

A PHASE I, OPEN-LABEL, SINGLE DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS (PK), SAFETY AND TOLERABILITY OF DALBAVANCIN IN ADOLESCENTS AGE 12 TO 17 YEARS

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ABSTRACT

Background and Objectives: Dalbavancin is a lipoglycopeptide with a gram-positive spectrum of activity and novel pharmacokinetic properties that may allow for once weekly dosing in children. Dosing in adults has been established and confirmed in phase 3 studies. The primary objective of this study was to characterize the pharmacokinetics (PK) of dalbavancin in pediatric subjects aged 12 to <17 years, administered as either a fixed single dose or adjusted by weight.

Methods: Open-label, intravenous dalbavancin was administered to hospitalized subjects in addition to background treatment for a bacterial infection. A single dose of 1000 mg was given to subjects weighing ≥ 60 kg, and 15 mg/kg for subjects weighing <60 kg. The dose was infused over 30 minutes on the study day.

Results: Dalbavancin plasma exposures (C_{max} , AUC_{inf} and AUC_{last}), administered as 1000 mg to subjects weighing ≥ 60 kg (61.9–105.2 kg), were similar compared to administration as 15 mg/kg to those weighing <60 kg (47.9–58.9 kg) and similar to exposures in adults observed in prior studies. The mean CL, Vss and CLr was marginally higher for subjects weighing ≥ 60 kg.

Conclusions: Mean plasma exposures for dalbavancin, based on AUC_{inf} and C_{max} , were similar when administered as 1000 mg to children (12 to 17 years) weighing ≥ 60 kg or as 15 mg/kg to those weighing <60 kg. The terminal $t_{1/2}$ was approximately 9 days. Dalbavancin was well tolerated in these subjects. Given similar drug exposures in children ages 12–17 years to that of adults, similar efficacy in treatment of skin/skin structure infections to that of adults might be expected.

BACKGROUND AND OBJECTIVES

Background:

- Dalbavancin is a lipoglycopeptide with a gram-positive spectrum of activity and novel pharmacokinetic properties that may allow for once weekly dosing in children.
- Dosing in adults has been established and confirmed in phase 3 studies.
- The primary objective of this study was to characterize the pharmacokinetics (PK) of dalbavancin in pediatric subjects aged 12 to 17 years, administered as either a fixed single dose or adjusted by weight.

METHODS

Study Design:

- This was an open-label, multi-center study to investigate the PK, safety and tolerability of a single dose of IV dalbavancin in pediatric subjects aged from 12 to 17 years, inclusive (adolescents).
- Dalbavancin was administered to hospitalized subjects in addition to background anti-infective treatment for a known or suspected bacterial infection.

Diagnosis and Main Criteria for Inclusion:

- Hospitalized male and female subjects from 12 to 17 years of age (inclusive) receiving systemic antibiotic treatment for known or suspected bacterial infections.

Study Treatment:

- A single dose of 1000 mg of dalbavancin was administered to subjects weighing 60 kg or greater, and 15 mg/kg for subjects weighing <60 kg. The dose was given as a 30 minute iv infusion on Day 1.
- Dalbavancin for Injection, 500 mg in each vial, was provided for all subjects at all sites.

Pharmacokinetic Evaluations:

- Blood samples to provide plasma for pharmacokinetic assessment were taken at the following specified timepoints:
 - Day 1: 0 hour (prior to the start of the infusion), 0.5 hour (within 2 minutes before the end of the infusion).
 - Post the end of infusion: 1, 2, 4, 12 hours post-start of infusion.
 - Day 2: 24 hours post-start of infusion on Day 1.
 - Day 3: 48 hours post-start of infusion on Day 1.
 - Day 7: 144 hours post-start of infusion on Day 1.
 - Day 14: 312 hours (+/- 1 day) post-start of infusion on Day 1.
 - Day 21: 480 hours (+/- 2 days) post-start of infusion on Day 1.
 - Day 28: 648 hours (+/- 2 days) post-start of infusion on Day 1.
 - Day 56: 1320 hours (+/- 4 days) post-start of infusion on Day 1.
- A 24-hour urine collection was done on Days 1 and 2.

RESULTS

Table 1. Subject Demographics

| | Dalbavancin 1000 mg | | | Dalbavancin 15 mg/kg | | |
|---|---------------------|-------------|-------------|----------------------|--------|-------------|
| | Male | Female | Total | Male | Female | Total |
| Number of Subjects | 3 | 2 | 5 | 4 | 1 | 5 |
| Age (years) | | | | | | |
| 12 | 0 | 1 | 1 | 1 | 0 | 1 |
| 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| 14 | 0 | 0 | 0 | 2 | 0 | 2 |
| 15 | 2 | 0 | 2 | 0 | 1 | 1 |
| 16 | 1 | 1 | 2 | 1 | 0 | 1 |
| Mean | 15.3 | 14.0 | 14.8 | 14.0 | 15.0 | 14.2 |
| SD | 0.6 | 2.8 | 1.6 | 1.6 | 0 | 1.5 |
| Range | 15–16 | 12–16 | 12–16 | 12–16 | 15–15 | 12–16 |
| Race | | | | | | |
| White | 2 | 1 | 3 | 2 | 0 | 2 |
| Black | 1 | 1 | 2 | 2 | 1 | 3 |
| Weight (kg) | | | | | | |
| Mean | 65.6 | 101.0 | 79.8 | 51.3 | 55.3 | 52.1 |
| SD | 3.7 | 6.0 | 19.8 | 5.1 | 0 | 4.8 |
| Range | 61.9–69.3 | 96.8–105.2 | 61.9–105.2 | 47.9–58.9 | NA | 47.9–58.9 |
| Body Mass Index (kg/m²) | | | | | | |
| Mean | 23.6 | 37.5 | 29.1 | 20.2 | 19.4 | 20.0 |
| SD | 3.1 | 5.1 | 8.3 | 1.7 | 0 | 1.5 |
| Range | 21.2–27.1 | 33.9–41.1 | 21.2–41.1 | 18.2–22.2 | NA | 18.2–22.2 |
| Height (cm) | | | | | | |
| Mean | 167.3 | 164.5 | 166.2 | 159.5 | 169.0 | 161.4 |
| SD | 6.4 | 6.4 | 5.7 | 8.4 | 0 | 8.4 |
| Range | 160.0–171.0 | 160.0–169.0 | 160.0–171.0 | 148.0–168.0 | NA | 148.0–169.0 |

NA=not applicable; SD=standard deviation

Pharmacokinetic Results:

- The range of observed plasma exposures (C_{max} , AUC_{inf} and AUC_{last}) for dalbavancin, administered as 1000 mg to pediatric subjects weighing 60 kg or greater, was similar when compared to dalbavancin administered as 15 mg/kg to pediatric subjects weighing <60 kg.
- The median plasma concentrations over time as shown in Figures 1 and 2 are virtually identical between the two treatment groups.

Figure 1. Median Dalbavancin Concentration-Time Profiles

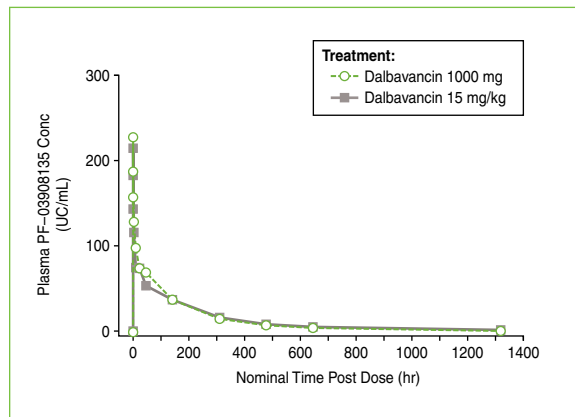
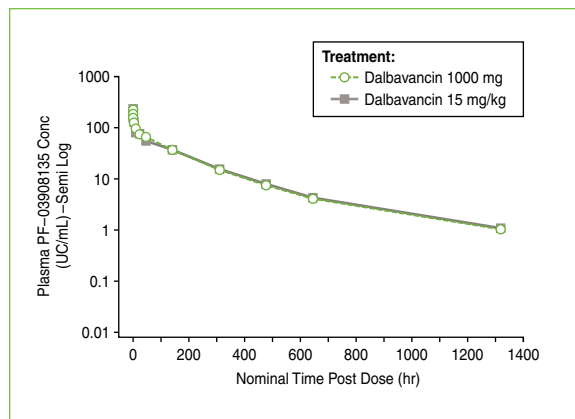


Figure 2. Median Dalbavancin Concentration-Time Profiles



- As expected, the median T_{max} for both the treatments was the same (0.5 hours), corresponding to the end of infusion. Following the end of infusion the plasma concentrations showed a multi-phasic decline for both treatment groups.
- Apparent terminal $t_{1/2}$ was similar for dalbavancin 1000 mg and dalbavancin 15 mg/kg, with mean values of 227 and 202 hours, respectively.
- The mean CL, Vss and CLr were found to be 16%, 23%, and 33% higher, respectively for subjects weighing >60 kg compared with subjects weighing <60 kg (Table 2).
- The total amount of dalbavancin eliminated in urine during the 48-hour period (Ae) after dosing was 5–6% for both treatment groups (Table 2).
- Variability for AUC_{inf} and AUC_{last} , based on % coefficient of variance (CV) (Table 2), was similar for both treatments.

Table 2. Summary of Plasma Dalbavancin Pharmacokinetic Parameter Values Following a Single Intravenous Infusion

| Parameter, Units | Parameter Summary Statistics ^a by Treatment | |
|--|--|----------------------|
| | Dalbavancin 1000 mg | Dalbavancin 15 mg/kg |
| N | 5 | 5 |
| AUC_{48} , $\mu\text{g}\cdot\text{hr}/\text{mL}$ | 4006 (30) | 3438 (26) |
| AUC_{last} , $\mu\text{g}\cdot\text{hr}/\text{mL}$ | 17258 (28) | 15973 (21) |
| AUC_{inf} , $\mu\text{g}\cdot\text{hr}/\text{mL}$ | 17495 (28) | 16248 (20) |
| C_{max} , $\mu\text{g}/\text{mL}$ | 212 (12) | 191 (27) |
| T_{max} , hr | 0.500 (0.47–1.00) | 0.500 (0.47–1.00) |
| $t_{1/2}$, hr | 227 (7) | 202 (20) |
| CL, mL/hr | 57.2 (28) | 48.1 (25) |
| Vss, mL | 15232 (29) | 11816 (11) |
| CLr, mL/hr | 15.7 (37) | 9.97 (48) |
| Ae_{48} , μg | 63705 (19) | 40213 (60) |
| $Ae_{48}\%$, μg | 6.37 (19) | 5.31 (65) |

^aGeometric mean (%CV) for all except: median (range) for T_{max} , arithmetic mean (%CV) for $t_{1/2}$, Ae_{48} and $Ae_{48}\%$

Safety:

- There were no treatment-related adverse events (AEs) and no severe AEs.
- There was 1 SAE, mild ileus, experienced by 1 subject in the 15 mg/kg group. This SAE was considered by the investigator to be related to complications following an intra-abdominal abscess and not related to treatment.
- AE's experienced in the 1000 mg group were headache diarrhea, nausea, vomiting, increased blood bilirubin, headache, nasal congestion and hypotension. AE's experienced in the 15 mg/kg group were headache abdominal pain, constipation, ileus, hyperbilirubinemia, skin laceration, wound, dehydration, dizziness, headache and rash macular.

Table 3. Summary of Treatment-Emergent Adverse Events

| | Dalbavancin 1000 mg N=5 | | Dalbavancin 15 mg/kg N=5 | |
|--|----------------------------|-----------------------|-----------------------------|-----------------------|
| | All Causality | Treatment- Related | All Causality | Treatment- Related |
| Number of AEs | 7 | 0 | 10 | 0 |
| Subjects with AEs | 5 | 0 | 4 | 0 |
| Subjects with SAEs | 0 | 0 | 1 | 0 |
| Subjects with severe AEs | 0 | 0 | 0 | 0 |
| Subjects who discontinued due to AEs | 0 | 0 | 0 | 0 |
| Subjects who dose reduced or temporary discontinuations due to AEs | 0 | 0 | 0 | 0 |

AE=adverse event, N=number of subjects

CONCLUSIONS

- Mean plasma exposures for dalbavancin, based on AUC_{inf} and C_{max} , were similar when administered as 1000 mg to pediatric subjects (12 to 17 years) weighing >60 kg (61.9–105.2 kg) or as 15 mg/kg to pediatric subjects weighing <60 kg (47.9–58.9 kg).
- Apparent terminal $t_{1/2}$ was similar for dalbavancin dosages of 1000 mg and 15 mg/kg, with mean values of 227 and 202 hours, respectively.
- The significance of the observation of greater renal clearance in the 5 children >60 kg is not known.
- The safety profile of dalbavancin in the subjects aged between 12 to 17 years in this study was acceptable.

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