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

Daniel Gonzalez[1], John S. Bradley[2], Jeffrey Blumer[3], Ram Yogev[4]; Kevin M. Watt[5,6], Laura P. James[7], Debra L. Palazzi[8], Varsha Bhatt-Mehta[9], Janice E. Sullivan[10], Li Zhang[11], Jennifer Murphy[6], Xilla T. Ussery[12], Sailaja Puttagunta[12], Michael W. Dunne[12], Michael Cohen-Wolkowiez[5,6]

[1]Univ. of North Carolina, Chapel Hill, NC, USA; [2]Univ. of California, San Diego, CA, USA; [3]Univ. of Toledo, Toledo, OH, USA; [4]Northwestern Univ., Chicago, IL, USA; [5]Duke Univ., Durham, NC, USA; [6]Duke Clinical Res. Inst., Durham, NC, USA; [7]Arkansas Children Res. Inst., Little Rock, AR, USA; [8]Baylor Coll. of Med., Houston, TX, USA; [9]Univ. of Michigan, Ann Arbor, MI, USA; [10]Univ. of Louisville, Louisville, KY, USA; [11]Institute for Clinical Pharmacodynamics, Latham, NY, USA; [12]Durata Therapeutics, Branford, CT, USA.

Poster #1970

Daniel Gonzalez, Pharm.D., Ph.D.
3312 Kerr Hall, Campus Box # 7569
Chapel Hill, NC 27599-7569
UNC Eshelman School of Pharmacy
daniel.gonzalez@unc.edu
919-966-9273 (o); 919-962-0644 (f)

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 (ver. 7.1.2). We then used the model to perform simulations and identified pediatric dosing that matches exposure observed in the phase 3 adult studies.

Results: The dataset used for PK model development included 311 dalbavancin plasma concentrations from 43 subjects. The median (range) age and dose were 5.9 years (0.3-16.9) and 400 mg (60–1000). A three-compartment, linear PK model described the data well. Based on simulations, the following age-dependent dosing regimens were found to achieve similar exposure to that in adults receiving a 2-dose regimen (1000 mg on day 1 and 500 mg given on day 8): age 6 to < 18 years, 12 mg/kg (1000 mg maximum) on day 1 and 6 mg/kg (500 mg maximum) on day 8; age 3 months to < 6 years, 15 mg/kg (1000 mg maximum) on day 1 and 7.5 mg/kg (500 mg maximum) on day 8. Similarly, the following age-dependent regimens were found to match adult exposure after a single-dose (1500 mg): age 6 to < 18 years, 18 mg/kg (1500 mg maximum) on day 1, and age 3 months to < 6 years, 22.5 mg/kg (1500 mg maximum) on day 1. Thirty-six treatment-emergent adverse events were reported; 5 of which were possibly or probably related to dalbavancin.

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.[1]
- Available pediatric dalbavancin PK data is limited to adolescents 12 to 17 years of age.[2]
- 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 (±5 min), 4 (±2), 12 (±2), 24 (±4), 144 (±48), and 648 hours (±96) after the start of the IV infusion.
- A population PK analysis was performed using NONMEM® (ver. 7.1.2) after combining the pediatric PK data from the current study of subjects 3 months to 11 years of age with previously collected adolescent PK data (Study A8841004).[2] To account for the growth effects, actual body weight (WT) was included in the base model using allometric scaling prior to assessment of other covariates.
- The statistical significance of other covariate relationships was evaluated using a forward inclusion ($p<0.05$) and backward elimination ($p<0.001$) approach.
- Using the final model, Monte Carlo simulations were performed to identify pediatric dosing that matches the dalbavancin $AUC_{0\text{-}120}$ distribution observed in a phase 3 adult program.

Results

Table 1. Clinical data.

Study	DUR001-106			A8841004[2]	
Variable	3 months to <2 years (N=11)	2 to <6 years (N=11)	6 to 11 years (N=11)	12 to 17 years (N=10)	Total (N=43)
Dalbavancin dose (mg/kg)	10.2 (9.7-10.6)	25.1 (15.1-25.7)	15.0 (10.9-15.2)	15.0 (9.5-16.2)	15.0 (9.5-25.7)
Age (years)	0.8 (0.3-1.6)	3.0 (2.3-5.9)	9.0 (6.8-11.8)	15.7 (12.4-16.9)	5.9 (0.3-16.9)
Weight (kg)	9.6 (5.7-13.0)	15.7 (10.7-18.9)	31.4 (19.8-92.0)	60.4 (47.9-105.2)	18.9 (5.7-105.2)
Albumin (g/dL)	3.4 (2.9-4.5)	3.6 (2.2-4.5)	4.1 (3.1-4.4)	3.0 (1.9-4.6)	3.6 (1.9-4.6)
Calculated creatinine clearance[a] (mL/min/1.73 m^2)	70.7 (49.8-174.9)	154.1 (94.5-206.5)	127.5 (91.8-191.6)	101.3 (54.7-132.2)	115.4 (49.8-206.5)
Male (%)	9 (82)	6 (55)	9 (82)	7 (70)	31 (72)

[a]Values reported as median (range) or count (%).
[a]For children 3 months to 11 years of age, CrCl was calculated using the Schwartz equation, whereas for adolescents 12 to 17 years of age the Cockcroft and Gault equation was used and then values were normalized to body surface area.

Table 2. Final population PK model parameter estimates.

	Final Model	
Parameter	Estimate	% SEM
CL (L/hr)	0.033	6.90
V_c (L)	2.46	7.80
CL_{d1} (L/hr)	0.51	15.0
V_{p1} (L)	2.90	9.40
CL_{d2} (L/hr)	0.0065	12.3
V_{p2} (L)	2.93	62.1
Power coefficient of weight on CL parameters	0.71	8.70
Power coefficient of weight on volume parameters	0.95	5.80
Power coefficient of albumin on CL	-0.78	34.1
Power coefficient of albumin on V_c	-0.73	47.1
ω^2_CL (IIV as %)	0.034 (18.4)	44.4
ω^2_Vc (IIV as %)	0.035 (18.8)	35.7
ω^2_Vp1 (IIV as %)	0.090 (29.9)	36.9
σ^2_Plasma proportional error	0.01	5.30
σ^2_Plasma additive error	0.25	Fixed

CL: clearance; V_c: central volume of distribution; CL_{d1}: distributional clearance to peripheral compartment 1; CL_{d2}: distributional clearance to peripheral compartment 2; V_{p1}: volume of distribution for peripheral compartment 1; V_{p2}: volume of distribution for peripheral compartment 2. IIV: inter-individual variability. NE: not evaluable.

Figure 1. Visual predictive check of the final model.

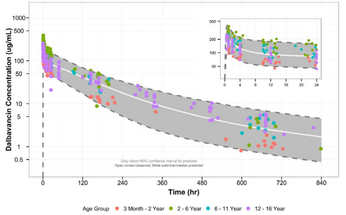
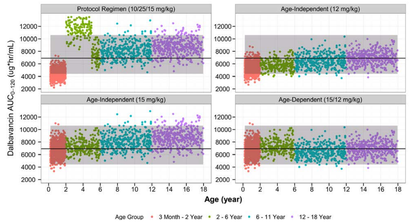


Figure 2. Comparison of the simulated dalbavancin $AUC_{0\text{-}120}$ estimates in pediatric subjects of age 3 months to 18 years using various dosing regimens to the distribution of $AUC_{0\text{-}120}$ estimates from the adult, phase 3 program (top figure: dalbavancin day 1 dose of 1000 mg; bottom figure: dalbavancin day 1 dose of 1500 mg).



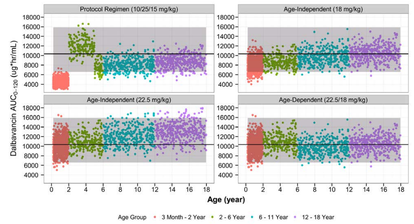


Table 3. Recommended dosing based on simulations designed to match exposure in adults.

	2-dose regimen	1-dose regimen
6 to < 18 years	12 mg/kg (1000 mg maximum) on day 1 and 6 mg/kg (500 mg maximum) on day 8	18 mg/kg (1500 mg maximum) on day 1
3 months to < 6 years	15 mg/kg (1000 mg maximum) on day 1 and 7.5 mg/kg (500 mg maximum) on day 8	22.5 mg/kg (1500 mg maximum) on day 1

- 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, urticaria, and asymptomatic hepatic enzyme elevation. One subject had infusion site discomfort that was probably related to study treatment.

Conclusions

- Age-dependent dalbavancin dosing is required for pediatric patients 3 months to 18 years of age to achieve antibiotic exposures effective in adults.
- Dalbavancin was well tolerated in this study and no serious or severe AEs related to treatment were reported. No “red man” syndrome occurred in study patients, nor were significant renal or ototoxicity events identified.

Acknowledgments

The study was funded by Durata Therapeutics, Inc.

D.G. receives support for research from the National Institute for Child Health and Human Development (K23HD083465) and the nonprofit organization Thrasher Research Fund. J.S.B. received no personal compensation for participation in the study or generation of the manuscript, but his employer, the University of California, received funds for conduct of the study and consultation with Durata Therapeutics, Inc. J.B., R.Y., K.M.W., L.P.J., D.L.P., V.B-M, J.E.S., and M.C-W. received research support from Durata Therapeutics, Inc. to serve as an investigator in this study. X.U. was a consultant to Allergan, Inc. and received a consultant fee for her contributions to this study. S.P. was an employee of Allergan, Inc. and received salary and stock options for her contributions to this study. M.W.D. was an employee of Allergan, Inc. and received salary and speaker honorarium for his contributions to this study.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Dalbavance® package insert. Accessed via: http://www.allergan.com/assets/pdf/dalvance_pi.
2. Bradley J, Puttagunta S, Rubino C, Blumer J, Dunne M, Sullivan J. Pharmacokinetics, safety and tolerability of single dose dalbavancin in children 12 through 17 years of age. *Pediatr Infect Dis J.* 2015;34(7):748-52.