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MICROBIOLOGIC ANALYSES OF TARGET PATHOGENS IDENTIFIED IN THE DALBAVANCIN DISCOVER PROGRAM

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ABSTRACT

Background: Dalbavancin a lipoglycopeptide antibiotic with potent in vitro activity against Gram-positive pathogens is in development for the treatment of acute bacterial skin and skin structure infections (ABSSSI). The DISCOVER program comprised two global phase 3 trials comparing dalbavancin alone to vancomycin with an option to switch to oral linezolid.

Methods: Gram-positive pathogens including *Staphylococcus aureus* and streptococcal spp. isolated at baseline in the two DISCOVER studies were tested in a central laboratory in vitro for susceptibility to a panel of antibiotics and underwent polymerase chain reaction (PCR) testing for mecA and the Panton-Valentine Leukocidin (PVL) toxin.

Results:

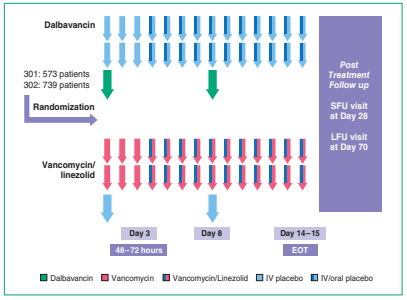
	S. aureus					
	All	MRSA	MSSA	*S. pyogenes*	*S. agalactiae*	*S. constellatus*
Number of Pathogens	511	135	361	77	20	25
MIC Range	0.008–0.25	0.015–0.25	0.015–0.25	0.002–0.25	<0.001–0.06	<0.001–0.06
MIC_{50}	0.06	0.06	0.06	0.015	0.015	0.008
MIC_{90}	0.06	0.06	0.06	0.06	0.03	0.015

No Gram-positive organism identified after treatment with either dalbavancin or vancomycin/linezolid was found to have a >2× increase in in vitro susceptibility relative to baseline. 357 of the 639 (56%) *Staphylococcus aureus* isolates recovered at baseline from 572 patients were positive for the PVL toxin.

Conclusion: Consistent with ongoing surveillance studies, in the DISCOVER registration studies the MIC_{90} of dalbavancin for *S. aureus* (whether MRSA or MSSA) was <0.06 mg/ml; the MIC_{90} for target streptococci was <0.06 mg/ml. These data confirm the potent activity of dalbavancin against key Gram-positive pathogens in ABSSSIs.

STUDY DESIGN

Figure 1. DISCOVER Study Design



METHODS

- Both DISCOVER trials were double-blind, double dummy, randomized trials in which patients with ABSSSI and either a fever, an elevated white blood cell count or immature neutrophils >10% were randomized to receive dalbavancin on Days 1 and 8 or IV Vancomycin for at least three days with an option to switch to oral linezolid to complete 10–14 days of therapy.
- Gram-positive pathogens including *Staphylococcus aureus* and streptococcal spp. isolated at baseline in the two DISCOVER studies were tested in a central laboratory *in vitro* for susceptibility to a panel of antibiotics and underwent polymerase chain reaction (PCR) testing for *mecA* and the Panton-Valentine Leukocidin (PVL) toxin.
- 7 Phase 2/3 studies including a total of 3002 patients have been completed with dalbavancin in treatment of CRBSI, ABSSSI, CSSSI, and USSSI.
- Methods for specimen collection were generally similar throughout the dalbavancin development program and investigator response was defined similarly in each study. Organisms were characterized at a central laboratory in all studies.

Table 1. Distribution of Key Pathogens – DISCOVER Program (Micro-ITT Population)

	Dalbavancin (N=337)	Vancomycin/Linezolid (N=329)
Staphylococcus aureus, N (%)	254 (75.4)	253 (76.9)
MRSA	90 (26.7)	67 (20.4)
MSSA	164 (48.7)	186 (56.5)
Streptococcus pyogenes	36 (10.7)	36 (10.9)
Streptococcus anginosus gp	21 (6.2)	24 (7.3)
Streptococcus agalactiae	8 (2.4)	13 (4.0)
Streptococcus Group C	5 (1.5)	4 (1.2)
Streptococcus viridans	7 (2.1)	5 (1.5)

RESULTS

Table 2. Key Target Pathogens – DISCOVER Program

Baseline Pathogen	Statistic	Dalbavancin	Vancomycin	Linezolid
Gram-positive organisms (aerobes)				
Staphylococcus aureus	N	511	511	511
	Range	0.008–0.25	≤0.25–1	1–4
	MIC_{50}	0.06	0.5	2
	MIC_{90}	0.06	1	2
MRSA	N	150	150	150
	Range	0.008–0.25	0.5–1	1–2
	MIC_{50}	0.06	0.5	2
	MIC_{90}	0.06	1	2
MSSA	N	361	361	361
	Range	0.015–0.25	≤0.25–1	1–4
	MIC_{50}	0.06	0.5	2
	MIC_{90}	0.06	1	2
Streptococcus pyogenes	N	77	77	77
	Range	0.002–0.25	0.25–0.5	≤0.25–1
	MIC_{50}	0.015	0.25	0.5
	MIC_{90}	0.06	0.25	1
Streptococcus anginosus group	N	49	49	49
	Range	≤0.001–0.12	≤0.015–1	≤0.25–1
	MIC_{50}	0.008	0.5	1
	MIC_{90}	0.015	1	1
Streptococcus agalactiae	N	26	26	26
	Range	≤0.001–0.06	≤0.015–1	≤0.25–1
	MIC_{50}	0.015	0.5	1
	MIC_{90}	0.03	0.5	1

Table 3. mecA and PVL Toxin by Region – DISCOVER Program

	Dalbavancin				Vancomycin/Linezolid			
	mecA gene		PVL toxin		mecA gene		PVL toxin	
Region	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
North America								
MRSA	87	0	85	2	73	0	68	5
MSSA	2	51	19 (14%)	34	6	68	26	48
Europe/ROW								
MRSA	8	0	1	7	3	0	1	2
MSSA	0	154	47 (29%)	107	0	169	50	119

- The MRSA rate was higher in the US
  - US=160/287 (55.7%); EU=11/323=3.4%
- The proportion of *S. aureus* that carried the PVL toxin was higher in Europe/ROW
  - US=14%; EU/ROW=29%
- 7 patients presented with a MSSA isolate that was mecA positive and all isolates had a MIC less than or equal to 0.06

Table 4. Comparative Distribution of Key Pathogens Across Skin and Soft Tissue (SSSI) Studies

	ABSSSI Studies			SSSI Studies				
	DUR001-301	DUR001-302	VER001-9 Subset	VER001-9 (cSSSI)	VER001-8 (uSSSI)	VER001-16 (uSSSI or cSSSI)	VER001-5 (cSSSI) Single and Two-Dose Regimens	Total
Microbiologically Evaluable, N, (%)	N=130	N=190	N=88	N=301	N=173	N=60	N=25	N=967
S. aureus (all)	103 (79.2)	119 (62.6)	64 (72.7)	250 (83.1)	121 (70)	54 (90)	20 (80.0)	**731 (75.6)**
MRSA	35 (26.9)	43 (22.6)	35 (39.8)	146 (48.5)	0 (0)	42 (70)	11 (44.0)	**312 (32.3)**
S. pyogenes	11 (8.5)	23 (12.1)	6 (6.8)	13 (4.3)	27 (16)	2 (3)	1 (4.0)	**83 (8.6)**
S. agalactiae	3 (2.3)	9 (4.7)	6 (6.8)	10 (3.3)	9 (5)	1 (2)	2 (8.0)	**40 (4.1)**
S. dysgalactiae/Group C	1 (0.8)	3 (1.6)	3 (3.4)	6 (2.0)	3 (2)	0 (0)	1 (4.0)	**17 (1.8)**
Streptococcus/Group G	0 (0)	0 (0)	3 (3.4)	7 (2.3)	6 (4)	1 (2)	1 (4.0)	**18 (1.9)**
S. anginosus group	6 (4.6)	15 (7.9)	0 (0)	2 (0.7)	1 (0.6)	0 (0)	0 (0)	**24 (2.5)**

CONCLUSIONS

- Consistent with ongoing surveillance studies, in the DISCOVER registration studies the MIC_{90} of dalbavancin for *S. aureus*, whether MRSA or MSSA, was <0.06 µg/ml; the MIC_{90} for target streptococci was <0.06 µg/ml.
- No Gram-positive organism identified after treatment with either dalbavancin or vancomycin/linezolid was found to have a >2× increase in MIC to either study drug relative to baseline.
- These data confirm the potent in vitro activity and excellent clinical efficacy of dalbavancin against key Gram-positive pathogens including MRSA (n=273), MSSA (n=396) and streptococci (n=151) causing ABSSSI.

Table 5. By Pathogen Microbiological Outcomes in Phase 3 SSSI Studies, Dalbavancin Arm

	ABSSSI Studies				SSSI Studies							
	DUR001-301 and DUR001 302		DUR001-301, DUR001-302 and VER001-9 Subset		VER001-9 (cSSSI)		VER001-8 (uSSSI)		VER001-16 (uSSSI or cSSSI)		Total	
Baseline Pathogen	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
ME at EOT (Day 14)												
S. aureus (All)	211/222	95.0	268/286	93.7	223/258	86.4	112/125	89.6	60/64	93.0	**606/669**	**90.6**
MRSA	77/78	98.7	108/113	95.6	127/144	88.2	Not ME	–	47/51	92.2	**251/273**	**91.9**
S. pyogenes	33/34	97.1	39/40	97.5	14/16	87.5	28/29	96.6	1/2	50	**76/81**	**93.8**
S. agalactiae	10/12	83.3	15/18	83.3	11/11	100	8/9	88.9	2/2	100	**31/34**	**91.2**
S. dysgalactiae/												
Group C	3/3	100	6/6	100	6/6	100	3/3	100	0/0	–	**12/12**	**100**
S. anginosus group viridans streptococci	21/21[b]	100	21/21[b]	100	1/2	50	1/1	100	0/0	–	**23/24**	**95.8**
ME at SFU/TOC[a] (Day 28)												
S. aureus (All)	205/210	97.6	261/272	96.0	221/250	88.4	110/129	90.9	50/54	92.6	**586/643**	**91.1**
MRSA	72/73	98.6	104/107	97.2	133/146	91.1	Not ME	–	38/42	90.5	**243/261**	**93.1**
S. pyogenes	31/32	96.9	36/37	97.3	11/13	84.6	26/27	96.3	1/2	50.0	**69/74**	**93.2**
S. agalactiae	10/12	83.3	16/18	88.9	10/10	100	8/9	88.9	1/1	100	**29/32**	**90.6**
S. dysgalactiae/												
Group C	3/3	100	6/6	100	6/6	100	3/3	100	0/0	–	**12/12**	**100**
S. anginosus group viridans streptococci	20/20	100	20/20	100	1/2	50	1/1	100	0/0	–	**22/23**	**95.7**

[a] SFU (Short-Term Follow-Up, DUR001-301 and DUR001-302); TOC (Test of Cure, VER001-9, VER001-8, VER001-16)
[b] Includes *S. anginosus* (6), *S. constellatus* (11), *S. intermedius* (4).

ME = Microbiologically Evaluable; n/N = Success/Total; ABSSSI = acute bacterial skin and skin structure infection; SSSI = skin and skin structure infection; Investigator's assessment of response.

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