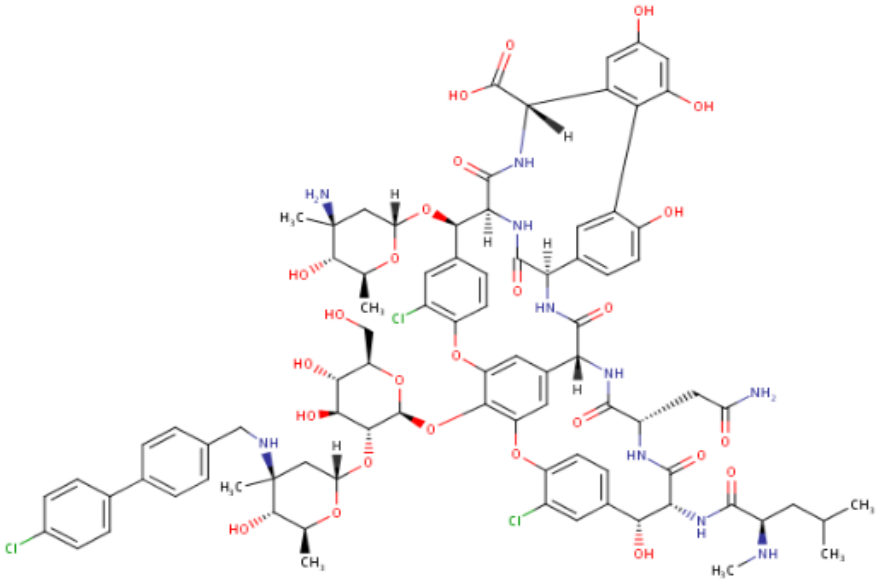
Pharmacokinetics (PK) of Oritavancin in Children: The ORKIDS Trial

Interim Report for Ages 2 to <18 years



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Oritavancin (ORBACTIV®) Overview

- Novel lipoglycopeptide antibiotic
- Approved in adults in 2014 as a single 1200 mg IV dose over 3 hours for the treatment of ABSSSI caused by susceptible Gram-positive pathogens, including MRSA
- Rapid, concentration-dependent bactericidal activity
- Long acting, unique PK allowing for a single 1200 mg dose IV administration over 3 hours compared with multiple daily doses of vancomycin
- Efficacy and safety demonstrated in 2 Phase 3 adult clinical studies with single treatment dose to treat ABSSSI
- No dose adjustment for renal/hepatic impairment in adults

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Study Objectives

PRIMARY OBJECTIVE

- The primary objective is the evaluation of pharmacokinetic profile (AUC) after a single oritavancin infusion in pediatric patients.

SECONDARY OBJECTIVES

- The secondary objective is the evaluation of noncompartmental pharmacokinetic parameters (C_{max}, half-life [t1/2], t_{max}, volume of distribution [Vd], and CL) after a single oritavancin infusion in pediatric subjects.
- Safety and tolerability assessments evaluated up to 60 days following the oritavancin infusion.

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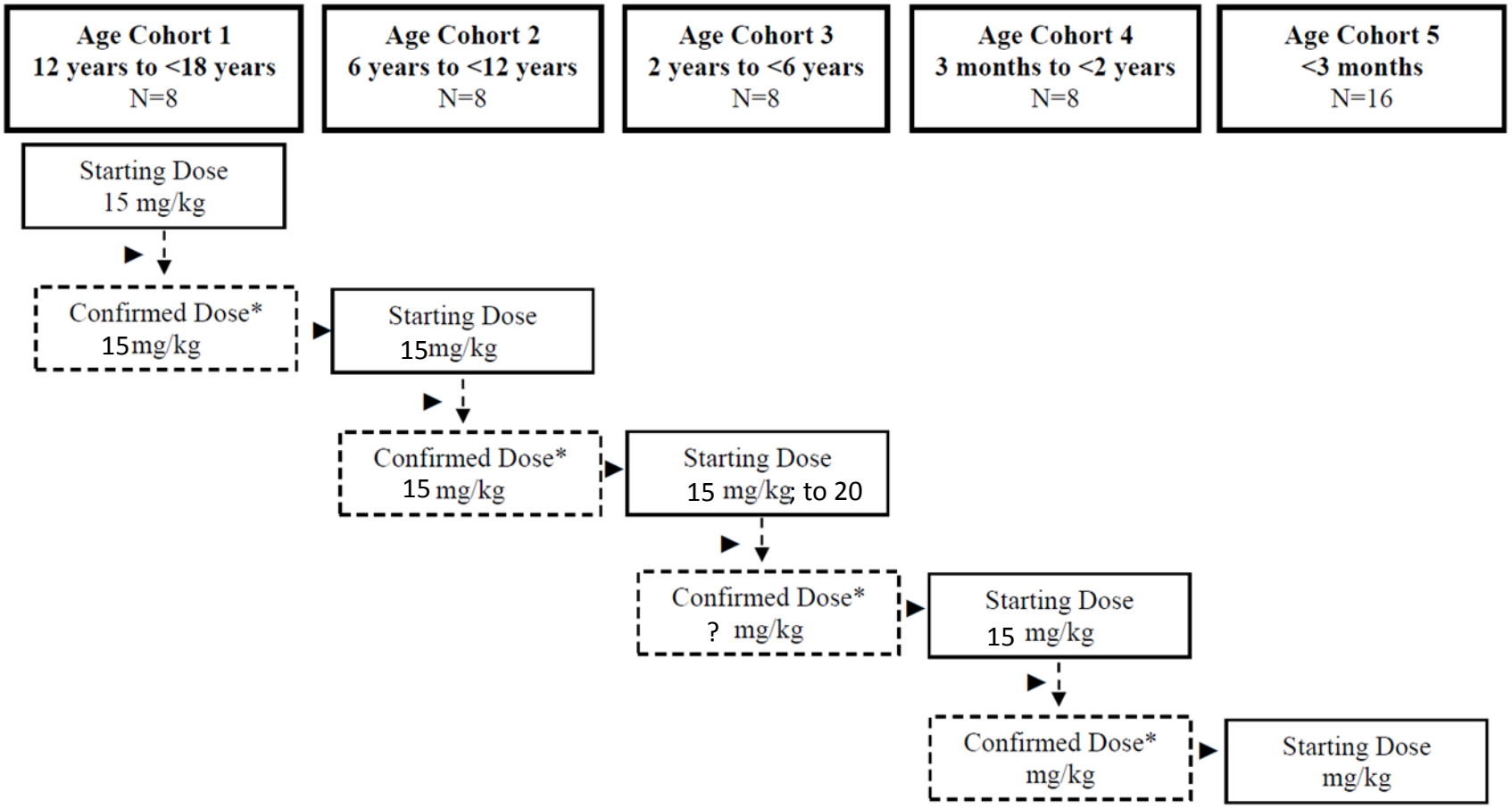
Pediatric Pharmacokinetics Study Design



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Study Population

- 24 pediatric male and female children with a suspected or confirmed Gram-positive bacterial infection receiving antibiotic therapy except vancomycin
- Patients were enrolled in a stepwise approach according to the following age cohorts:
    - 12 to <18 years (8 patients)
    - 6 to <12 years (8 patients)
    - 2 to <6 years (8 patients)
- Two additional age cohorts are planned : 3 months to <2 years and birth to <3 months (including neonates from 0 to 28 days)

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Subject Demographics

	12 to <18 years (Cohort 1) N=8	6 to <12 years (Cohort 2) N=8	2 to <6 years (Cohort 3) N=8
Age (years)			
n	8	8	8
Mean (SD)	15.3 (1.49)	9.1 (1.64)	2.5 (0.53)
Median	15.5	8.5	2.5
Q1, Q3	15.0, 16.0	8.0, 11.0	2.0, 3.0
Min, Max	12, 17	7, 11	2, 3
Sex, n (%)			
Male	4 (50.0)	2 (25.0)	4 (50.0)
Female	4 (50.0)	6 (75.0)	4 (50.0)
Race, n (%)			
White	6 (75.0)	7 (87.5)	6 (75.0)
Black or African American	2 (25.0)	1 (12.5)	2 (25.0)
Ethnic Group, n (%)			
Hispanic or Latino	2 (25.0)	3 (37.5)	4 (50.0)
Not Hispanic or Latino	6 (75.0)	5 (62.5)	4 (50.0)

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Types of Infections

	12 to <18 years (Cohort 1) N=8	6 to <12 years (Cohort 2) N=8	2 to <6 years (Cohort 3) N=8
Cellulitis	1 (12.5)	1 (12.5)	2 (25.0)
Appendicitis perforated	1 (12.5)	1 (12.5)	1 (12.5)
Pneumonia	0	2 (25.0)	1 (12.5)
Abdominal abscess	0	1 (12.5)	1 (12.5)
Arthritis bacterial	1 (12.5)	1 (12.5)	0
Bacteraemia	0	0	2 (25.0)
Lobar pneumonia	1 (12.5)	1 (12.5)	0
Abdominal infection	1 (12.5)	0	0
Impetigo	0	1 (12.5)	0
Pelvic abscess	1 (12.5)	0	0
Periorbital cellulitis	1 (12.5)	0	0
Peritonitis	1 (12.5)	0	0
Peritonsillar abscess	1 (12.5)	0	0
Postoperative wound infection	1 (12.5)	0	0
Pyelonephritis	1 (12.5)	0	0
Sepsis	0	0	1 (12.5)
Upper respiratory tract infection	0	0	1 (12.5)

Overview of Adverse Events

	12 to <18 years (Cohort 1) N=8 n (%)	6 to <12 years (Cohort 2) N=8 n (%)	2 to <6 years (Cohort 3) N=8 n (%)
Number of Subjects with any TEAE*	5 (62.5)	5 (62.5)	5 (62.5)
Number of Subjects with Study Drug Related* TEAE	2 (25.0)	3 (37.5)	3 (37.5)
Number of Subjects with any TEAE Leading to Study Drug Discontinuation	0	0	0
Number of Subjects with Serious Adverse Event	1 (12.5)	1 (12.5)	1 (12.5)
Number of Subjects with any AE Leading to Fatal Outcome	0	0	0

*TEAEs are AEs which occurred or whose severities worsened on or after the initiation of study drug.

*Includes AEs considered by the Investigators as definitely related or possibly related to study drug.

Serious Adverse Events

Age Sex Infection	Verbatim Term	Date of Oritavancin Dosing	Event Dates Start Stop	Severity	Relation to Study Drug (PI)	Study Drug Action Taken	Outcome
15 years Male Ruptured Appendix	Postoperative worsening small bowel obstruction due to postoperative adhesions	9/18/2014	9/18/2014 10/2/2014	Mod	Not related	Dose not changed	Recover/ Resolved
9 years Female CAP	Clostridium difficile colitis	1/30/2015	2/21/2015 2/27/2015	Mild	Possibly related	NA	Recover/ Resolved
2 years Female Bacteremia	Enterococcal endocarditis	9/1/2015	9/25/2015 10/22/15	Severe	Not related	NA	Recover/ Resolved

Treatment Emergent Adverse Events

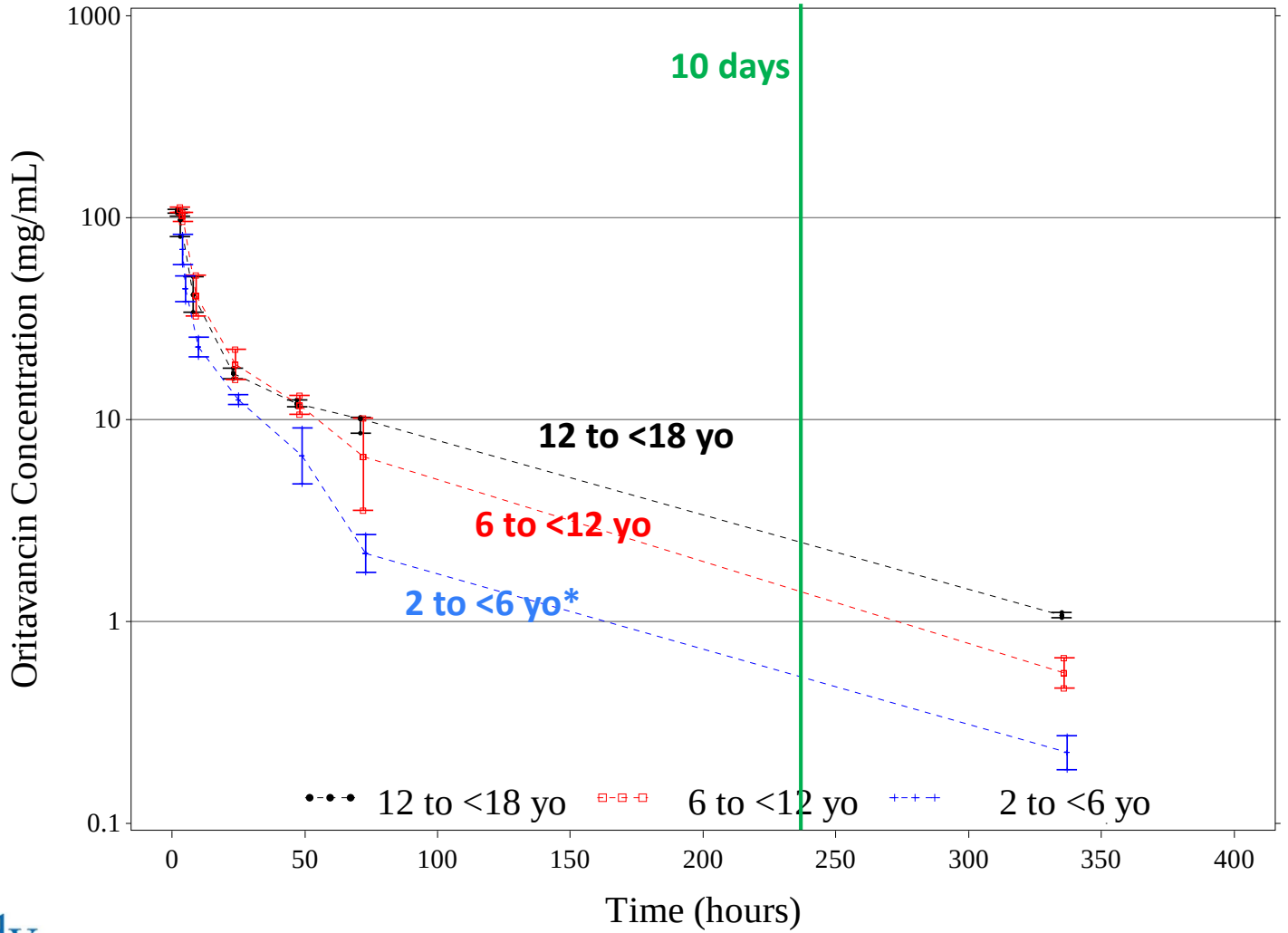
	12 to <18 years (Cohort 1) N=8 n (%)	6 to <12 years (Cohort 2) N=8 n (%)	2 to <6 years (Cohort 3) N=8 n (%)	All Subjects (N=24) n (%)
Number of Subjects with Any TEAE*	5 (62.5)	5 (62.5)	5 (62.5)	15 (62.5)
Hepatic enzyme increased	2 (25.0)	0	1 (12.5)	3 (12.5)
Anaemia	0	0	2 (25.0)	2 (8.3)
Clostridium difficile colitis	0	1 (12.5)	0	1 (4.2)
Electrocardiogram QT prolonged	0	0	1 (12.5)	1 (4.2)
Haematochezia	0	0	1 (12.5)	1 (4.2)
Haematuria	0	0	1 (12.5)	1 (4.2)
Leukopenia	0	0	1 (12.5)	1 (4.2)
Pyelonephritis fungal	0	0	1 (12.5)	1 (4.2)
Pyrexia	0	0	1 (12.5)	1 (4.2)
Tachycardia	0	0	1 (12.5)	1 (4.2)
Thrombocytopenia	0	0	1(12.5)	1 (4.2)
Urinary tract infection	1 (12.5)	0	0	1 (4.2)
Urinary tract infection	1 (12.5)	0	0	1 (4.2)
Viral upper respiratory tract infection	0	1 (12.5)	0	1 (4.2)
Wound infection	0	0	1 (12.5)	1 (4.2)

Treatment Emergent Adverse Events – Continued

	12 to <18 years (Cohort 1) N=8 n (%)	6 to <12 years (Cohort 2) N=8 n (%)	2 to <6 years (Cohort 3) N=8 n (%)	All Subjects (N=24) n (%)
Constipation	1 (12.5)	1 (12.5)	0	2 (8.3)
Vomiting	0	1 (12.5)	1 (12.5)	2 (8.3)
Local swelling	0	0	1 (12.5)	1 (4.2)
Abdominal Tenderness	0	1 (12.5)	0	1 (4.2)
Diarrhea	0	0	1 (12.5)	1 (4.2)
Dermatitis diaper	0	0	1 (12.5)	1 (4.2)
Ocular hyperaemia	0	1 (12.5)	0	1 (4.2)
Otitis media acute	0	0	1 (12.5)	1 (4.2)
Photophobia	0	1 (12.5)	0	1 (4.2)
Irritability	0	0	1 (12.5)	1 (4.2)
Facial Pain	1 (12.5)	0	0	1 (4.2)
Fatique	0	1 (12.5)	0	1 (4.2)
Headache	0	1 (12.5)	0	1 (4.2)
Hypersensitivity	0	0	1 (12.5)	1 (4.2)
Ileus	0	1 (12.5)	0	1 (4.2)
Skin exfoliation	0	1 (12.5)	0	1 (4.2)
Small intestinal obstruction	1 (12.5)	0	0	1 (4.2)
Stoma site irritation	0	0	1 (12.5)	1 (4.2)

Concentration-Time Profile of Oritavancin

Ages 2 to <18 years (15 mg/kg)



*Increase clearance in 2 to <6 years

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Pharmacokinetics of Oritavancin 15 mg/kg

	Cohort 1 12- <18 years (n=8)	Cohort 2 6- <12 years (n=8)	Cohort 3 2-<6 years (n=8)	Mean (CV%)/Range in Pooled Adult SOLO Trials^ (n=297)
Cmax (ug/ml)	127	136	84	Mean: 138 (23.0%) Range: 106-170
AUC 0-inf (h*ug/ml)	Mean: 4014 (17%) Range:3067-4692	Mean: 3709 (51%) Range:2062-8199	**Mean: 1963 (30%)** Range: 1189-2718	Mean: 2800 (29%) Range:1999-3600

CV% = % Coefficient of variation
^ Phase III clinical trials

Conclusions

- Oritavancin was relatively safe and well tolerated following single-dose administration to pediatric patients 2 to <18 years old.
- These results are consistent with the overall safety profile seen in adults.
- AUC target was not met in 2 to <6 years with 15 mg/kg dose; four additional 2 to <6 year old subjects will be dosed with 20 mg/kg.

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