Dalbavancin Pharmacokinetics and Safety in Children 3 Months to 11 Years of Age

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Abstract

Background: Dalbavancin is a novel lipoglycopeptide antibiotic that has potent in vitro activity against Gram-positive microorganisms.

Methods: We performed a phase 1, open-label, multi-center study to investigate the pharmacokinetics (PK) and safety of a single-dose of intravenous dalbavancin in hospitalized pediatric subjects 3 months to 11 years of age. We combined these data with previously collected adolescent PK data and performed a population PK analysis using NONMEM (version 7.1.2). When we used the model to perform simulations and identified pediatric dosing that matched exposure observed in the phase 1 adult studies.

Results: The results used for the model development included 311 dalbavancin plasma concentrations from 43 subjects. The median (range) age and dose were 5.0 (0.9-16.8) years and 400 mg (200-6000 mg), respectively. A three-compartment, linear PK model described the data well based on simulations. The following age dependent dosing regimens were found to be similar to adult in achieving a 2-dose regimen (1000 mg on day 1 and 500 mg on day 8) or a single intravenous infusion of 1500 mg on day 1. Similarity to adult was assessed using a visual predictive check of the final model.

Conclusions: Dalbavancin pediatric dosing that matches adult exposure was identified. Overall, dalbavancin was well tolerated in our study population.

Introduction

• Dalbavancin is approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of acute bacterial skin and skin structure infections in adults.

• Dalbavancin can be prescribed to adults using a 2-dose regimen (1000 mg given intravenously on day 1 and 500 mg given intravenously on day 8) or a single intravenous infusion of 1500 mg.

• Available pediatric dalbavancin PK data is limited to adolescents 12 to 17 years of age.

• We performed an open-label, multi-center study to characterize the PK and safety of dalbavancin in hospitalized children 3 months to 11 years of age.

Methods

• A single, intravenous (IV) dose of dalbavancin 10-25 mg/kg (not to exceed the 1000 mg adult dose) based on age was administered. PK samples were collected at 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 120, 180, 240, 360, and 480 hours after the start of the IV infusion.

• A population PK analysis was performed using NONMEM (version 7.2) after combining the pediatric PK data with a previous adult population PK study of subjects ages 12 to 17 years of age previously collected adolescent PK data (Study A8841004). To account for the growth effects, we used a population PK model utilizing allometric scaling to adjust for the growth of lean body mass and body weight. The EMA recommends that the PK and safety of dalbavancin in pediatric subjects less than 11 years of age be evaluated. To ensure robustness, we performed a sensitivity analysis using a visual predictive check of the final model.

• The safety of dalbavancin in this study and no severe or serious adverse events related to treatment were reported. No new or serious adverse events related to treatment were observed in any of the patients, nor were significant renal or ototoxicity events identified.

• There were 36 treatment-emergent AEs and 5 subjects experienced a serious AE. None of the serious or severe treatment-emergent AEs were considered related to study treatment.

• The following AEs were deemed possibly related to dalbavancin treatment (N=1 each): rash, diaper dermatitis, oral ulceration, and asymptomatic hepatic enzyme elevation. One subject had infusion site discomfort that was probably related to study treatment.

• Dalbavancin was well tolerated in this study and no serious or severe AEs related to treatment were reported. "No "not" mean" symptom occurred in study patients, nor were significant renal or ototoxicity events identified.

Figure 1. Visual predictive check of the final model.

Table 1. Final population PK model parameter estimates.

Parameter | Estimate | 95% CI | p-value
--- | --- | --- | ---
Dose (mg/kg) | 1.02 | (0.71, 1.45) | <0.001
Vc (L) | 3.88 | (3.38, 4.44) | <0.001
CL (L/hr) | 0.033 | (0.016, 0.060) | <0.001
CLd1 (L/hr) | 0.0065 | (0.0028, 0.014) | <0.001
ω | 0.75 | (0.68, 0.82) | <0.001
φ | 0.80 | (0.70, 0.90) | <0.001

Table 2. Recommended dosing based on simulations.

| Dose Regimen | 3 months to 11 years of age | 12 mg/kg on day 1 and 5.0 mg/kg on day 8 | 15 mg/kg on day 1 and 7.5 mg/kg on day 8 |
| --- | --- | --- |
| 0 to 19 days | 15 mg/kg (1000 mg maximum) on day 1 and 7.5 mg/kg (500 mg maximum) on day 8 | 18 mg/kg (1000 mg maximum) on day 1 and 10.5 mg/kg (500 mg maximum) on day 8 |

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