GEOGRAPHIC DIFFERENCES IN THE PRESENTATION AND OUTCOMES OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) IN THE DISCOVER PROGRAM

Sailaja Puttagunta, MD[1], George H. Talbot, MD[2], Mark Wilcox, MD[3], Helen W. Boucher, MD[4] and Michael Dunne, MD[1]

[1]Durata Therapeutics, Inc., Branford, CT, USA; [2]Talbot Advisors LLC, Anna Maria, FL, USA; [3]Leeds Teaching Hospitals, Leeds, UK; [4]Tufts Medical Center, Boston, MA, USA

ABSTRACT

Objective: To evaluate for any differences in presentation and outcomes of ABSSSI based on geographic location.

Methods: Dalbavancin is a lipoglycopeptide antibiotic with activity against Gram-positive pathogens and a long half-life allowing weekly dosing. DISCOVER 1 and 2 were double-blind, double-dummy, pharmacist-unblinded randomized trials in which patients with ABSSSI were randomized to receive IV dalbavancin or Vancomycin with an option to switch to oral linezolid to complete 10–14 days of therapy. The primary endpoint was measured at 48–72 h of therapy with success requiring both cessation of spread of the lesion and complete resolution of fever. Secondary endpoints included clinical status at the end of therapy. We analyzed efficacy outcomes by geographic region on pooled data from these identically designed trials.

Results: A total of 1312 patients were enrolled in the two regions: 49 centers enrolled 473 patients in North America and 91 centers enrolled 839 patients in Europe/Asia (Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Lithuania, Romania, Russia, Serbia, Slovakia Ukraine, Israel, South Africa, South Korea and Taiwan).

Table 1. Infection Type and Frequently Isolated Pathogens Causing ABSSSI by Region

	North America n/N (%)	Europe/Asia n/N (%)	p value
Type of Infection			
Cellulitis	179/473 (37.8)	524/839 (62.5)	<0.001
Major Abscess	214/473 (45.2)	121/839 (14.4)	<0.001
Wound/surgical site infection	80/473 (16.9)	193/839 (23.0)	0.012
Pathogen			
Staphylococcus aureus	265/323 (82.0)	247/323 (76.5)	0.113
MSSA	115/265 (43.4)	240/247 (97.2)	<0.001
MRSA	150/265 (56.6)	7/247 (2.8)	<0.001
Streptococcus pyogenes	5/323 (1.6)	68/323 (21.1)	<0.001
Streptococcus anginosus group	38/323 (11.8)	9/323 (2.8)	<0.001

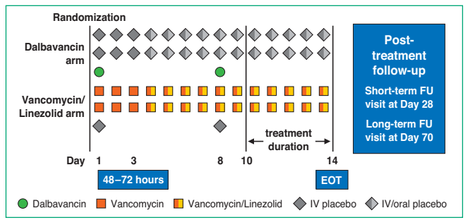
Table 2. Clinical Outcome by Region

	DISCOVER 1 and DISCOVER 2	
Region	Dalbavancin n/N (%)	Vancomycin/Linezolid n/N (%)
Clinical Responders at 48–72 h (ITT population)		
US/Canada	196/238 (82.4)	189/235 (80.4)
Europe/Asia	329/421 (78.1)	332/418 (79.4)
Clinical Status at EOT (Clinically evaluable population)		
US/Canada	175/193 (90.7)	169/185 (91.4)
Europe/Asia	342/377 (90.7)	333/360 (92.5)

Conclusion: Among ABSSSI patients enrolled in these studies, cellulitis was most common in Europe/Asia, versus major abscess in North America. *S. aureus* was the most common pathogen isolated in both regions, but the proportion of MRSA was higher in North America. *S. pyogenes* was more frequently isolated in Europe/Asia. Early response rates were slightly higher in North America, but clinical success rates at EOT were comparable in both regions. Outcomes were similar for patients treated with either dalbavancin or the comparator.

METHODS

Figure 1. Study Design: Studies DUR001-301/302



- Patients had:
  - cellulitis, abscess or wound infection with erythema >75 cm^2 and
  - either a fever, an elevated white blood cell count >12k cells/mm^3 or immature neutrophils >10%
- Patients received:
  - Dalbavancin 1 gram IV over 30 minutes on Day 1 and 500 mg IV on Day 8, or
  - Vancomycin 1 gram (or 15 mg/kg) IV every 12 hours (q12h) for at least three days with an option to switch to oral linezolid 600 mg q12h to complete 10–14 days of therapy
- The primary endpoint was measured at 48–72 hours of therapy with success requiring both cessation of spread of the lesion and complete resolution of fever.
  - Secondary endpoints included an investigator assessment of outcome at Day 14 and Day 28
  - Efficacy results from both trials were pooled
- Data was analyzed by geographic region.

RESULTS

Table 1. Demographics

Characteristic	North America N=473	Europe/Asia N=839	p value
Mean age (years)	44.0	52.8	<0.001
Male gender, n (%)	301 (63.6)	466 (55.5)	0.004
Race, n (%)			
White	391 (82.7)	780 (93.0)	<0.001
American Indian or Alaska Native	9 (1.9)	0 (0.0)	<0.001
Asian	7 (1.5)	53 (6.3)	<0.001
Black or African American	60 (12.7)	5 (0.6)	<0.001
Other	6 (1.3)	1 (0.1)	
Mean BMI (kg/m^2)	29.6	28.9	0.095
Creatinine clearance <30 mL/min, n/N (%)	2/454 (0.4)	31/825 (3.8)	<0.001
History of Diabetes Mellitus, n (%)	58 (12.3)	112 (13.3)	0.574
Elevated fasting glucose, n (%)	24 (5.1)	175 (20.9)	<0.001
History of intravenous drug use, n (%)	195 (41.2)	6 (0.7)	<0.001
Location of treatment, n (%)			
Inpatients*	33 (7.0)	808 (96.3)	<0.001
Outpatients	315 (66.6)	2 (0.2)	<0.001
Sub-type of infection, n (%)			
Cellulitis	179 (37.8)	52 (62.5)	<0.001
Major Abscess	214 (45.2)	121 (14.4)	<0.001
Wound/Surgical Site Infection	80 (16.9)	193 (23.0)	0.012
Met SIRS criteria, n (%)	175 (37.0)	493 (58.8)	<0.001
Baseline pathogen, n/N (%)			
Staphylococcus aureus	265/323 (82.0)	247/323 (76.5)	0.113
MSSA	115/265 (43.4)	240/247 (97.2)	<0.001
MRSA	150/265 (56.6)	7/247 (2.8)	<0.001
Streptococcus pyogenes	5/323 (1.6)	68/323 (21.1)	<0.001
Streptococcus anginosus group	38/323 (11.8)	9/323 (2.8)	<0.001

*Inpatients for all doses for at least the first 72 hrs

Table 2. Duration of Antibiotic Therapy (days)

Study Drug Therapy	North America	Europe/Asia	p value
IV Drug	2.9	4.9	<0.001
Oral Drug	7.0	5.4	<0.001
Total Drug	10.7	11.1	0.048

Table 3. Clinical Success by Region

	North America			Europe/Asia			
Timepoint	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)	All n/N (%)	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)	All n/N (%)	Difference for "All" category (95% CI)
Clinical response at 48–72 hours	196/238 (82.4)	189/235 (80.4)	385/473 (81.4)	329/421 (78.1)	332/418 (79.4)	661/839 (78.8)	2.6 (–2.0, 7.0)
≥20% reduction in lesion size at 48–72 hrs	215/238 (90.3)	210/235 (89.4)	425/473 (89.9)	369/421 (87.6)	365/418 (87.3)	734/839 (87.5)	2.4 (–1.3, 5.8)
Clinical Status at EOT	175/193 (90.7)	169/185 (91.4)	344/378 (91.0)	342/377 (90.7)	333/360 (92.5)	675/737 (91.6)	–0.6 (–4.4, 2.8)
Investigator assessment of Success at D14	184/192 (95.8)	177/183 (96.7)	361/375 (96.3)	363/377 (96.3)	350/360 (97.2)	713/737 (96.7)	–0.5 (–3.1, 1.7)
Investigator assessment of Success at D28	161/168 (95.8)	158/162 (97.5)	319/330 (96.7)	333/344 (96.8)	323/327 (98.8)	656/671 (97.8)	–1.1 (–3.8, 0.9)

DISCUSSION

- Patients enrolled in Europe/Asia, as compared to those enrolled in North America, were:
  - younger
  - more often White
  - presenting with cellulitis versus major abscess, and accordingly with evidence of SIRS and S.pyogenes as the baseline pathogen
  - less likely to have a history of intravenous drug use
- Virtually all patients treated entirely in the outpatient setting were enrolled in North America.
- The vast majority of patients enrolled in Europe/Asia were inpatients for the first 72 hours of treatment.
- Patients enrolled in North America had a shorter duration of intravenous antibiotic therapy.

CONCLUSIONS

- Baseline demographic and many other important characteristics differed significantly between patients enrolled in North America and those enrolled in Europe/Asia.
- Nevertheless, early response rates and clinical success rates at EOT were comparable in both regions.
- Outcomes were similar for patients treated with either dalbavancin or the comparator.

Presented at ECCMID 2014, May 10–13, 2014, Barcelona, Spain.
Research funding provided by Durata Therapeutics, Inc.