CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Deputy Office Director Decisional Memo
NDA #	21-883
Applicant Name	Durata Therapeutics, Inc.
Date of Submission	September 26, 2013
PDUFA Goal Date	May 26, 2014
Proprietary Name / Established (USAN) Name	Dalvance™/ (dalbavancin) for injection
Dosage Forms / Strength	Lyophilized powder for injection /500 mg vial
Proposed Indication	Acute bacterial skin and skin structure infections
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Dmitri Iarikov, M.D., Ph.D.
Statistical Review	Christopher Kadoorie, Ph.D.
Pharmacology Toxicology Review	Terry Miller, Ph.D.
Chemistry, Manufacturing, and Controls / Biopharmaceutics / Product Quality Reviews	Mark Seggel Ph.D., Balajee Shanmugam Ph.D., Steven Donald, M.S., Houda Mahayni, Ph.D.
Microbiology Review	Peter Coderre, Ph.D.
Clinical Pharmacology Review	Yang He, Ph.D.
OPDP	Christine Corser, Pharm.D.
OSI	Lauren Iacono-Connors, Ph.D.
OSE/DMEPA	Aleksander Winiarski, Pharm.D.
OSE/DRISK	Bob Pratt, Pharm.D.
CDTL Review	John Alexander, M.D., M.P.H.
Division Director Review	Sumathi Nambiar, M.D., M.P.H.

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DRISK=Division of Risk Management

1. Introduction

Dalbavancin is a lipoglycopeptide antibacterial drug, interfering with cell wall synthesis. It is obtained by chemical modification of a natural glycopeptide, A-40,926, a fermentation product of *Nonomuraeae* sp. The drug has activity against certain Gram-positive bacteria including *Staphylococci and Streptococci.* The proposed indication is the treatment of acute bacterial skin and skin structure infections (ABSSSI). Dalbavancin for injection will be available as a lyophilized powder for injection. The proposed dosing regimen for adults is 1000 mg intravenous (IV) followed one week later by 500 mg IV.

The efficacy review for this NDA relies primarily upon the results of two adequate and well-controlled Phase 3 trials conducted by the applicant in patients with ABSSSI. Trials DUR001-301 and DUR001-302 were Phase 3, randomized, double-blind, multicenter trials comparing IV dalbavancin to IV vancomycin (with or without switch to oral linezolid).

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of dalbavancin for the indication proposed. For a detailed discussion of NDA 21-883, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader (CDTL) Review, and the Division Director Review.

2. Background/Regulatory

An NDA for dalbavancin was originally submitted by Vicuron Pharmaceuticals, a subsidiary of Pfizer Pharmaceuticals, on December 21, 2004 seeking an indication for the treatment of complicated skin and skin structure infections. An approvable letter was issued on September 21, 2005 pending resolution of a manufacturing issue and agreement on final labeling. A second approvable letter was issued on June 21, 2006 due to outstanding Chemistry Manufacturing and Controls (CMC) issues. On December 20, 2007, a third approvable letter was issued. In addition to GMP compliance issues, another of the deficiencies listed in the December 20, 2007 letter was that an adequate justification for a non-inferiority (NI) margin had not been provided for Study VER001-8, which had enrolled patients with uncomplicated skin and skin structure infections. On December 11, 2009, Durata Therapeutics Inc. assumed ownership of dalbavancin and subsequently initiated a clinical development program that included two new Phase 3 trials in ABSSSI, Trials DUR001-301 and DUR001-302.

Throughout the period that dalbavancin was under development, there was considerable public discussion regarding the design of NI trials for serious bacterial infections including ABSSSI, particularly the primary endpoints for which a NI margin could be justified. In 2010, FDA issued a draft Guidance entitled, *Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment*. The draft Guidance recommended a primary efficacy endpoint of clinical response (cessation of spread of lesion, and the absence of fever) at 48 to 72 hours for NI trials in ABSSSI. Trials DUR001-301 and DUR001-302 were designed with primary endpoints consistent with this recommendation. Following further public discussion, including input from the

Foundation for the National Institutes of Health Biomarkers Consortium, a final Guidance was published October 16, 2013[1]. The final Guidance recommended a primary endpoint of ≥20% reduction in lesion size from baseline (no fever component) at 48-72 hours. Evaluation of this endpoint was a pre-planned sensitivity analysis in Trials DUR001-301 and DUR001-302.

Dalbavancin had been granted Fast Track status prior to Durata Therapeutics Inc. assuming ownership. On October 25, 2012, Durata's dalbavancin product for IV use was designated as a Qualified Infectious Disease Product (QIDP) for the following indication: treatment of ABSSSI. The NDA received a priority review.

3. Chemistry Manufacturing and Controls (CMC) / Product Quality Microbiology

The CMC Reviewers concluded that the NDA provides sufficient information to assure the identity, strength, quality, and potency of dalbavancin. They recommended approval pending satisfactory cGMP inspections and issuance of an overall acceptable recommendation from the Office of Compliance. There is a (b) (4) and adequate in-process controls and regulatory testing were described in the NDA. The Reviewers noted that, in preparing the Master Cell Bank, (b) (4) is used. The applicant agreed to a 2 year timeline post-approval to replace (b) (4) This will be included in the Approval Letter as a Post-Marketing Commitment (PMC). The drug product is manufactured in (b) (4) Adequate in-process controls and regulatory testing were described in the NDA. Stability studies support an expiration dating period of 36 months at 25°C.

Product quality microbiology was reviewed and all procedures to maintain sterility were assessed as adequate. The Product Quality Microbiology Reviewer recommended approval.

Manufacturing site inspections were completed and the Office of Compliance deemed all sites as acceptable for this NDA. Of note, following an inspection of the manufacturing site responsible for drug product manufacture, drug product packaging and labeling, drug product release testing, and drug product stability, the Office of Compliance requested a commitment from the manufacturing site to amend the process validation approach. The applicant agreed to a PMC to submit batch release test results from upcoming process performance qualification lot(s) when process performance qualification activities have been completed. See the May 23, 2014 Memo from the Office of Compliance for additional detail.

[1] Available at: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf

I conclude that there are no outstanding CMC or Product Quality Microbiology issues precluding approval.

4. Non-Clinical Pharmacology Toxicology

The Pharmacology Toxicology Reviewer concluded that the non-clinical studies conducted with dalbavancin are adequate for approval. Safety pharmacology studies were conducted in mice, rats, and rabbits. The pharmacokinetic (PK) properties of dalbavancin were noted to be consistent amongst a number of animal species, with a very long half-life in both plasma and tissues. The toxicologic profile of dalbavancin was similar among species; local injection site toxicity, histamine related infusion reactions, and target organ toxicity to the liver and kidney were noted in several species. Histologic correlates including hepatocellular and renal tubular cell necrosis, vacuolation, and degeneration were associated with prolonged elevation of serum liver tests and creatinine observed with high dose administration. An in-vitro hERG channel assay and in-vivo studies in dogs found no significant effects on cardiac function. Juvenile animal toxicology was similar to adults. Dalbavancin was not a mutagen nor clastogen based on a testing battery and was not teratogenic in pregnant rats and rabbits up to maternal toxic doses. The Reviewer recommended Pregnancy Category C in labeling. Prenatal and postnatal development studies in rats noted an increased number of deaths in the high dose treatment group compared with controls. There were no novel excipients and no impurities or degradants of concern.

The findings regarding animal hepatotoxicity, renal toxicity, and reproductive toxicology will be described in labeling. I concur that there are no outstanding Pharmacology Toxicology concerns precluding approval.

5. Clinical Pharmacology

The Clinical Pharmacology Reviewer found the NDA to be acceptable from a Clinical Pharmacology perspective. The applicant submitted studies to assess single and multiple dose pharmacokinetics, excretion and metabolism, penetration into skin blister fluid, pharmacokinetics in patients with renal and hepatic impairment, a thorough QT study, and a PK study in adolescent patients 12-16 years of age. Dalbavancin has a terminal half-life of 346 hours and mean plasma protein binding is approximately 93%. Dalbavancin is excreted in urine and feces. The Reviewer concurred with the applicant's proposed dosage regimen for most adults of 1000 mg followed one week later by 500 mg. This was the dosage regimen studied in Trials DUR001-301 and DUR001-302.

In patients with renal impairment, clearance of dalbavancin was reduced and the AUC was increased compared to subjects with normal renal function. Dalbavancin is not appreciably removed after 3 hours of hemodialysis. In patients with severe renal impairment (creatinine clearance < 30 ml/min) and not receiving regular hemodialysis, the Reviewer recommended a dose adjustment to 750 mg followed one week later by 375 mg.

The effect of hepatic impairment (Child-Pugh Class A, B, or C) on dalbavancin pharmacokinetics was also evaluated. Compared to controls with normal hepatic function, mean C_{max} and AUC_{inf} were 29% and 36% lower in patients with severe hepatic impairment. Mean C_{max} and AUC_{inf} were 18% and 30% lower in patients with moderate hepatic impairment. Patients with mild hepatic impairment had similar results to the control subjects. The Reviewer recommended no dose adjustment in patients with mild hepatic impairment and that labeling should state that caution should be exercised when prescribing dalbavancin to patients with mild or severe hepatic impairment as no data are available to determine the appropriate dosing.

In in-vitro studies, dalbavancin was not a substrate or inhibitor of CYP450 isoenzymes or the P-gp efflux transporter. No clinical drug interaction studies were considered necessary.

The thorough QT study was reviewed by the QT interdisciplinary review team. The applicant conducted a single-center, randomized, single-dose, placebo- and positive-controlled, partially double-blind, parallel group ECG study. The applicant concluded that an effect on the QTcF interval exceeding 10 msec could be excluded for the single doses of 1000 mg and 1500 mg included in the trial. The QT IRT review concluded that no significant QTc prolongation effect of dalbavancin was noted in the study.

With respect to establishment of susceptibility test interpretive criteria (breakpoints), the Reviewer re-analyzed a target attainment analysis based on efficacy in a mouse thigh infection model. In addition, a clinical PK/PD analysis using PK and efficacy data from Study VER001-09, a previously conducted Phase 3 trial in complicated skin and skin structure infection, was reviewed. The Reviewer concluded that the applicant's originally proposed breakpoint of 0.25 mcg/mL was not acceptable. This is further discussed in Section 6 of this memo.

I conclude that there are no outstanding Clinical Pharmacology issues precluding approval.

6. Clinical Microbiology

The Clinical Microbiology Reviewer concluded that there were no outstanding Clinical Microbiology issues precluding approval. The mechanism of action of dalbavancin involves the interruption of cell wall synthesis by binding to the terminal D-ala-D-ala of the stem peptide in cell wall peptidoglycan, preventing cross-linking of disaccharide subunits. Dalbavancin was found to be bactericidal in-vitro against *Staphylococcus (Staph.) aureus* and *Streptococcus (Strep.) pyogenes* at concentrations similar to those sustained in humans with the labeled recommended dosing regimen. Resistance to dalbavancin would be expected among glycopeptide-resistant bacteria and to bacteria expressing the VanA phenotype of acquired resistance. However, the development of bacterial isolates resistant to dalbavancin was not observed in-vitro, in studies using serial passage, or in animal infection experiments. A PMR for a surveillance study to monitor for the development of in-vitro resistance to dalbavancin in the first five years of

marketing, with annual interim reports to be submitted, will be included in the Approval Letter. This will be particularly important considering the long half-life of this antibacterial drug. The PMR will also include a study to evaluate the mechanisms of resistance to dalbavancin.

In-vitro and clinical trial data supported the inclusion of the following micro-organisms in the *Indications and Usage* section of the label: *Staph. aureus, Strep. pyogenes, Strep. agalactiae, Strep. anginosus* group.

The review team agreed with the Microbiology Reviewer that the susceptible breakpoint of $\leq$0.12 mcg/mL is acceptable for *S. aureus* and relevant streptococcal species. The rationale for this decision is detailed in the Division Director review for this NDA. Briefly, the decision is based upon surveillance data, animal model target attainment analysis, clinical response in trials DUR001-301 and 302, and a clinical PK/PD analysis. Surveillance data provided by the applicant showed a dalbavancin MIC_{90} value for *S. aureus* of 0.06 mcg/mL in 8 of the 11 years of the study and 0.12 mcg/mL for three years (2007-2009). The dalbavancin MIC_{90} for *S.pyogenes* was $\leq$0.03 mcg/mL for all years and for *S. agalactiae* it ranged from $\leq$ 0.03- 0.12 mcg/mL. In the mouse thigh infection model, free 24h AUC/MIC (AUC0-6days/6) was the best PK/PD parameter associated with efficacy. A target attainment analysis based on the mouse model incorporating free 24h AUC/MIC of 160 as a static effect target and 266 as a 2-log kill target supported a susceptible breakpoint as high as 0.25 mcg/mL. In trials DUR001-301 and 302, clinical efficacy data are only available for three patients with *Staph. aureus* MIC of 0.12 mcg/mL and one patient with *Staph. aureus* MIC of 0.25 mcg/mL. For clinical response at 48-72 hours, there were two successes (66.7%) at an MIC of 0.12 mcg/mL and one success (100%) at an MIC of 0.25 mcg/mL. For the clinical PK/PD analysis, the applicant used PK and efficacy data from Study VER001-09, a previously conducted Phase 3 trial in complicated skin and skin structure infection as no PK data were collected in Trials DUR001-301 and 302. There was an important limitation of the clinical PK/PD analysis as the proposed univariable relationships between efficacy endpoints and AUCavg/MIC were mathematically bounded by the percentage of patients $<$ or $\geq$ the AUCavg/MIC threshold; thus, the predicted response rate would not fall below 89.1% for subjects with AUCavg/MIC below the threshold with increasing MIC values. The mean clinical PK/PD model-predicted probabilities of response by MIC supported a susceptible breakpoint of 0.06 mcg/mL. The review team concluded that, taking into consideration all available clinical and non-clinical data and given the limitations of the clinical PK-PD analysis, a susceptible breakpoint of 0.12 mcg/mL is acceptable for *Staph. aureus*. As the targets for streptococci are lower than that for *Staph. aureus*, a susceptible breakpoint of 0.12 mcg/mL is also acceptable for the streptococcal species included in labeling (*Strep. pyogenes, Strep. agalactiae*, and *Strep. anginosus* group). The applicant agreed and I concur. (b) (4)

I conclude that there are no outstanding Clinical Microbiology issues precluding approval.

7. Clinical/Statistical Efficacy

The Statistical and Clinical Reviewers, the CDTL, and the Division Director all agreed that Trials DUR001-301 and 302 both met their primary objectives of demonstrating non-inferiority of dalbavancin to comparator therapy (vancomycin/linezolid) based on early clinical response at 48-72 hours using a 10% margin. Therefore, overall evidence of efficacy was considered to be adequate.

While data for the legacy study in complicated skin and skin structure infections (Study VER001-9) were available, there were limitations in the design and endpoints of Study VER001-9. The Reviewers focused on evidence obtained from Trials DUR001-301 and 302. The Agency had agreed to the design of Trials DUR001-301 and 302 under an SPA. An overview of the trial designs is shown in TABLE 1.

TABLE 1: Comparison of Trials DUR001-301 & 302

	Trial 301	**Trial 302**
Type of Trial:	Phase 3 multicenter, randomized, double-blind comparative trial to evaluate the safety and efficacy of dalbavancin vs. vancomycin + linezolid in adults with ABSSSI	
Objective:	Demonstrate noninferiority (NI) in early clinical response of dalbavancin treatment vs. vancomycin plus linezolid in adults with ABSSSI. The NI margin was pre-specified at 10%.	
Treatment Arms:	Two arms: IV dalbavancin (1000mg on Day 1 & 500mg on Day 8)[1] and IV vancomycin plus oral linezolid (1000mg or 15mg/kg vancomycin for 3 to 14 days plus linezolid 600mg q12h)[2]	
Sample Size:	573 ITT patients[3]	739 ITT patients[3]
Primary Endpoint:	Early clinical response at 48-72 hours in ITT subjects	
Study Design:	Baseline: within 24 hours of first dose of study drug, randomization Study drug administration: Day 1 to EOT (for 10 to 14 days) EOT: Day 14-15 SFU: Day 28 Long term follow-up (LFU): Day 70	
Statistical Methods:	The observed treatment difference in response with 95% confidence interval (CI) computed stratifying for the presence or absence of fever at Baseline. If the lower limit of the 95% CI for the difference in response rates was greater than -10%, the non-inferiority of dalbavancin to vancomycin/linezolid was concluded.	

[1] Patients with creatinine clearance values < 30 mL/min not receiving hemodialysis or peritoneal dialysis received reduced dalbavancin doses of 750 mg on Day 1 and 375 mg on Day 8.
[2] Following at least 72 hours of study drug treatment, patients could have been switched from q12h IV study drug (either dalbavancin and placebo or vancomycin and placebo) to oral therapy for patients in the vancomycin/linezolid treatment group or matching placebo for patients in the dalbavancin treatment group, if the criteria for IV to oral switch had been met.
[3] A blinded SSR was performed when 60% of patients had early clinical response data available. SSR was only recommended in trial 302.
Source: Statistical Review Table 1

There were no notable imbalances between study arms with respect to demographic characteristics, infection type, or disease severity at baseline. In Trial DUR001-301, 518

of 573 patients randomized completed the study. In Trial DUR001-302, 665 of 739 patients randomized completed the study. The major reason for premature discontinuation was loss to follow-up and this was balanced between arms.

The primary outcome measure was clinical response at 48-72 hours (± 3 hours, i.e., 45-75 hours) post study drug initiation. Responders were defined according to the following criteria:

- The patient had no increase in lesion area at 48 to 72 hours after the first dose of study drug therapy compared with the baseline measurement, and
- The patient had a temperature ≤ 37.6°C within 48 to 72 hours after the first dose of study therapy followed by 2 additional temperature measurements ≤ 37.6°C separated by at least 3 hours and no more than 9 hours apart, and no intervening temperature >37.6°C (any method of temperature measurement).

The applicant had pre-planned a sensitivity analysis of responder rates defined as at least a 20% reduction in lesion size at 48-72 hours with no fever component, and the Agency considered this a key secondary analysis based on the recommendations in the final guidance document. (See Section 2 of this memo.) The Statistical Reviewer analyses of the primary outcome measure and the key secondary analysis are shown in TABLE 2.

TABLE 2: Statistical Reviewer Analyses: Responder Rates at 48-72 hours (ITT)

	Trial 301			**Trial 302**		
Responder Rates:	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI)[1]	Comparator (N=371) n (%)	Dalbavancin (N=368) n (%)	Difference (95% CI)[1]
Primary Cessation of spread & afebrile at 48-72 hrs	240 (83.3)	233 (81.8)	1.5 (-4.6, 7.9)	285 (76.8)	288 (78.3)	-1.5 (-7.4, 4.6)
Key Secondary ≥ 20% reduction in lesion area at 48-72 hrs	259 (89.9)	259 (90.9)	-1.0 (-5.7, 4.0)	325 (87.6)	316 (85.9)	1.7 (-3.2, 6.7)

[1] 95% CIs were calculated using the Miettinen and Nurminen approach, adjusted for baseline fever status. Responders also could not use new non-study systemic antibiotics or have a death in the study period up to 48-72 hours.
Source: Statistical Review Table 11

The review team concluded that in Trials DUR001-301 and 302, dalbavancin was non-inferior to the comparator regimen of vancomycin/linezolid.

The Statistical Reviewer noted that there is still some uncertainty regarding the efficacy at later endpoints such as clinical status at EOT (Day 14-15) and clinical status at short term follow-up (SFU) (Day 26-30) as the results varied across the two trials, favoring the

comparator in Trial DUR001-301 and dalbavancin in Trial DUR001-302. For success rates in clinical status at EOT and SFU, Trial DUR001-301 comparisons were 81.3% vs. 86.7%, -5.4% (-11.5%, 0.6%) and 83.7% vs. 88.1%, -4.4% (-10.2%, 1.3%), respectively, while Trial DUR001-302 comparisons were 88.7% vs. 85.3%, 3.4% (-1.5, 8.3) and 88.1% vs. 84.5%, 3.6% (-1.3, 8.7).

I agree with the conclusions of the review team that substantial evidence of efficacy has been demonstrated based upon findings of non-inferiority for both the primary analyses and key secondary analyses in both trials. I agree with the Statistical Reviewer that the later success rates at EOT and SFU are difficult to interpret because the definitions of success at those endpoints used in the trials may not be clinically meaningful (for example, any decrease in lesion size was used as part of the success definition at EOT and SFU). In addition, there is not an established treatment effect at later time points.

8. Safety

The Clinical Reviewer concluded that the safety profile of dalbavancin was acceptable. A number of previously conducted Phase 2 and 3 trials using the same dosage regimen for dalbavancin as Trials DUR001-301 and 302 were included in the evaluation of safety. Overall, there were 1778 dalbavancin patients and 1224 comparator patients in the Phase 2/3 safety database. As dalbavancin has not been approved for marketing in the U.S. or abroad, there was no post-marketing data available.

The frequency of deaths was comparable for dalbavancin and comparator: 10 (0.6%) deaths in dalbavancin patients, and 15 (1.2%) deaths in comparator patients. There were no specific findings to relate deaths in the dalbavancin patients to drug treatment. The only drug-related serious adverse reaction in the dalbavancin group was an anaphylactoid reaction. The most common adverse reactions for dalbavancin-treated patients were nausea (5.5%), headache (4.7%), diarrhea (4.4%), vomiting (2.8%), rash (2.7%) and pruritus (2.1%). The frequency of these common adverse reactions among dalbavancin patients was similar to controls.

A number of special safety concerns are described in *Warnings and Precautions* in labeling. These include:

- Hypersensitivity reactions: There was one patient treated with dalbavancin who experienced an anaphylactoid reaction, and several patients treated with dalbavancin with rash and pruritus.
- Infusion-related reactions: There is a known association of glycopeptides with infusion reactions. While the frequency of infusion reactions in the Phase 2/3 safety database was low and similar to comparator, there was one subject in the QT trial reported with “red man syndrome” after receiving a 1500 mg dose of dalbavancin.
- Hepatic effects: In the Phase 2/3 safety database, overall abnormalities in AST, ALT, and bilirubin were similar in frequency in dalbavancin and comparator arms. However, among patients with normal baseline transaminase levels, more dalbavancin than comparator patients had post-baseline ALT elevations greater

than 3 times the upper limit of normal (ULN), 12 (0.8%) vs. 2 (0.2%), respectively, including three subjects with post-baseline ALT values greater than 10 times the ULN. ALT elevations were reversible in all subjects. The review team analyses with respect to hepatic effects are discussed in further detail in the Division Director review.

- *Clostridium difficile*-Associated Diarrhea (CDAD): In the phase 2/3 safety database, there were 4 (0.2%) dalbavancin patients and 1 (0.2%) comparator patient with CDAD.

The DRISK Reviewer concurred with the review team that, based on the available data, and benefits and risks, a REMS requirement for dalbavancin would not be established at this time.

I conclude that there are no safety-related issues precluding approval.

9. Advisory Committee Meeting

This NDA was discussed by the Anti-Infective Drugs Advisory Committee on March 31, 2014. There was a single voting question: "Has the applicant provided substantial evidence of the safety and effectiveness of dalbavancin for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of the designated microorganisms?" There were 12 votes "Yes" and 0 votes "No". In discussion, panel members recommended labeling concerning the hepatic effects noted in the clinical trials.

10. Pediatrics

The applicant requested deferral of required pediatric studies, because adult trials of ABSSSI were completed and the product is ready for approval. The Pediatric Review Committee agreed with deferral of pediatric studies for the entire pediatric population. PMRs for pediatric PK and safety studies will be included in the Approval Letter.

11. Other Relevant Regulatory Issues

There were two concerns noted in the clinical site inspection summary:

- Three sites that enrolled patients in Trial DUR001-301 had been closed down by the applicant due to concerns related to study conduct by personnel at the sites. Inspection of the three sites revealed deviations from GCP related to records management and drug accountability. Ultimately, the Office of Scientific Investigations concluded that the inspectional findings from these three sites were insufficient to conclude that the data from these sites were unreliable.
- In addition, it was noted that drug administration records were missing for 6 of 16 patients at one of these clinical sites in Trial DUR001-301. Based on sensitivity analyses, the review team concluded that exclusion of data from these patients would not affect the overall conclusions for Trial DUR001-301. Thus, data for these six patients were included in the ITT population.

There are no unresolved relevant regulatory issues.

12. Labeling

The proposed proprietary name, Dalvance, was found acceptable by the OSE/DMEPA Reviewer.

Physician labeling and carton/container labels were reviewed by OPDP and DMEPA and recommendations included as appropriate.

13. Decision/Action/Risk Benefit Assessment

Regulatory action: Approval

Risk benefit assessment: I agree with the conclusions of the review team that substantial evidence of efficacy has been demonstrated for dalbavancin for the treatment of ABSSSI. I also agree that the safety profile of dalbavancin is acceptable, and that the safety concerns noted in clinical trials can be addressed in labeling. Dalbavancin offers a dosing regimen which provides a useful treatment option for the treatment of ABSSSI for patients and their health care providers. Overall, the risk benefit is favorable.

Recommendations for Post-marketing Risk Evaluation and Mitigation Strategies: None

Recommendation for Postmarketing Requirements:

2145-1: Conduct a single dose pharmacokinetic (PK) study in children from 3 months to less than 12 years of age.

2145-2: Conduct a single dose PK study in neonates/infants from 0 to less than 3 months of age.

2145-3: Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in children from 3 months to 17 years of age with ABSSSI.

2145-4: Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in neonates/infants from birth to less than 3 months of age with ABSSSI.

2145-5: Conduct US surveillance studies for five years from the date of marketing DALVANCE to determine if resistance to dalbavancin has developed in those organisms specific to the indication in the label for ABSSSI.

2154-6: Conduct studies to define the mechanism(s) of resistance for isolates identified as being resistant to dalbavancin during the surveillance period (five years from the date of marketing).

Recommendation for Postmarketing Commitments:

2145-7: Replace [redacted] (b) (4) used for preparing the Master Cell Bank with a [redacted] (b) (4)

2145-8: Submit batch release test results from upcoming process performance qualification lot(s) when process performance qualification activities have been completed.

Exclusivity: Dalbavancin has been granted QIDP designation. Dalbavancin will be approved for the treatment of ABSSSI, the same indication identified in the QIDP designation letter of October 25, 2012. Dalbavancin has not previously received a 5-year GAIN exclusivity extension. Therefore, the NDA meets the criteria for the 5-year GAIN exclusivity extension under section 505E(a) of the Act.

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/s/

JOHN J FARLEY
05/23/2014