CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 14, 2014
From	John Alexander, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA #	21-883
Applicant	Durata Therapeutics, Inc.
Date of Submission	September 26, 2013 (NDA Re-submission)
PDUFA Goal Date	May 26, 2014
Proprietary Name / Established (USAN) names	Dalvance™ (Dalbavancin) for Injection
Dosage forms / Strength	Lyophilized Powder for Injection / 500 mg
Proposed Indication(s)	1. Acute Bacterial Skin and Skin Structure Infections
Recommended:	Approval

1. Introduction

Durata Therapeutics, Inc. (Applicant) has re-submitted NDA 21-883 for Dalvance™ (Dalbavancin) for Injection. The Applicant is seeking approval of Dalvance for the treatment of acute bacterial skin and skin structure infections (ABSSSI). To support the proposed indication, the applicant has submitted the results of two pivotal trials of ABSSSI. The safety and efficacy results of these two trials and the NDA resubmission will be the main topic of this memorandum.

2. Background

Dalbavancin is a lipoglycopeptide antibacterial, manufactured as a lyophilized powder for injection. Dalbavancin has demonstrated in vitro antibacterial activity against certain Gram-positive bacteria, with a mechanism of action similar to that of the glycopeptide, vancomycin. After reconstitution, dalbavancin is administered by intravenous infusion over 30 minutes.

The initial NDA submission for dalbavancin was made in December 2004 by Vicuron, later acquired by Pfizer, Inc. This prior NDA included trials to support indications for complicated and uncomplicated skin and skin structure infections. However, chemistry and manufacturing controls issues resulted in several approvable actions on the NDA application; though the last approvable action letter, dated December 20, 2007, also noted the need for justification of the non-inferiority margin for uncomplicated skin and skin structure infections as a deficiency. Ultimately, the applicant chose to withdraw the NDA application (withdrawal letter dated September 15, 2008). The letter cited Pfizer's intent to conduct an additional trial of complicated skin and skin structure infections to support the NDA application. Subsequent to the withdrawal of the NDA, there was a change in sponsorship for the dalbavancin IND to the current NDA applicant. Durata Therapeutics, Inc. conducted two clinical trials of dalbavancin

for the treatment of ABSSSI as pivotal trials for the NDA resubmission. The results of these trials are discussed further in subsequent sections of this memo.

3. CMC/Device

The chemistry and manufacturing controls (CMC) review was conducted by Drs. Mark Seggel and Balajee Shanmugam. The product quality microbiology (PQM) review was conducted by Steven Donald, MS. The ONDQA biopharmaceutics review was conducted by Dr. Houda Mahayni. All reviewers recommended approval of Dalvance, though the CMC recommendation was conditioned on an overall acceptable recommendation from the Office of Compliance. The facilities inspections were pending at the time the CMC review was finalized. The reader is referred to the individual reviews for detailed information about the review findings.

- General product quality considerations

The drug substance, dalbavancin hydrochloride, is derived from a fermentation product of *Nonomurea* spp. (A-40,926) that undergoes further chemical modification. Dalbavancin consists of 5 homologs with the B components (B_0, B_1 and B_2) representing (b) (4) of the drug substance, while the A components (A_0 and A_1) account for approximately (b) (4) The homologs vary in the length and branching of two fatty acid side chain of the lipoglycopeptide core.

The drug product consists of single use vials containing 500 mg of dalbavancin free base, with mannitol (b) (4) mg) and lactose monohydrate (b) (4) mg) as excipients. Sodium hydrochloride or hydrochloric acid are used as pH adjusters. The container/closure system consists of glass vials (b) (4)

No deficiencies were noted in the product quality microbiology review. The API and excipients are dissolved in water for injection. The solution is (b) (4) .

As noted above, the final drug product consists of a single use vial with 500 mg dosage strength, but the applicant had two other dosage strengths (200 mg, 250 mg) during development. The 500 mg dosage strength proposed for marketing was used in the pivotal clinical trials for ABSSSI, so no waiver for bioavilability studies was needed for the application. The ONDQA biopharmaceutics review considered it acceptable to bridge across the phases of product development.

- Facilities review/inspection

The drug substance manufacturing site (b) (4) was inspected and a form FDA 483 with inspectional findings was issued. The drug product manufacturing site (b) (4) was inspected and a form FDA 483 with

inspectional findings was issued. This facility is also responsible for drug product packaging, release testing, and stability. At the time this memo was written, the inspection was still pending at the facility that conducts endotoxin testing (b) (4)

The facilities inspection results and recommendation from the office of compliance were pending at the time this memo was written.

- Other notable issues

Long-term and accelerated stability studies support an expiration period of 36 months at 25°C.

The CMC review noted the use of (b) (4) in the preparation of the master cell bank, and the applicant has committed to the (b) (4)
This was proposed by ONDQA as a post-marketing commitment for the applicant.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review was conducted by Dr. Terry Miller. Dr. Miller considered the nonclinical studies conducted with dalbavancin adequate for approval of the NDA. The reader should refer to his review for detailed information about the nonclinical findings.

- General nonclinical pharmacology/toxicology considerations

Most of the nonclinical studies had been reviewed during or before the first NDA submission of dalbavancin. Only the toxicology study in juvenile rats (submitted to IND (b) (4)) was a relatively new study. Safety pharmacology studies in mice rats and rabbits showed no effects on respiration, body temperature, behavioral or autonomic nervous system parameters. No significant potential for QT prolongation was noted in hERG assay or telemetered dogs. PK distribution studies showed wide distribution, except to the brain, and were consistent across species, including humans. The toxicological profile across species included local injection site toxicity, histamine-related infusion reactions, and liver and kidney toxicity in several species. Histologic findings of hepatocellular and renal tubular cell necrosis, vacuolization and degeneration were noted with "high dose dalbavancin treatment" and associated with elevated LFT, BUN and creatinine levels. The toxicological profile of dalbavancin in juvenile rats was consistent with that seen in adults.

- Carcinogenicity

Dalbavancin was not mutagenic or clastogenic, based on appropriate in vitro and in vivo studies. No carcinogenicity studies were conducted with dalbavancin. Carcinogenicity studies were considered unnecessary, based on the indication for short-term use.

- Reproductive toxicology

Reproductive toxicology studies were conducted in rats and rabbits. Decreased fertility index was noted at 45 mg/kg/day (maximum tested dose) in rats. The NOEL for fertility was 15/mg/kg/day. Dalbavancin was not teratogenic in rats and rabbits. There was no effect on fetal or maternal body weights up to the maternal toxic dose in rabbits (15 mg/kg/day). The NOAEL for fetal development was 15 mg/kg/day in both species. Prenatal and postnatal development studies in rats indicated a "significant number of deaths (18.7%) in the high dose treatment group", nearly twice that seen in the controls. Plasma levels in pups were approximately $1/10^{th}$ that of dams, and parent drug was detected in secreted mother's milk at levels $1/10^{th}$ of maternal plasma.

The findings regarding reproductive toxicology for dalbavancin were included in product labeling.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review for the NDA resubmission was conducted by Dr. Yang He. Dr. He concluded that the NDA resubmission was acceptable from a clinical pharmacology perspective. The reader is referred to the clinical pharmacology review for detailed information about the clinical pharmacology findings.

- General clinical pharmacology/biopharmaceutics considerations

Dalbavancin is a lipoglycopeptide antibacterial drug, intended for intravenous administration. The proposed dose regimen involves two doses separated by a week, 1000 mg followed by 500 mg, for most adults with ABSSSI. The pharmacokinetic parameters of dalbavancin in healthy subjects are described in the clinical pharmacology review. One notable factor is the long terminal half-life of 346 hours. Because of the long half-life, dalbavancin is administered in a two-dose regimen, 1000 mg on the first day followed by 500 mg given one week later. Dalbavancin is reversibly bound to plasma proteins; the mean protein binding is 93% and is independent of concentration. Penetration into skin blister fluid was 60%, based on $AUC_{0\text{-}7days}$ (blister fluid)/$AUC_{0\text{-}7days}$ (plasma). A minor metabolite of dalbavancin is detected in urine, but plasma concentrations of this metabolite are less than the lower limit of quantitation for the assay.

- Drug-drug interactions

Findings from in vitro metabolism and transporter studies showed that dalbavancin is neither an inhibitor nor substrate of CYP 450 isoenzymes or P-gp efflux transporter. No clinical drug interaction studies were considered necessary.

- Pathway of elimination

Dalbavancin is excreted in both urine and feces. In studies of a single 1000 mg dose, approximately 27-45% of the dose is excreted in urine, including unchanged dalbavancin (19-33%) and a hydroxyl metabolite (8-12%). Approximately 20% of the dose was excreted in feces through 70 days after dose administration.

- Intrinsic factors/specific populations

Age, gender, albumin, body surface area (BSA), and creatinine clearance were identified as covariates in the population pharmacokinetic analysis of dalbavancin. BSA and creatinine clearance were considered the most influential covariates on clearance. There was a positive correlation between increasing BSA and clearance, but this was expected to have limited clinical effect with the proposed dose. No dose adjustment for BSA was recommended.

Renal impairment did have an effect on the pharmacokinetics of dalbavancin. Mean clearance was 11% and 35% lower, and mean AUC_{inf} was 10% and 53% higher in patients with mild or moderate renal impairment, respectively. For patients with severe renal impairment, mean clearance was 50% lower and mean AUC_{inf} was 100% higher. Dalbavancin is not appreciably removed after 3 hours of hemodialysis; however, changes in mean clearance and AUC_{inf} of dalbavancin given to patients before or after dialysis appeared similar to those seen in patients with mild or moderate renal impairment. Based on these findings, dose adjustment is recommended only for patients with severe renal impairment who are not receiving regularly scheduled hemodialysis. In these patients, the recommended two-dose regimen of dalbavancin is 750 mg followed by 375 mg, given one week apart.

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 had similar results to the control subjects. No dose adjustment was recommended for patients with mild hepatic impairment.

The pharmacokinetics of dalbavancin were evaluated in hospitalized adolescents (12-16 years of age). The reader is referred to the clinical pharmacology review for detailed information about the pK results in adolescents, but additional studies are needed to evaluate PK in pediatric patients less than 12 years of age, and safety in the entire pediatric population. (See the Pediatrics section of this memo for additional information.

- Thorough QT study

The thorough QT study was reviewed by the QT interdisciplinary review team (IRT). The applicant conducted a single-center, randomized, single-dose, placebo- and positive-controlled, partially double-blind, parallel group ECG study. The placebo was 5% dextrose (blinded) and the positive control was moxifloxacin tablets, 400 mg. The applicant concluded that an effect on 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 TQT study.

- Other notable issues

The NDA applicant proposed a susceptibility breakpoint of ≤0.25 for *Staphylococcus aureus* and *Streptococci* in section 12.4 of the proposed label. The clinical pharmacology review included an evaluation of the interpretive breakpoint criteria, because the applicant had performed a PK-PD analysis of clinical trials conducted in the original NDA submission for dalbavancin. The reviewer concluded that there were limitations to the analysis provided by the applicant, and did not agree with the applicant's proposed breakpoint. At the time this memo was written, there were still ongoing discussions to determine the appropriate susceptibility breakpoint for dalbavancin.

6. Clinical Microbiology

The clinical microbiology review for the NDA resubmission was conducted by Dr. Peter Coderre. The reviewer considered the NDA approvable, contingent on acceptance of labeling recommendations.

- General considerations

Dalbavancin is a lipoglycopeptide antibacterial drug, structurally related to teicoplainin. It is active against certain Gram-positive bacteria, including *Staphylococci* and *Streptococci* that are the causative pathogens in ABSSSI. Dalbavancin appears to retain activity against some teicoplainin-resistant, coagulase-negative *Staphylococci*. Dalbavancin is not expected to be active in vitro against vancomycin-resistant *Staphylococci*, since vancomycin resistance mediated by the VanA genotype also results in reduced susceptibility to dalbavancin. *Staphylococcus aureus* isolates with reduced susceptibility to vancomycin (VISA, hVISA) may still be susceptible to dalbavancin. Bacteria with intrinsic resistance to glycopeptides (e.g., *Pediococcus* and *Leuconostoc* spp.) are also expected to be resistant to dalbavancin.

The applicant has proposed susceptibility interpretive criteria of ≤0.25 mcg/mL for both *Staphylococcus aureus* and *Streptococci* listed in the indication. The reviewer has concluded that there is insufficient information to support that applicant's proposal. The microbiology reviewer recommended ≤0.12 mcg/mL for susceptibility, considering limited clinical experience with infections caused by organisms with MIC ≥0.12 mcg/mL, surveillance data showing listed pathogens with MIC_{90} generally ≤0.06 mcg/mL, and the results of modeling for both animal and clinical data.

- Other notable issues

The reviewer recommended against the inclusion of *Streptococcus anginosus* group in the indication for ABSSSI, because of a limited number patients with these bacteria in the microbiologically evaluable population, as well as limited amounts of MIC data for the

specific species in this group from surveillance data. The applicant has stated they have a larger number of patients with *Streptococcus anginosus* group at baseline. The discrepancies in datasets were resolved and the group was included in the indication.

The determination of the appropriate susceptibility interpretive criteria for dalbavancin is still under internal discussion at the time this section is being written. This discussion involves the both the clinical microbiology and clinical pharmacology teams.

The review division has proposed postmarketing requirements (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. The PMR also include a study to evaluate the mechanisms of resistance to dalbavancin.

7. Clinical/Statistical- Efficacy

The clinical review was conducted by Dr. Dmitri Iarikov. The statistical review was conducted by Dr. Christopher Kadoorie. The reader is referred to their respective reviews for detailed information about the clinical and statistical findings. The reviewers concluded that adequate evidence of efficacy had been provided, though the statistical review noted some uncertainty regarding the efficacy outcomes at later time points. The concerns about the analyses at later time points appeared to be related to variability in findings across the two trials and in the response definitions; the reviewer tried to address these issues through exploratory analyses described in the statistical review. The clinical and statistical reviewers were in agreement regarding the primary efficacy conclusions and overall interpretation of the trial results, supporting the indication of dalbavancin for ABSSSI.

The applicant conducted two clinical trials of ABSSSI, DUR001-301 and DUR001-302. These trials were phase 3, randomized, double-blind, multicenter trials comparing intravenous (IV) dalbavancin to IV vancomycin (with or without switch to oral linezolid). Dalbavancin was given in a two-dose regimen in the clinical trials; most dalbavancin-treated patients in the clinical trials received 1000 mg of dalbavancin on day 1, followed by 500 mg of dalbavancin on day 8 (one week later). In patients with creatinine clearance (CrCl) < 30 mL/min, the dalbavancin regimen was 750 mg administered on day 1, followed by 375 mg on day 8. Intravenous vancomycin was administered to comparator subjects for 3-14 days, with the option to switch to oral linezolid. Intravenous vancomycin was given according to the local standard of care (1000 mg or 15 mg/kg given every 12 hours), and an unblinded pharmacist adjusted vancomycin dosing for patients with renal impairment. Dummy infusions were given to both treatment groups to maintain blinding.

The trials were conducted in 2011-2012, as the FDA recommendations regarding the design of ABSSSI trials were evolving. The protocol of these identical trials was the subject of special protocol assessment, and agreement was reached on the trial design, including the primary endpoint. Subsequently, the Agency has published final guidance for acute bacterial skin and skin structure infection, though the trial was complete at the time this guidance was finalized. Despite this, the pivotal trials are consistent with the trial design recommended in the

guidance, with the exception of the primary endpoint for the trial. The primary endpoint recommended in guidance (≥20% reduction in lesions size at 48-72 hours, compared to baseline) differs from the primary endpoint in these trials, but was evaluated as a secondary endpoint. The selection criteria for the trials were consistent with the guidance recommendations, as evidenced by the mean lesion size for dalbavancin-treated patients of 498 cm^2 and 512 cm^2, in studies 301 and 302, respectively. Lesion type was also consistent with guidance: most lesions (53-54% of dalbavancin patients) were categorized as cellulitis, and abscess was reported as the baseline lesion type in 24-25% of dalbavancin-treated patients. The reader is referred to the clinical and statistical reviews for additional detailed information about the study design, patient demographics, and baseline characteristics.

The primary endpoint for the clinical trial was clinical response at 48 to 72 hours in the Intent-to-Treat (ITT) population. The ITT population included all randomized patients, regardless of whether they received the assigned drug. Clinical response was defined as cessation of spread of the skin lesion compared to baseline, and temperature ≤37.6°C on repeated measurements between 48 and 72 hours after starting drug treatment. Patients who died, used non-trial antibacterial therapy, or had missing measurements (lesion size or temperature) were classified as non-responders. The results of the primary analysis are shown in the table below. Dalbavancin meets the pre-specified criteria for non-inferiority to the comparator in these two trials.

Primary Analysis: Clinical Response Rates at 48-72 Hours in the ITT Population

	Dalbavancin n/N (%)	**Vancomycin/Linezolid n/N (%)**	**Difference (95% CI)**
DUR001-301	240/288 (83.3%)	233/285 (81.8%)	1.5% (-4.6, 7.9)
DUR001-302	285/371 (76.8%)	288/368 (78.3%)	-1.5% (-7.4, 4.6)

As noted above, the current guidance for ABSSSI recommends a 20% or greater reduction in lesion size at 48-72 hours after the start of drug treatment as the primary endpoint for ABSSSI trials. The following table shows the analysis of patients meeting the criteria for 20% or greater reduction in lesion size at 48-72 hours in the clinical trials. As with the primary analysis, patients who died, used non-trial antibacterial therapy, or had missing measurements (lesion size) were classified as non-responders. Dalbavancin meets the criteria described in the ABSSSI guidance for non-inferiority to the comparator on this endpoint.

Secondary Analysis: 20% or Greater Reduction in Lesion Size at 48-72 Hours in the ITT Population

	Dalbavancin n/N (%)	**Vancomycin/Linezolid n/N (%)**	**Difference (95% CI)**
DUR001-301	259/288 (89.9%)	259/285 (90.9%)	-1.0% (-5.7, 4.0)
DUR001-302	325/371 (87.6%)	316/368 (85.9%)	1.7% (-3.2, 6.7)

The clinical and statistical reviews include additional analyses of outcomes at the end of treatment visit (day 14-15, representing the end of comparator drug treatment) as well as the follow-up visit (day 26-30). The outcomes for the ITT population and clinical evaluable population at the follow-up visit were included in proposed product labeling. Additional subgroup analyses by gender, infection type, baseline pathogen, and other baseline characteristics are also described in the reviews. The statistical review also included some analyses evaluating the effect of exclusion of 6 patients from the efficacy analyses for trial DUR001-301 (see section 11 of this memo). The statistical review also provided other analyses varying percent reduction in lesion size or evaluating specific components of the outcome definitions for the end-of-treatment and follow-up visit. The reader is referred to the reviews for detailed information about the subgroup analyses.

- Other notable issues

There was agreement by the clinical and statistical reviewers regarding the primary and secondary analyses of efficacy in the ABSSSI trials. The trials did provide substantial evidence of efficacy for the treatment of ABSSSI. At the time this memo was written, the labeling was still pending, with ongoing internal discussion of inclusion of *Streptococcus anginosus* group in the indication, the appropriate description of data for ABSSSI patients with positive baseline blood cultures, and susceptibility breakpoints to be included.

8. Safety

As noted previously, the clinical review was conducted by Dr. Dmitri Iarikov. He recommended approval of the NDA application for dalbavancin. The risk benefit assessment noted an "acceptable safety profile of dalbavancin".

The safety database included not only the 652 dalbavancin-treated patients and comparator patients from the phase 3 ABSSSI trials, but also included the patients treated in prior phase 2/3 trials in the original NDA application. The prior trials involved mainly treatment of skin infections, and the dose regimen of dalbavancin was the same two-dose regimen in the ABSSSI trials. Overall, there were 1778 dalbavancin patients and 1224 comparator patients in the phase 2/3 safety database. As dalbavancin has not been approved for US or foreign marketing, there are no domestic or foreign postmarketing data available.

The frequency of deaths in the clinical trial database was comparable in the two treatment arms: 10 (0.6%) deaths in dalbavancin patients, and 15 (1.2%) deaths in comparator patients. Looking only at the new ABSSSI trials, there was one death (0.15%) in the dalbavancin arm and there were 8 deaths (1.2%) in the comparator arm. The clinical review provides narratives of the deaths as well as summary information about deaths in the previous trials. There were no specific findings to relate deaths in the dalbavancin patients to drug treatment.

In the two new clinical trials, non-fatal serious adverse reactions were reported in 17 (2.6%) dalbavancin patients and 29 (4.4%) comparator patients. The system organ class (SOC) with

the highest number of non-fatal serious adverse reactions was the Infections and Infestations SOC. There were 9 patients in each treatment arm in this SOC, with most reactions related to skin infections. The only drug-related serious adverse reaction in the dalbavancin group was an anaphylactoid reaction. As noted in proposed labeling, serious adverse reactions were reported in 109 /1778 (6.1%) dalbavancin patients and 80/1224 (6.5%) patients. Treatment was discontinued due to adverse reactions in 53/1778 (3%) dalbavancin patients and 35/1224 (2.8%) comparator patients.

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%). Special safety concerns for dalbavancin (described in Warnings and Precautions in proposed labeling) include:

- Hypersensitivity Reactions – In addition to a patient with an anaphylactoid reaction, reported as a serious adverse reaction, there were several patients with rash and pruritus in the dalbavancin treatment group.
- Infusion-Related Reactions – Because of the known association of glycopeptides with infusion reactions and infusion reactions in non-clinical studies, this was investigated in clinical trials. In the new clinical trials, infusion reactions were reported in 12 (1.8%) dalbavancin patients, and 14 (2.1%) comparator patients. Dalbavancin was administered by slow infusion over 30 minutes in these trials. There was one patient in a QT trial reported with "red man syndrome" after receiving 1500 mg of dalbavancin. In the phase 2/3 safety database, infusion-related reactions were reported in 51/1778 (2.9%) dalbavancin patients and 53/1224 (4.3%) comparator patients.
- Hepatic Effects – There were dalbavancin-treated patients with significant elevations of ALT in clinical trials. In the new clinical trials, among patients with normal ALT at baseline, there were 26 (4%) dalbavancin patients and 15 (2.3%) comparator patients with post-baseline ALT >3 times the upper limit of normal (xULN). This included 3 dalbavancin patients with ALT 5-10xULN and another 3 patients with ALT >10xULN. Among comparator patients with normal ALT at baseline, there were no patients with ALT elevations greater than 5xULN in the new clinical trials. This was consistent with findings in all phase 2/3 clinical trials where 12 (0.8%) dalbavancin patients and 2 (0.2%) comparator patients had ALT elevation of >3xULN from a normal baseline. Hepatic effects were also noted in animal toxicology studies in rats and dogs. No dalbavancin patients were considered to meet criteria for Hy's Law.
- *Clostridium difficile*-Associated Diarrhea (CDAD) – CDAD is a known adverse reaction associated with use of antibacterial agents. There were no patients in the new clinical trial with CDAD. In the phase 2/3 safety database, there were 4 (0.2%) dalbavancin patients and 1 (0.2%) comparator patient with CDAD.

The clinical review details other investigations of adverse reactions. This includes investigations of renal effects, hyperglycemia/hypoglycemia, hematological effects, and nervous system disorders. The reader is referred to the clinical review for detailed information.

9. Advisory Committee Meeting

A meeting of the Anti-Infective Drugs Advisory Committee (AIDAC) was held on March 31, 2014 to discuss NDA 21-883 for Dalvance™ (dalbavancin) for Injection. The presentations by the FDA described the safety evaluation of the new clinical trials, in addition to the available safety data for previously conducted clinical trials. The efficacy presentation focused on the results of the two new trials submitted in the current review cycle, trials DUR001-301 and DUR001-302. The committee was asked,

> "Has the applicant provided substantial evidence of the safety and effectiveness of dalbavancin for the treatment of ABSSSI caused by susceptible isolates of the designated microorganisms?

The committee vote on this question was Yes = 12 and No = 0 with no abstentions. The committee comments supported approval with comments for labeling regarding potential for liver toxicity, particularly in patients with underlying liver disease. There were individual committee members making recommendations regarding post-marketing trials of adolescents, safety evaluation of pregnant women, recommendations for liver function testing in clinical use (i.e., when liver enzymes should be measured, potentially to allow intervention before administration of the 2nd dose), and evaluation of data for including *Streptococcus agalactiae* and *Streptococcus anginosus* group, since the committee members did not see information related to these specific pathogens in the applicant presentations.

10. Pediatrics

The NDA applicant requested deferral of required pediatric studies, because adult trials of ABSSSI were completed and the product is ready for approval. The NDA application included a single-dose PK study of adolescent patients, though additional safety data is needed to support safety in this population. Extrapolation of efficacy from adults to the pediatric population is considered appropriate for the ABSSSI indication due to the similar pathogenesis of disease in adult and pediatric patients, and a similar expected response to treatment. This is consistent with what has been done in the past for extrapolation of complicated and uncomplicated skin and skin structure infections.

The applicant has proposed additional PK studies of pediatric patients from (b) (4) The application was discussed with the Pediatric Review Committee (PeRC) on April 9, 2014. The PeRC agreed with deferral of pediatric studies for the entire pediatric population. Postmarketing requirements for pediatric PK and safety studies have been proposed. Because of specific concerns regarding poor localization of infection and the risk of CNS infection with *S. aureus* in the neonatal population, the division has proposed separate PK and safety studies for the neonatal population (0-3 months of age) from the studies of pediatric patients three month of age or older.

11. Other Relevant Regulatory Issues

A clinical inspection summary (CIS) by Lauren Iacono-Connors, PhD, was archived to the NDA file on April 10, 2014. In this document, the overall data for the pivotal studies were acceptable, but the data generated at three sites in Study DUR001-301 were considered unreliable. In response to these findings, the review division conducted analyses excluding the data from these three sites. The exclusion of patient data from these sites did not substantively change the conclusions from the affected study.
Subsequently, an addendum to the CIS was archived to the NDA file on May 6, 2014. In this addendum, the Office of Scientific Investigations (OSI) team revised their recommendation after complete review of the final establishment inspection reports (EIR). The addendum indicated that the findings from the final EIR were not sufficient to conclude that data from these sites were unreliable. The CIS addendum noted issues with drug transportation records for the three sites, but stated "there is evidence that the drug was prepared and administered to the patients". The report indicated the unreliable drug transportation records should not affect data integrity. The CIS addendum did not that drug administration records were missing for 6 of 16 patients at one of the clinical sites (site 118). The OSI team stated that the review division could consider excluding these subjects, or assess the treatment received for each of these patients. They included 5 patients who received dalbavancin (all considered successes in the primary and secondary outcomes) and one vancomycin patient (considered failure for the primary endpoint, but success for the secondary endpoint of 20% reduction). The outcomes described in labeling represent ITT analyses, the exclusion of these patients would not affect the overall conclusions for the involved study, and the data integrity regarding the involved study sites was no longer being questioned. Therefore, the division elected to keep the data for these patients in the analyses presented.

Financial disclosure information is included in an appendix to the clinical review. There were no reportable financial disclosures for the investigators in the clinical trials.

12. Labeling

The proprietary name review was conducted by Dr. Aleksander Winiariski. The proposed proprietary name, Dalvance, was considered acceptable. Dr. Winiarski also conducted the labeling review for the Division of Medication Errors and Prevention Analyses (DMEPA). Dr. Christine Corser conducted the Office of Prescription Drug Promotion (OPDP) labeling review. The recommendations from these reviews were incorporated in the labeling recommendations to the applicant. The remaining unresolved labeling issues were described in previous sections of this memo.

Dr. Bob Pratt conducted the Risk Evaluation and Mitigation Strategy (REMS) review for the Division of Risk Management. The review concurred that a REMS was not necessary based on the available data.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of the NDA application for Dalvance, if the facilities inspections are completed and the Office of Compliance concludes that the manufacturing facilities are acceptable.

- Risk Benefit Assessment

The applicant has provided substantial evidence of safety and effectiveness of dalbavancin for the treatment of acute bacterial skin and skin structure infections. The benefits of treatment outweigh the known risks as demonstrated in clinical trials. All the reviewers recommended approval of the application from their perspectives.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS was not considered necessary based on the available data for dalbavancin.

- Recommendation for other Postmarketing Requirements and Commitments

The postmarketing requirements included two microbiology studies, a US surveillance study to monitor for the development of in vitro resistance to dalbavancin and a microbiology study to evaluate resistance mechanisms for isolates identified in the surveillance study. These studies are necessary to determine whether widespread use of dalbavancin will quickly engender resistance, but these studies can only be performed after NDA approval.

The recommended postmarketing requirements include four pediatric studies to evaluate both PK and safety in the pediatric population. Separate trials were recommended for pediatric patients from birth to 3 months of age and pediatric patients 3 months of age to adults. The studies of neonates are expected to be delayed relative to those in the older age group. Separate trials would allow for submission of pediatric studies for the older age group while studies of the neonatal population are ongoing.

A postmarketing commitment from the CMC review team was also recommended. The applicant has previously committed to replace (b) (4) with another (b) (4) is used in the preparation of the master cell bank.

The postmarketing requirements and commitments and the proposed timelines for reporting are provided below:

REQUIRED PEDIATRIC ASSESSMENTS

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

Final Protocol Submission: May 2013 (submitted)
Trial Completion: March 2015
Final Report Submission: September 2015

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

  Final Protocol Submission: May 2015
  Trial Completion: November 2016
  Final Report Submission: May 2017

- 2145-3: Conduct a Phase 3, randomized, comparator-controlled trial of dalbavancin in children from 3 months to 17 years of age with acute bacterial skin and skin structure infections (ABSSSI).

  Final Protocol Submission: December 2014
  Trial Completion: December 2016
  Final Report Submission: June 2017

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

  Final Protocol Submission: December 2016
  Trial Completion: December 2019
  Final Report Submission: June 2020

POSTMARKETING REQUIREMENTS UNDER 505(o)

- 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.

  Final protocol submission: September 2014
  First interim report: March 2016
  Second interim report: March 2017
  Third interim report: March 2018
  Fourth interim report: March 2019
  Fifth interim report: March 2020
  Study completion date: September 2019
  Final report submission: September 2020

- 2145-6: 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).

Final protocol submission:	September 2014
First interim report:	March 2016
Second interim report:	March 2017
Third interim report:	March 2018
Fourth interim report:	March 2019
Fifth interim report:	March 2020
Study completion date:	September 2019
Final report submission:	September 2020

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

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

  Interim Report Submission: June 2015
  Final Report Submission: June 2016

- Recommended Comments to Applicant

None

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/s/

JOHN J ALEXANDER
05/16/2014