P1618

A Multicenter Evaluation of *In Vitro* Activity of Oritavancin and Comparators Against Staphylococci, Enterococci and Streptococci – The ORION Study

Contact info:
Francis Arhin, Ph.D.
The Medicines Company
7170 Frederick Banting Street
Second Floor
Ville Saint Laurent, QC
Canada H4S 2A1
Tel: 514-332-1008 ext 231
Email: francis.arhin@themedco.com

R. Badal[1], S. Bouchillon[1], D. Hoban[1], S. Hawser[2], A. Johnson[1], M. Hackel[1], **J. Johnson[1]**, G. Moeck[3] and F.F. Arhin[3]

[1]International Health Management Associates, Inc., Schaumburg, IL, USA [2]International Health Management Associates Europe, Sàrl, Epalinges, Switzerland [3] The Medicines Company, St.-Laurent, Quebec, Canada

Revised Abstract

Objectives. Oritavancin (ORI) is a bactericidal lipoglycopeptide with multiple modes of action, and has superior pharmacodynamic properties compared to vancomycin. The ORI Susceptibility Profile Initiative (ORION) study determined the activity of ORI against a variety of gram-positive pathogens collected in the USA and South Korea. This analysis focuses on the *in vitro* activity of ORI and comparators against common clinical staphylococcal, streptococcal, and enterococcal species and resistant phenotypes.

Methods. 2,766 clinical isolates were collected from 33 labs in the USA (19) and Korea (14) in 2007-2008. MICs were determined using broth microdilution according to CLSI guidelines and interpretive criteria (M7-A7 and M100-S18).

Results. ORI MIC_{90} (mg/L) and % susceptible (%S) compared to vancomycin (VAN), daptomycin (DAP), and linezolid (LIN) are presented in the following table:

	ORI		VAN		DAP		LIN	
Organism or phenotype (n)	**MIC_{90}**	**%S**	**MIC_{90}**	**%S**	**MIC_{90}**	**%S**	**MIC_{90}**	**%S**
S. agalactiae (121)	0.12	na	1	100	0.5	100	2	100
S. pyogenes (114)	0.25	na	0.5	100	0.25	100	2	100
Viridans group strep (90)	0.06	na	1	100	1	100	2	100
S. aureus (1438)	0.25	na	1	99.9	1	100	4	100
MRSA (661)	0.25	na	2	99.9	1	100	4	100
MSSA (777)	0.25	na	1	100	0.5	100	4	100
Coag-neg Staph (159)	0.12	na	2	100	1	100	2	100
E. faecalis (455)	0.12	na	4	96.0	2	100	2	96.9
VAN-RES (16)	0.25	na	>128	0	2	100	2	100
E. faecium (389)	0.12	na	>128	45.2	4	99.2	4	90.5
VAN-RES (213)	0.12	na	>128	0	4	99.5	4	87.3

na=breakpoints not defined.

Conclusions. ORI had the lowest MICs against most clinical isolates compared to VAN, DAP, and LIN. Against all species and phenotypes, ORI MIC_{90}s were usually 2- to >1024-fold lower than comparators, except for DAP vs. *S. pyogenes*, where DAP and ORI MIC_{90}s were both 0.25 mg/L. Notably, ORI demonstrated potent *in vitro* activity against both wild-type sensitive isolates and those resistant to VAN, DAP, or LIN.

Introduction

Oritavancin is a semisynthetic lipoglycopeptide antibiotic with rapid bactericidal activity against both vancomycin-susceptible, –intermediate and –resistant gram-positive bacteria. Like vancomycin, oritavancin inhibits cell wall synthesis (Arhin et al. 2007; Kim et al. 2008). However, unlike vancomycin and other glycopeptides, oritavancin exerts additional activity through cooperative interactions derived from dimerization and membrane anchoring, including disruption of membrane potential and partial inhibition of RNA synthesis (Allen and Nicas 2003; McKay et al. 2006; Arhin et al. 2007). These additional modes of killing may provide for the observed increased activity of oritavancin against such important drug-resistant pathogens such as vancomycin-intermediate and –resistant *S. aureus* (VISA and VRSA) and vancomycin-resistant enterococci (VRE).

The purpose of this study was to document the *in vitro* activity of oritavancin and comparable antimicrobial agents in a surveillance of hospital-acquired *Enterococcus faecalis* and *E. faecium* clinical pathogens, including vancomycin-resistant and linezolid non-susceptible isolates, and of clinically-important streptococci and staphylococci including MRSA, from a multicenter population within the United States and Korea.

Methods

- Fresh clinical isolates were derived from blood or skin and skin structure defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between December 2007 – January 2009 from 19 investigative sites from the United States and 14 sites in South Korea. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism transport, confirmation of organism identification, storage and development and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI broth microdilution testing method M7-A7 (CLSI 2006) using Research Use Only (RUO) custom Sensititre® panels (TREK Diagnostics Systems, Cleveland, OH). MIC interpretive criteria followed CLSI M100-S18 guidelines (CLSI 2008) where available.
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. faecalis* ATCC 29212, *E. faecalis* ATCC 51299, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619.
- Percent susceptibilities for each species with at least 10 isolates were compared between South Korea and the United States to determine if the data from both countries could be combined or should be analyzed separately. Statistical significance was determined used Fisher's Exact Test, and species showing at most one drug with a P value <0.05 were deemed sufficiently similar to be grouped together in the tables shown in the Results section; species showing two or more drugs with P values <0.05 were summarized by country.

Results - 1

At least 10 isolates were collected for 10 of the 27 species encountered in this study therefore only those 10 species were included in Tables 1-6. Examination of regional differences in antibiotic susceptibility for the tested drugs revealed that 6 of those 10 species (*E. faecalis, S. capitis, S. epidermidis, S. agalactiae, S. mitis,* and *S. pyogenes*) had no significant (P<0.05) difference in %susceptibility for any antibiotic or had a significant difference for only 1 antibiotic and so the US and Korean isolates of these 6 species were combined in Tables 2, 5 and 6. The other 4 species/oxacillin susceptibility phenotypes (*E. faecium*, MRSA, MSSA, and *S. pneumoniae*) each had significant (P<0.05) regional differences for at least 4 drugs and so are shown by country in Tables 1, 3 and 4.

Table 1. Activity of oritavancin and comparators against *E. faecium*, by country

Organism/Country/N	Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S	%I	%R	MIC_{Min} (mg/L)	MIC_{Max} (mg/L)
E. faecium/Korea/184	Oritavancin	0.008*	0.03	NA[1]	NA	NA	0.002	0.25
	Ampicillin	128	> 128	8.2	0.0	91.9	0.5	> 128
	Daptomycin	2	4	100	0.0	0.0	0.12	4
	Gentamicin 500	> 500	> 500	NA	NA	NA	<= 500	> 500
	Levofloxacin	> 4	> 4	4.4	1.6	94.0	0.25	> 4
	Linezolid**	2	2	95.7	4.4	0.0	0.5	4
	Quinupristin Dalfopristin	1	4	78.8	9.2	12.0	0.5	16
	Streptomycin 1000	<= 1000	> 1000	NA	NA	NA	<= 1000	> 1000
	Teicoplanin	0.5	> 32	75.0	4.9	20.1	<= 0.03	> 32
	Tetracycline	0.5	64	72.8	1.6	25.5	<= 0.12	> 64
	Vancomycin	1	> 128	73.4	0.0	26.6	0.5	> 128
E. faecium/USA/205	Oritavancin	0.06	0.12	NA	NA	NA	0.0	0.25
	Ampicillin	> 128	> 128	9.8	0	90.2	0.5	> 128
	Daptomycin	2	4	98.5	0.0	1.5	0.1	> 8
	Gentamicin 500	<= 500	> 500	NA	NA	NA	<= 500	> 500
	Levofloxacin	> 4	> 4	6.3	4.7	89.3	<= 0.03	> 4
	Linezolid	2	4	85.9	13.7	0.5	<= 0.12	> 32
	Quinupristin Dalfopristin	1	2	71.7	18.5	9.8	<= 0.12	32.0
	Streptomycin 1000	<= 1000	> 1000	NA	NA	NA	<= 1000	> 1000
	Teicoplanin	> 32	> 32	22.9	0.5	76.6	0.1	> 32
	Tetracycline	16	> 64	46.3	1.5	52.2	<= 0.12	> 64
	Vancomycin	> 128	> 128	20.0	0.0	80.0	0.5	> 128

*Green highlighting denotes lowest MIC50/90 values.
** Yellow highlighting denotes drugs with significantly different (P<0.05) %S between countries.
1No breakpoints established.

Table 2. Activity of oritavancin and comparators against *E. faecalis*: combined US and Korean data.

Organism/N	Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S	%I	%R	MIC_{Min} (mg/L)	MIC_{Max} (mg/L)
E. faecalis/455	Oritavancin	0.03*	0.12	NA[1]	NA	NA	0.004	0.25
	Ampicillin	1	2	98.7	0.0	1.3	<= 0.25	> 128
	Daptomycin	1	2	100	0.0	0.0	0.03	4
	Gentamicin 500	<= 500	> 500	NA	NA	NA	<= 500	> 500
	Levofloxacin	2	> 4	63.5	0.9	35.6	0.25	> 4
	Linezolid	2	2	96.9	3.1	0.0	0.25	4
	Quinupristin Dalfopristin	16	32	0.9	2.6	96.5	1	> 32
	Streptomycin 1000	<= 1000	> 1000	NA	NA	NA	<= 1000	> 1000
	Teicoplanin	0.25	0.5	96.3	0.4	3.3	0.06	> 32
	Tetracycline	32	64	23.1	0.4	76.5	<= 0.12	> 64
	Vancomycin	2	4	96.0	0.4	3.5	0.25	> 128

*Green highlighting denotes lowest $MIC_{50/90}$ values.
1No breakpoints established.

Table 3. Activity of oritavancin and comparators against methicillin-resistant *S. aureus* (MRSA), by country.

Organism/Country/N	Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S	%I	%R	MIC_{Min} (mg/L)	MIC_{Max} (mg/L)
MRSA/Korea/293	Oritavancin	0.12*	0.25	NA	NA	NA	0.015	0.5
	Clindamycin**	> 2	> 2	21.5	0.0	78.5	0.06	> 2
	Daptomycin	0.5	1	100	0.0	0.0	0.25	1
	Erythromycin	> 4	> 4	8.9	1.7	89.4	0.25	> 4
	Levofloxacin	> 4	> 4	20.8	0.7	78.5	<= 0.03	> 4
	Linezolid	2	2	100	0.0	0.0	0.5	4
	Teicoplanin	1	4	100	0.0	0.0	0.25	8
	Tetracycline	> 32	> 32	22.9	1.0	76.1	0.12	> 32
	Trimethoprim/Sulfa	<= 0.25	> 4	83.6	0.0	16.4	<= 0.25	> 4
	Vancomycin	1	2	100	0.0	0.0	0.5	2
MRSA/USA/368	Oritavancin	0.06	0.25	NA	NA	NA	0.002	1
	Clindamycin	0.12	> 2	70.4	1.4	28.3	0.06	> 2
	Daptomycin	0.5	1	100	0.0	0.0	0.12	1
	Erythromycin	> 4	> 4	5.7	1.1	93.2	0.25	> 4
	Levofloxacin	> 4	> 4	32.9	0.3	66.9	0.12	> 4
	Linezolid	2	4	100	0.0	0.0	0.5	4
	Teicoplanin	0.5	1	99.7	0.0	0.3	<= 0.06	32
	Tetracycline	0.5	2	94.0	0.8	5.2	0.12	> 32
	Trimethoprim/Sulfa	<= 0.25	<= 0.25	96.7	0.0	3.3	<= 0.25	> 4
	Vancomycin	1	1	99.7	0.3	0.0	0.5	8

*Green highlighting denotes lowest $MIC_{50/90}$ values.
** Yellow highlighting denotes drugs with significantly different (P<0.05) %S between countries.
1No breakpoints established.

Table 4. Activity of oritavancin and comparators against methicillin-susceptible *S. aureus* (MSSA), by country.

Organism/Country/N	Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S	%I	%R	MIC_{Min} (mg/L)	MIC_{Max} (mg/L)
MSSA/Korea/339	Oritavancin	0.06*	0.25	NA[1]	NA	NA	0.008	0.5
	Clindamycin**	0.12	0.25	97.6	0.3	2.1	<= 0.03	> 2
	Daptomycin	0.5	0.5	100	0.0	0.0	0.12	1
	Erythromycin	0.5	> 4	76.7	4.7	18.6	0.12	> 4
	Levofloxacin	0.25	0.5	96.5	0.6	3.0	0.12	> 4
	Linezolid	2	2	100	0.0	0.0	0.5	4
	Teicoplanin	0.5	1	100	0.0	0.0	0.12	8
	Tetracycline	8	16	88.2	0.9	10.9	0.12	> 32
	Trimethoprim/Sulfa	<= 0.25	<= 0.25	99.7	0.0	0.3	<= 0.25	4
	Vancomycin	1	1	100	0.0	0.0	0.5	2
MSSA/USA/438	Oritavancin	0.06	0.25	NA	NA	NA	0.008	1
	Clindamycin	0.12	0.5	90.4	1.6	8.0	<= 0.03	> 2
	Daptomycin	0.5	1	100	0.0	0.0	0.12	1
	Erythromycin	1	> 4	48.9	9.1	42.0	0.12	> 4
	Levofloxacin	0.25	> 4	81.3	1.8	16.9	0.06	> 4
	Linezolid	2	4	100	0.0	0.0	1	4
	Teicoplanin	0.5	1	100	0.0	0.0	0.25	8
	Tetracycline	0.5	2	89.4	1.1	5.5	0.12	> 32
	Trimethoprim Sulfa	<= 0.25	<= 0.25	97.0	0.0	3.0	<= 0.25	> 4
	Vancomycin	1	1	100	0.0	0.0	0.5	2

*Green highlighting denotes lowest $MIC_{50/90}$ values.
** Yellow highlighting denotes drugs with significantly different (P<0.05) %S between countries.
1No breakpoints established.

Results - 2

Table 5. Activity of oritavancin and comparators against *S. epidermidis* and *S. capitis*, combined US and Korea data.

Organism/N	Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S	%I	%R	MIC_{Min} (mg/L)	MIC_{Max} (mg/L)
S. epidermidis/84	Oritavancin	0.06*	0.12	NA[1]	NA	NA	0.015	0.25
	Clindamycin	> 2	> 2	44.1	1.2	54.8	0.06	> 2
	Daptomycin	0.5	1	100	0.0	0.0	0.25	1
	Erythromycin	> 4	> 4	26.2	2.4	71.4	0.12	> 4
	Levofloxacin	> 4	> 4	29.8	1.2	69.1	0.12	> 4
	Linezolid	1	2	100	0.0	0.0	<= 0.25	4
	Oxacillin	> 4	> 4	8.3	0.0	91.7	0.12	> 4
	Teicoplanin	4	8	95.2	4.8	0.0	0.25	16
	Tetracycline	1	> 32	78.6	2.4	19.1	0.12	> 32
	Trimethoprim Sulfa	1	> 4	56.0	0.0	44.1	<= 0.25	> 4
	Vancomycin	2	2	100	0.0	0.0	0.5	4
S. capitis/27	Oritavancin	0.015	0.06	NA	NA	NA	0.004	0.25
	Clindamycin	0.12	> 2	51.9	0.0	48.2	0.06	> 2
	Daptomycin	1	1	100	0.0	0.0	0.06	1
	Erythromycin	> 4	> 4	48.2	0.0	51.9	0.12	> 4
	Levofloxacin	0.5	> 4	55.6	3.7	40.7	0.25	> 4
	Linezolid	1	2	100	0.0	0.0	<= 0.25	2
	Oxacillin	4	> 4	44.4	0.0	55.6	<= 0.06	> 4
	Teicoplanin	0.25	1	100	0.0	0.0	0.12	8
	Tetracycline	0.5	0.5	96.3	0.0	3.7	0.25	> 32
	Trimethoprim Sulfa	<= 0.25	4	88.9	0.0	11.1	<= 0.25	> 4
	Vancomycin	1	2	100	0.0	0.0	0.5	2

*Green highlighting denotes lowest $MIC_{50/90}$ values.
1No breakpoints established.

Table 6. Activity of oritavancin and comparators against *S. agalactiae, S. mitis,* and *S. pyogenes*, combined US and Korea data.

Organism/N	Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S	%I	%R	MIC_{Min} (mg/L)	MIC_{Max} (mg/L)
S. agalactiae/121	Oritavancin	0.06*	0.12	NA[1]	NA	NA	0.004	1
	Clindamycin	0.06	> 1	65.3	0.0	34.7	<= 0.015	> 1
	Daptomycin	0.25	0.5	100	0.0	0.0	<= 0.03	1
	Erythromycin	0.06	> 2	55.4	0.0	44.6	<= 0.015	> 2
	Levofloxacin	1	1	99.2	0.8	0.0	0.25	4
	Linezolid	1	2	100	0.0	0.0	0.5	2
	Penicillin	0.06	0.12	100	0.0	0.0	<= 0.015	0.12
	Teicoplanin	0.06	0.12	NA	NA	NA	<= 0.03	0.5
	Tetracycline	32	> 32	17.4	0.8	81.8	0.25	> 32
	Trimethoprim Sulfa	0.12	0.25	NA	NA	NA	<= 0.06	1
	Vancomycin	0.5	1	100	0.0	0.0	<= 0.06	1
S. mitis/33	Oritavancin	0.015	0.06	NA	NA	NA	0.002	0.12
	Clindamycin	0.03	> 1	81.8	0.0	18.2	<= 0.015	> 1
	Daptomycin	0.5	1	100	0.0	0.0	<= 0.03	1
	Erythromycin	2	> 2	27.3	0.0	72.7	<= 0.015	> 2
	Levofloxacin	1	2	93.9	0.0	6.1	0.12	> 4
	Linezolid	1	2	100	0.0	0.0	<= 0.25	2
	Penicillin	0.25	1	45.5	54.6	0.0	<= 0.015	2
	Teicoplanin	0.06	0.12	NA	NA	NA	<= 0.03	0.12
	Tetracycline	1	> 32	54.6	0.0	45.5	0.25	> 32
	Trimethoprim Sulfa	0.12	> 4	NA	NA	NA	<= 0.06	> 4
	Vancomycin	0.5	1	100	0.0	0.0	<= 0.06	1
S. pyogenes/114	Oritavancin	0.03	0.25	NA	NA	NA	<= 0.0005	1
	Clindamycin	0.06	0.12	95.6	0.0	4.4	<= 0.015	> 1
	Daptomycin	0.06	0.25	100	0.0	0.0	<= 0.03	0.5
	Erythromycin	0.06	2	88.6	0.9	10.5	<= 0.015	> 2
	Levofloxacin	0.5	1	100	0.0	0.0	<= 0.03	2
	Linezolid	1	2	100	0.0	0.0	<= 0.25	2
	Penicillin	<= 0.015	0.03	100	0.0	0.0	<= 0.015	0.12
	Teicoplanin	<= 0.03	0.06	NA	NA	NA	<= 0.03	0.5
	Tetracycline	0.5	32	81.6	0.0	18.4	<= 0.06	> 32
	Trimethoprim Sulfa	0.25	> 4	NA	NA	NA	<= 0.06	> 4
	Vancomycin	0.5	0.5	100	0.0	0.0	<= 0.06	1

*Green highlighting denotes lowest $MIC_{50/90}$ values.
1No breakpoints established.

Table 7. Oritavancin MIC_{90} values for various resistance phenotypes; yellow-highlighting denotes ≥2 doubling dilutions difference between susceptible and non-susceptible groups.

	MIC_{90} (mg/L)																			
	Van*-NS	Van-S	Dap-NS	Dap-S	Tei-NS	Tei- S	Lzd-NS	Lzd-S	GmS-R	GmS-S	StS-R	StS-S	Ox-R	Ox-S	Pen-NS	Pen-S
E. faecalis	0.25 N=18	0.12 N=437	-	0.12 N=455	0.25 N=17	0.12 N=438	0.25 N=14	0.12 N=441	0.25 N=180	0.12 N=275	0.12 N=103	0.12 N=352	-	-	-	-
E. faecium	0.12 N=213	0.015 N=176	0.06 N=3	0.12 N=386	0.12 N=204	0.015 N=185	0.12 N=37	0.12 N=352	0.06 N=180	0.12 N=209	0.25 N=130	0.06 N=256	-	-	-	-
S. aureus	-	-	-	-	-	-	-	-	-	-	-	-	0.25 N=66 1	0.25 N=77 7	-	-
S. pneumoniae	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.015 N=54	0.008 N=62

*Van=vancomycin; Dap=daptomycin; Tei=teicoplanin; Lzd=linezolid; GmS=gentamicin synergy screen; StS=streptomycin synergy screen; Ox=oxacillin; Pen=penicillin; NS=non-susceptible; S=susceptible.

Conclusions

- Oritavancin had the lowest MIC_{50} and lowest MIC_{90} against all of the gram-positive species studied, except for *S. pyogenes*
- Against *S. pyogenes*, penicillin and teicoplanin had lower MIC_{50} and MIC_{90} values and daptomycin was equipotent to oritavancin.
- The highest oritavancin MIC recorded in this study was 1 mg/L, which was seen with 2/661 (0.3%) MRSA, 1/777 (0.1%) MSSA, 1/121 (0.8%) *S. agalactiae*, and 1/114 (0.9%) *S. pyogenes*.
- Although oritavancin's activity against most of the organisms studied was largely unchanged by the presence of various resistance mechanisms, oritavancin MIC_{90} values against *E. faecalis* were one doubling dilution higher for isolates non-susceptible to vancomycin, teicoplanin, or linezolid relative to their susceptible counterparts. Vancomycin- or teicoplanin-non-susceptible *E. faecium*, on the other hand, were 3 doubling dilutions less susceptible (by MIC_{90}) to oritavancin relative to glycopeptide-susceptible *E. faecium*, although this increased MIC_{90} value was still low (0.12 mg/L).
- Notable, significant (P<0.05) regional differences in susceptibilities:
  - US isolates of *E. faecium* were less susceptible than Korean strains to teicoplanin, vancomycin, and linezolid;
  - US isolates of MRSA were more susceptible than Korean strains to TMP/SMX, tetracycline, levofloxacin and clindamycin, which may reflect a different incidence of CA-MRSA in the US.
- Oritavancin shows promise as an antimicrobial agent that could be used to treat serious infections caused by gram-positive bacteria, especially those resistant to other commonly-used agents.

References

Kim SJ, Cegelski L, Stueber D, Singh M, Dietrich E, Tanaka KS, Parr TR Jr, Far AR, Schaefer J. 2008. J Mol Biol. 377(1):281-293.

McKay GA, Fadhil I, Beaulieu S, Ciblat S, Rafai Far A, Moeck G, Parr TR Jr. 2006. Poster C1-682. 46th ICAAC, San Francisco, CA, September 27-30, 2006.

Allen NE. and TI Nicas. 2003. FEMS Microbiol Rev, 2003. 26(5): p. 511-32.

Arhin, F.F., et al. 2007. 47th ICAAC; Sept 17 - 20. Chicago, IL. Poster C1-1471.

CLSI, 2008. Performance Standards for Antimicrobial Susceptibility Testing; Eighteenth Informational Supplement, document M100-S18. Clinical and Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.

CLSI, 2007. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition, document M7-A7. Clinical and Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.

This study was sponsored by a grant from Targanta Therapeutics, which is now owned by The Medicines Company. We gratefully acknowledge the contributions of all investigators, laboratory personnel, and the members of the ORION Surveillance Study group.