Background: Dalbavancin is a lipoglycopeptide with potent in vitro gram-positive antibacterial activity and novel pharmacokinetic properties that allow for once-weekly dosing. The primary objective of this study was to demonstrate that therapeutic and supratherapeutic plasma exposures to dalbavancin do not have an effect on the 12-lead electrocardiogram (EGC) QTcF interval exceeding 10 msec in healthy adult male and female subjects.

Methods: Two hundred healthy adult subjects were enrolled in this parallel group ECG study which evaluated single IV doses of 1000 mg (therapeutic dose) and 1500 mg (supratherapeutic dose) of dalbavancin, as well as placebo and positive (oral moxifloxacin 400 mg) controls. Subjects underwent continuous Holter monitoring for 24-hour periods on Day –1 and Day 1. All endpoint 12-lead ECGs were downloaded in replicate at nominal time points on Day 1 and at corresponding clock times on Day –1. Blood for PK analysis was collected immediately following each nominal ECG extraction time point. Cmax and AUC0–24h were calculated. Standard safety parameters were monitored.

Results: The largest mean placebo-corrected ΔΔQTcF (ΔΔQTcF) after dosing of dalbavancin 1000 mg was 1.5 msec (CI: –0.6 to 3.6) at 6 hours and after 1500 mg was 0.2 msec (CI: –1.7 to 2.0) at 24 hours. The study’s assay sensitivity was confirmed by the expected moxifloxacin mean peak effect of 12.9 msec at 2 hours after a single-dose of 400 mg moxifloxacin. Concentration effect modeling demonstrated a small, slightly negative concentration dependent effect of dalbavancin on the ΔΔQTcF. Concentration effect modeling further explored potential effects of dalbavancin on QTc interval in a clinically relevant way.

ECG Results: The primary endpoint of placebo-corrected, change from baseline ΔΔQTcF (ΔΔQTcF) across treatments is illustrated in Figure 1.

Conclusions: An effect of dalbavancin on QTcF exceeding 10 msec could be confidently excluded at all time points after a single IV dose of 1000 mg and after a single IV dose of 1500 mg. Concentration effect modeling was consistent with the time matched analyses, demonstrating that dalbavancin does not affect the QTc interval in a clinically relevant way.

Methods:

This was a single-center, randomized, single-dose, placebo- and positive-controlled, partially double-blind, parallel group ECG study to evaluate single IV doses of dalbavancin 1000 mg (therapeutic dose) and 1500 mg (supratherapeutic dose). Dosing in the current study was an optional 12-minute infusion, with all IV treatments administered over 30 minutes. IV infusions were double-blind; all IV treatments were administered over 30 minutes. IV infusions were double-blind; all IV treatments were administered over 30 minutes.

Results:

Dalbavancin 1000 mg (therapeutic) or 1500 mg (supratherapeutic) single IV doses, administered over 30 minutes, did not have a clinically relevant effect on the QTcF interval.

Safety Results:

- One serious adverse event (SAE) of ectopic pregnancy, unrelated to study drug, occurred in the dalbavancin 1000 mg treatment group.
- One subject administered dalbavancin 1000 mg with red man syndrome and 1 subject administered placebo with infusion site extravasation discontinued study medication.
- One serious adverse event (SAE) of ectopic pregnancy, unrelated to study drug, occurred in the dalbavancin 1000 mg treatment group.
- One subject administered dalbavancin 1000 mg with red man syndrome and 1 subject administered placebo with infusion site extravasation discontinued study medication.

CONCLUSIONS

- Dalbavancin 1000 mg (therapeutic) or 1500 mg (supratherapeutic) single IV doses, administered over 30 minutes, did not have a clinically relevant effect on the QTcF interval.
- An effect on ΔΔQTcF exceeding 10 msec could be confidently excluded at all time points after single IV dalbavancin doses of 1000 mg and 1500 mg.
- Assay sensitivity was confirmed by the expected moxifloxacin mean peak ΔΔQTcF effect of 12.9 msec at 2 hours after administration.
- Concentration effect modeling was consistent with the time matched analyses, confidently demonstrating that dalbavancin does not affect the QTc interval in a clinically relevant way.
- Overall, single IV doses of dalbavancin 1000 mg or 1500 mg administered over 30 minutes were well tolerated.
- These results correspond to a negative thorough QT/QTc study.