MRSA."

Targanta reaction to the Advisory Committee decisions

Mark Leuchtenberger, President/CEO of Targanta, told reporters after the panel meeting, "While clinical data certainly matters, we felt we proved the point on efficacy… We regard it as a split decision…That is about as split as you can get…It makes the path forward steep…Our next step will be to confer with the FDA."

Asked if the company has the resources to do another study if the FDA asks for that, Leuchtenberger said, "We have already announced…a cSSSI study as a single infusion and infrequent infusions – a more convenient dosing regimen vs. standard-of-care. How large that is and the inclusion criteria – and if it could be a Phase III trial – needs to be discussed with the FDA…Regardless of the outcome of this panel, we were planning a Phase III in cSSSI to test a single infusion."

Leuchtenberger also said there are results from a Phase II trial completed earlier this year that the FDA has not yet seen, "That was almost 60% MRSA…testing three dosing regimens of oritavancin: infrequent dosing on Days 1-5, 3 doses of oritavancin over 3-7 days, and a single infusion of 1200 mg over 2-3 hours…The results were presented at ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy in October 2008)…It wasn't presented to the FDA because the results were too late to include in this filing… They (FDA) only have the safety data…We had no way to submit (the full) data legally."

Asked if Targanta could submit this Phase II data before the PDUFA date and get an extension on the decision, Leuchtenberger would say only, "That is possible, but I'm not saying we will do that."

ARPIDA'S Iclaprim

Iclaprim was submitted to the FDA in March 2008, and the PDUFA date is January 16, 2009, but approval doesn't look likely. The advisory committee voted 17 to 2 that iclaprim failed to show sufficient safety and efficacy in cSSSI in the Phase III ASSIST-1 and ASSIST-2 trials. The panel also voted 15 to 3, with one abstention, that if the FDA approves iclaprim against the committee's recommendation, use should be restricted to refractory patients or those unable to take other approved antibiotics. The panel also recommended another clinical trial be conducted before approval, using vancomycin, not linezolid, as the comparator and with a non-inferiority margin of 10%.

Iclaprim is a dihydrofolate reductase (DHFR) inhibitor, similar in mechanism of action to trimethoprim, so it is synergistic with sulfonamides against a broad spectrum of bacterial species. At the proposed dose of 0.8 mg/kg, iclaprim has a mean C_{max} of 0.85 µg/mL at the end of infusion. Its half-life is ~2.5 hours, and there is no accumulation with repeat dosing.

The panel liked the idea of a potentially oral agent, the panel was uncomfortable with the use of linezolid as the comparator and the company's refusal to follow the FDA's advice and use a 10% non-inferiority margin, instead doing its pivotal trial with a 12.5% NI margin. Panel member Hilton, a biostatistician, said that she voted against iclaprim's safety and efficacy, but added, "I still have hope for this compound (especially because an oral formulation is in development)."

The FDA perspective on iclaprim

Dr. John Alexander, lead medical officer in the FDA's Division of Anti-Infective and Ophthalmology Products, said the FDA had advised Arpida to use a 10% NI margin. However, the FDA did tell Arpida that a 12.5% margin and linezolid as a comparator would be acceptable as long as non-inferiority was demonstrated and there were no safety issues with Iclaprim. However, safety issues did arise, and Dr. Alexander said that was the reason iclaprim was taken to an advisory committee.

Safety. Renal, hepatic, and cardiac events were reported in the ASSIST trials and a Phase II study (AR-100-SSTI-001). The FDA's analysis of the iclaprim data identified three patient deaths that the FDA staff deemed as "possibly related" to iclaprim. One of those patients died of acute renal failure. All three patients were found dead or unconscious in their hospital bed and had multiple pre-existing or comorbid conditions.

The key FDA safety concerns in the ASSIST trials and a Phase II study (AR-100-SSTI-001) were:

- **Renal toxicity.** Two patients were reported to have a serious renal adverse event possibly related to iclaprim, and one of these died.
- **Hepatic toxicity.** One patient experienced a severe hepatic adverse event in ASSIST-2, which was determined to be possibly related to iclaprim, though he recovered.
- **Cardiac events.** Preclinical and clinical studies showed a dose-dependent increase in QTc, and this occurred equally in men and women. There were no related torsades de pointes or ventricular arrhythmias, but two patients were withdrawn from the study because of QTc prolongation, and two deaths possibly related to iclaprim had cardiac etiology.

FDA View of Iclaprim Safety in ASSIST Trials

Measurement	Iclaprim	Linezolid
Any treatment-emergent adverse event	49.8%	52.3%
Nausea	6%	7.9%
ALT or AST elevation	7.2%	6.9%
ALT ≥3xULN (at TOC)	3.87%	2.86%
ALT ≥3xULN (at last follow-up)	5.25%	1.83%
Pyrexia, chills, feeling cold, cold sweat, or increase in body temperature	9.4%	5.3%
New abscess	3.4%	2%
Mean QT change on Day 1	12.1 msec	4.3 msec
Mean QT change on Day 4	22.3 msec	17.3 msec
QTC prolongation >30 msec	38.3%	29.2%
Any severe treatment-emergent adverse event	2.2%	1.2%
Deaths	1.2%	0.2%
Discontinued for treatment failure	5%	1%

Efficacy. In addition to the safety concerns, Dr. Alexander said the FDA's analysis of the primary endpoints found that iclaprim actually was less effective than linezolid against cSSSI. The upper limit of the 95% confidence interval for the treatment difference failed to cross zero in the intent-to-treat and per-protocol data in ASSIST-1 and in the per-protocol data in ASSIST-2, he explained. The FDA also reclassified the response rates for some study participants who experienced new or recurrent infections and were treated with other antibiotics. The responses for five study participants were changed from "cure" to "failed" and to "indeterminate" for two.

After the original briefing documents were prepared for the panel, the FDA staff revised their efficacy analysis of the ASSIST trials, and they presented a new analysis. In the briefing document, 17 patients who were considered cured in the company's analyses were assigned indeterminate outcomes by FDA reviewers because they received systemic antimicrobials after the start of study drug.

Arpida's perspective on iclaprim

Arpida officials disputed the FDA's reclassification of these patients, arguing that the company's original classifications occurred beyond the likely pharmacological effect of the drug.

Arpida officials declined to comment after the panel meeting, but the company said in a statement that it remained "confident" in iclaprim and would continue to work with the FDA to get it approved. Earlier this year, Arpida started a Phase II trial of iclaprim IV-to-oral switching in cSSSI patients. Patient enrollment was completed in September 2008, with results expected in December 2008. Arpida also has worldwide studies ongoing investigating the use of IV iclaprim in hospital-acquired pneumonia (HAP), ventilator-associated pneumonia, and healthcare-associated pneumonia.

Results of FDA Re-Analysis of Iclaprim Efficacy in ASSIST Trials

Measurement	ASSIST-1		ASSIST-2	
	Iclaprim n=249	Linezolid n=248	Iclaprim n=251	Linezolid n=243
Pre-study antibacterial therapy	39.8%	36.7%	12.7%	0.2%
Antibacterial therapy during study	37.8%	28.2%	39.8%	35.0%
Primary endpoint: **Clinical cure at TOC (by ITT)**				
All patients	81.9%	88.7%	80.1%	81.5%
North American patients	65.4%	77.4%	77.7%	74.6%
Eastern European patients	86.3%	91.8%	---	---
Rest of world patients	---	---	83.5%	91.1%
Clinical cure at TOC (per protocol)				
All patients	93.2%	99.1%	88.5%	95.9%
North American patients	80.6%	94.7%	87.0%	93.5%
Eastern European patients	95.9%	100%	---	---
Rest of world patients	---	---	90.7%	98.9%
Clinical cure by type of infection (by ITT)				
Infected ulcers	91.9%	91.7%	77.3%	77.8%
Burns (1st or 2nd degree)	79.4%	80.7%	80.0%	86.4%
Major abscesses	75.5%	88.7%	79.0%	77.5%
Cellulitis – deep or extensive	79.3%	88.9%	73.2%	79.7%
Wound infections	69.0%	83.7%	83.9%	82.9%
Clinical cure by pathogen (by MITT)				
MRSA	80.0%	94.4%	75.7%	77.5%
MSSA	84.9%	89.8%	83.6%	85.9%
Streptococcus agalactiae	33.3%	57.1%	60.0%	100%

Panel consideration of FDA questions

QUESTION 1a. Do the data presented demonstrate the safety and effectiveness of iclaprim for the treatment of cSSSI?

Vote: 17 NO, 2 YES

QUESTION 1b. If your answer is no, what additional data/studies are needed?

The panel also recommended **another clinical trail** be conducted before approval, using **vancomycin**, not linezolid, as the comparator and with a **non-inferiority margin of 10%**.

QUESTION 2. Should there be any limitations on the use of iclaprim?

Vote: 15 YES, 3 NO, 1 Abstention

The panel recommended that, if iclaprim is approved, it be a last-line agent, with use restricted to refractory patients or those patients unable to take other approved antibiotics.

Arpida reaction to the panel votes

Following the panel meeting, Arpida announced it was cutting its workforce – by up to 60 people. The company also plans to discuss the situation with outside experts to help decide whether to continue development of iclaprim.

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