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Comparison of the microbiological efficacy of tedizolid and linezolid in acute bacterial skin and skin structure infections: pooled data from phase 3 clinical trials

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ABSTRACT

We evaluated the microbiological efficacy of tedizolid compared with that of linezolid against common and emerging pathogens using pooled data from 2 phase 3 trials (NCT01170221 and NCT01421511) in patients with acute bacterial skin and skin structure infections. Patients received tedizolid 200 mg once daily for 6 days ($n = 664$) or linezolid 600 mg twice daily for 10 days ($n = 669$). Favorable microbiological outcome in both treatment groups, defined as eradication or presumed eradication at the end of treatment and at the posttherapy evaluation, exceeded 85% for most pathogens, including methicillin-resistant *Staphylococcus aureus*. Favorable microbiological response was observed for staphylococci and streptococci at tedizolid minimal inhibitory concentration values ≤0.5 mg/L and 0.25 mg/L, respectively. The studies demonstrated positive microbiological outcomes against common pathogens with a 6-day, once-daily regimen of tedizolid phosphate in patients with acute bacterial skin and skin structure infections.

1. Introduction

Acute bacterial skin and skin structure infections (ABSSSIs) are an increasing cause of hospitalization and an indication for antibacterial therapy worldwide (Hersh et al., 2008; Taira et al., 2009). Gram-positive pathogens, including *Staphylococcus aureus,* β-hemolytic streptococci, and certain coagulase-negative staphylococcus (CoNS), are the most frequent causes of ABSSSI (May et al., 2009). Infections with methicillin-resistant *S. aureus* (MRSA), a prominent pathogen in the United States and other countries (Dukic et al., 2013; Jones et al., 2014; King et al., 2006; Moet et al., 2007; Talan et al. 2011), are associated with worse outcomes than infections with methicillin-susceptible *S. aureus* (MSSA) (Davis et al., 2007; Engemann et al., 2003; Labreche et al., 2013; Tattevin et al., 2012). A family of community-associated MRSA isolates, termed USA300, is associated with severe skin and soft tissue infections and has become the most prevalent MRSA clone in the United States (Carrel et al., 2015; Tenover and Goering, 2009). USA300 isolates commonly contain genes for Panton-Valentine leucocidin (PVL); the production of PVL by community-acquired strains of either MRSA or MSSA is strongly associated with skin infections (Shallcross and Hayward, 2013).

Tedizolid is the active moiety of the prodrug tedizolid phosphate, an oxazolidinone antibacterial approved for the treatment of ABSSSI by the United States Food and Drug Administration in June 2014 and by the European Medicines Agency in March 2015 (Sivextro [prescribing information], 2016; Sivextro [summary of product characteristics], 2016). Tedizolid exerts antibacterial activity by binding to the 50S subunit of the bacterial ribosome and inhibiting protein synthesis (Locke et al., 2009; Shaw et al., 2008), and it has potent in vitro activity against a wide range of Gram-positive pathogens, including resistant strains such as MRSA, vancomycin-resistant enterococci, and *cfr*-bearing linezolid-resistant strains (Brown and Traczewski, 2010; Locke et al., 2010a, 2010b; Schaadt et al., 2009; Thomson and Goering, 2013). Clinical Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC susceptibility breakpoints for tedizolid were not available at the time of these early in vitro studies, but based on currently accepted breakpoints, tedizolid

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MIC data were within the range of susceptibility (≤0.5 mg/L for *Staphylococcus* spp., *Streptococcus pyogenes*, and *Enterococcus faecalis* [CLSI only], and ≤0.25 mg/L for *Streptococcus anginosus* group) (CLSI, 2018; EUCAST, 2018). Based on in vitro MIC values, tedizolid is typically at least 4-fold more potent in vitro than linezolid against susceptible strains of staphylococci, streptococci, and enterococci, including methicillin- and vancomycin-resistant strains (Brown and Traczewski, 2010; Prokocimer et al., 2012; Schaadt et al., 2009; Shaw et al., 2008; Thomson and Goering, 2013); however, both tedizolid and linezolid MIC values in these early studies were within susceptibility breakpoints (tedizolid: ≤0.5 mg/L for *Staphylococcus* spp., *Streptococcus pyogenes*, and *Enterococcus faecalis* [CLSI only], and ≤0.25 mg/L for *Streptococcus anginosus* group; linezolid: ≤4 mg/L for *Staphylococcus* spp. and *Enterococcus faecalis* [EUCAST only] and ≤2 mg/L for *Streptococcus pyogenes*, *Enterococcus faecalis* [CLSI only], and *Streptococcus anginosus* group [CLSI only]) (CLSI, 2018; EUCAST, 2018). Two phase 3 clinical trials, ESTABLISH-1 and ESTABLISH-2, demonstrated the noninferiority of tedizolid 200 mg once daily for 6 days compared with that of linezolid 600 mg twice daily for 10 days for treating patients with ABSSSI (Moran et al., 2014; Prokocimer et al., 2013).

We used pooled data from the 2 phase 3 trials to evaluate the microbiological outcomes and in vitro activity of tedizolid compared with those of linezolid against common and emerging ABSSSI pathogens, focusing on clinically relevant subgroups.

2. Patients and methods

2.1. Ethics

Both studies are registered at ClinicalTrials.gov (NCT01170221 and NCT01421511) and were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and all relevant international, national, and local rules and legislation. The protocol was approved by the Copernicus Group Independent Review Board and by institutional review boards or ethics committees at each participating center; study design and a list of study sites and investigators have been reported (Moran et al., 2014; Prokocimer et al., 2013). Studies were performed and analyzed in accordance with 2013 United States Food and Drug Administration and European Medicines Agency guidelines for ABSSSI trials (European Medicines Agency, 2011; US Food and Drug Administration, 2013), and all participants provided written informed consent.

2.2. Study design

Briefly, ESTABLISH-1 and ESTABLISH-2 were randomized, double-blind, double-dummy, noninferiority, phase 3 trials conducted in North America (United States, Canada), Europe (Czech Republic, Germany, Hungary, Latvia, Poland, Russia, Slovakia, Spain, Ukraine), and other regions (Latin America [Argentina, Brazil, Peru], South Africa [ESTABLISH-2 only], Australia/New Zealand [ESTABLISH-2 only]). Patients were randomized 1:1 to receive tedizolid 200 mg once daily for 6 days or linezolid 600 mg twice daily for 10 days. Randomization was stratified by clinical syndrome (cellulitis/erysipelas, wound infection, or major cutaneous abscess) and geographic region.

ESTABLISH-1 patients received oral therapy exclusively, whereas ESTABLISH-2 patients received intravenous therapy for 24 h and could then be switched, at the investigator's discretion, to oral therapy when prespecified clinical improvement criteria were met. Patients were evaluated at screening/day 1; days 2, 3, and 5 (if applicable); end-of-therapy (EOT) visit; posttherapy evaluation (PTE; 7–14 days after treatment); and late-follow-up visit (18–25 days after treatment).

2.3. Study population

Key inclusion criteria were age ≥18 years (ESTABLISH-2, ≥12 years) and a diagnosis of ABSSSI (cellulitis/erysipelas, wound infection, and major cutaneous abscess) with a lesion surface area of at least 75 cm^2 caused by a suspected or documented Gram-positive pathogen (Moran et al., 2014; Prokocimer et al., 2013). In addition, wound infections and abscesses required erythema extending ≥5 cm from the edge of the wound or abscess to the lesion margin. At least 1 regional or systemic sign of infection (lymphadenopathy, fever ≥38°C, white blood cell count ≥10,000 cells/mm^3 or < 4000 cells/mm^3 or immature neutrophils >10%) was required. Patients were ineligible if they had uncomplicated ABSSSI; used systemic or topical antibiotics with Gram-positive activity within the preceding 96 h; or had an infection close to a prosthetic device, severe sepsis, or known bacteremia at the time of enrollment.

2.4. Microbiological sampling and susceptibility testing

Mandatory specimens of the primary ABSSSI site (aspirate, biopsy, deep swab) and blood cultures (venepuncture, 1 aerobic and 1 anaerobic from 2 different veins) were collected from each patient at the screening visit (baseline). Specimens for cellulitis were collected according to each site's standard practice. Postbaseline microbiological samples were collected only from patients with easily accessible lesions who experienced no improvement or who had lesions that deteriorated. Isolates from the primary ABSSSI site and from blood were Gram-stained and cultured at a designated local/regional laboratory and then sent to a central laboratory (Eurofins Medinet USA, Chantilly, VA) for confirmatory identification and susceptibility testing.

Susceptibility testing was performed with broth susceptibility microdilution panels (frozen and dry lyophilized; ThermoFisher Scientific, Cleveland, OH) in accordance with CLSI guidelines. CLSI-recommended quality control strains of *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619 were used at the recommended ranges (Clinical and Laboratory Standards Institute, 2013). Minimum inhibitory concentration (MIC) panels of 5% lysed horse blood were used for streptococci. The MIC required to inhibit the growth of 50% (MIC_{50}) or 90% (MIC_{90}) of isolates was calculated when there were ≥6 and ≥10 isolates, respectively, in the test group. Susceptibility results for *S. aureus* (MRSA and MSSA) were interpreted according to CLSI and EUCAST criteria (CLSI, 2015; EUCAST, 2015).

2.5. Molecular analysis of MRSA isolates

Clinical isolates of MRSA, as determined by oxacillin susceptibility, were analyzed for USA300 type and for the presence of PVL by pulsed-field gel electrophoresis (PFGE). Chromosomal DNA was isolated from the organisms, and PFGE analysis of *Sma*I chromosomal macrorestriction fragments was performed as described (Goering et al., 2011). Chromosomal banding patterns from agarose gels were imported into BioNumerics version 7.0 (Applied Maths, Sint-Martens-Latem, Belgium) and compared with known US and international MRSA strains. For each isolate, the presence of PVL factor and isolate strain was inferred from the PFGE pattern and confirmed at the central laboratory using a triplex real-time polymerase chain reaction assay (McDonald et al., 2005).

2.6. Microbiological outcomes

Microbiological outcomes were designed to fulfill requirements from either the United States Food and Drug Administration and the European Medicines Agency. Microbiological outcome categories at the EOT and PTE visits were *eradication* (absence of baseline pathogen), *presumed eradication* (no source specimen to culture in a patient assessed as experiencing clinical success at EOT or at PTE), *persistence* (continued presence of the original baseline pathogen), *presumed persistence* (no source specimen to culture in a patient assessed as experiencing clinical failure), and *indeterminate* (clinical response was indeterminate or another circumstance precluded a microbiological

evaluation). A favorable microbiological outcome at EOT and PTE was defined as eradication or presumed eradication.

2.7. Statistical analysis

Three analysis populations of interest were defined to evaluate microbiological outcomes and included the microbiological intent-to-treat (micro-ITT) population, microbiologically evaluable (ME) population at the EOT visit (ME-EOT), and the ME population at the PTE visit (ME-PTE). All populations were summarized descriptively based on favorable microbiological response, but no statistical comparisons were made between treatment groups. The micro-ITT population included all randomized patients with ≥1 Gram-positive pathogen isolated at baseline. The ME-EOT and ME-PTE populations consisted of patients in the micro-ITT population who were clinically evaluable and who completed EOT and PTE assessments, respectively, without a protocol violation that impacted the assessment of efficacy, as determined by blinded review by the Evaluability Review Team before database lock. Patients in the ME-EOT and ME-PTE sets completed assessments for early clinical response at the 48- to 72-h visit and programmatic (ME-EOT only) and investigator assessments of clinical response at EOT and PTE, respectively. By definition, sufficient information had to be available for ME population outcomes to be determined; thus, patients with indeterminate responses were excluded.

3. Results

3.1. Patients

The distribution of patients in the 3 analysis populations is shown in Fig. 1. Of 1333 patients randomized to tedizolid ($n = 664$) or linezolid ($n = 669$)—micro-ITT analysis set—a Gram-positive pathogen was isolated at baseline in 61.4% of patients (tedizolid, 406 [61.1%]; linezolid, 412 [61.6%]). No organism was isolated in 27.6% of patients (tedizolid, 184 [27.7%]; linezolid, 184 [27.5%]), though an adequate specimen was obtained from each; 1.5% of randomized patients (tedizolid, 12 [1.8%], linezolid, 8 [1.2%]) did not have an acceptable specimen for culture (i.e., superficial swabs). Of the 72.4% of patients with a baseline isolate, 9.5% (tedizolid, 62 [9.3%]; linezolid, 65 [9.7%]) did not have a Gram-positive pathogen.

Analysis of patients' ABSSSI type revealed Gram-positive pathogens from 35.5% (216/608) of those with cellulitis/erysipelas (tedizolid, 104/301 [34.6%]; linezolid, 112/307 [36.5%]), 82.1% (321/391) of those with an infected wound (tedizolid, 156/195 [80.0%]; linezolid 165/196 [84.2%]), and 85.3% (285/334) of those with a major cutaneous abscess (tedizolid, 148/168 [88.1%]; linezolid, 137/166 [82.5%]); >97% were aerobic Gram-positive pathogens. The ME-EOT and ME-PTE populations comprised 54.3% (tedizolid, 358 [53.9%]; linezolid, 366 [54.7%]) and 51.2% (tedizolid, 342 [51.5%]; linezolid, 340 [50.8%]) of randomized patients, respectively.

As has been reported in detail (Moran et al., 2014; Prokocimer et al., 2013; Shorr et al., 2015) baseline characteristics of the pooled population were comparable between treatment arms. Median age of patients (ITT population) was 44 years (tedizolid, 44.5 years; linezolid, 44.0 years); 63.9% were enrolled in North America (tedizolid, 64.2%; linezolid, 63.7%), 24.8% in Europe (tedizolid, 24.8%; linezolid, 24.8%), and 11.3% in other countries (tedizolid, 11.0%; linezolid, 11.5%). The main clinical syndrome was cellulitis/erysipelas (45.6% [tedizolid, 45.3%; linezolid, 45.9%]); 75.3% of patients had lesions on the upper or lower extremities (tedizolid, 74.7%; linezolid, 75.9%). The patient population included a substantial proportion of patients with comorbidities or risk factors such as obesity (32.4% [tedizolid, 30.1%; linezolid, 34.7%]), intravenous drug use (29.2% [tedizolid, 27.6%; linezolid, 30.8%]), hepatitis C (26.9% [tedizolid, 24.8%; linezolid, 29.0%]), and diabetes (9.4% [tedizolid, 8.7%; linezolid, 10.0%]).

3.2. Primary infection site pathogens

Table 1 summarizes the type and frequency of the main pathogens isolated from patients with ABSSSI, which were similar in both treatment arms. Regardless of ABSSSI type, *S. aureus* was the predominant (>80%) Gram-positive organism isolated at baseline in each treatment group; 35% of isolates were MRSA. Other pathogens identified in >5% of patients were *S. pyogenes* and organisms from the *S. anginosus* group (*S. anginosus, S. constellatus*, and *S. intermedius*); CoNS *S. haemolyticus* and *S. lugdunensis* were isolated at a frequency of 1% to 2%. Enterococci (*E. faecalis* and *E. faecium*) were isolated from 2.1% of patients. Most patients in the tedizolid and linezolid groups (87.4% and 87.9%, respectively) with a positive culture had monomicrobial Gram-positive infections, but 10.3% and 10.0%, respectively, had polymicrobial Gram-positive infections, 2.2% each had Gram-negative infections, and 2.2% each had mixed infections with both Gram-positive and Gram-negative organisms.

3.2.1. Subgroup analyses

The distribution of pathogens from the primary infection site by geographic region and clinical syndrome is shown in Table 1. MRSA was isolated less frequently from European patients, who made up 19.7% of the

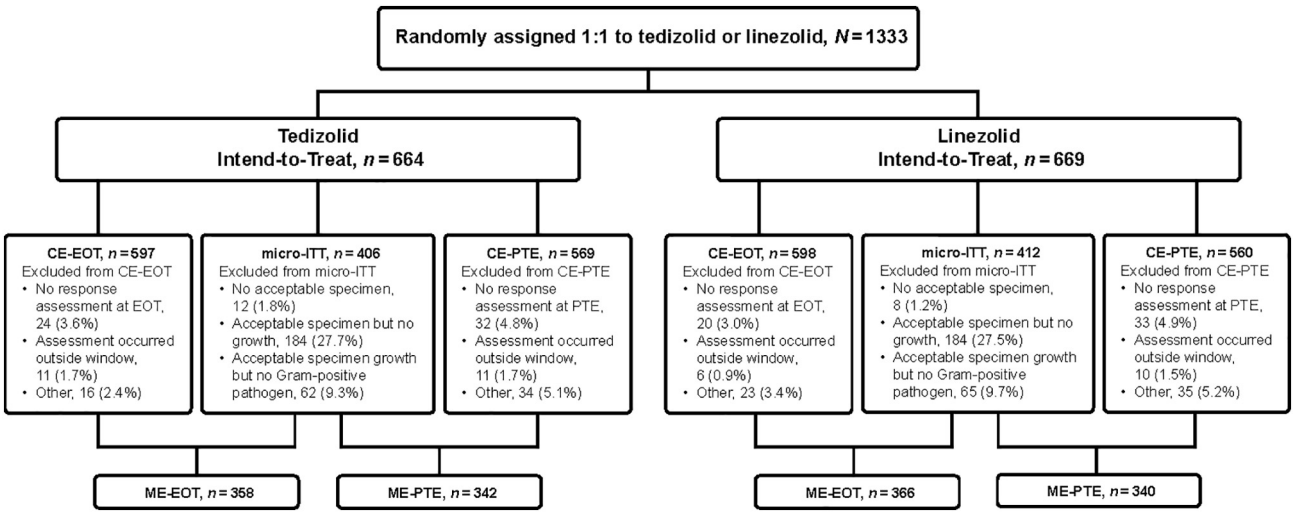

Fig. 1. Analysis populations for the microbiological analysis from pooled phase 3 studies. This figure shows the disposition of the 1333 patients randomly assigned 1:1 to tedizolid or linezolid and the distribution of the 3 analysis populations. CE = clinically evaluable; EOT = end of therapy; ME = microbiologically evaluable; micro-ITT = microbiological intent-to-treat; PTE = posttherapy evaluation.

Table 1
Analysis of baseline pathogens[a] overall and by subgroup (micro-ITT population).

Pathogen	All, *n* (%)		Geographic region						Clinical syndrome					
			North America, *n* (%)		Europe, *n* (%)		Other region, *n* (%)		Cellulitis, *n* (%)		Infected wound, *n* (%)		Major cutaneous abscess, *n* (%)	
	Tedizolid *n* = 406	Linezolid *n* = 412	Tedizolid *n* = 297	Linezolid *n* = 303	Tedizolid *n* = 77	Linezolid *n* = 84	Tedizolid *n* = 32	Linezolid *n* = 25	Tedizolid *n* = 105	Linezolid *n* = 112	Tedizolid *n* = 155	Linezolid *n* = 64	Tedizolid *n* = 146	Linezolid *n* = 136
Gram-positive aerobic organisms	398 (98.0)	401 (97.3)	291 (98.0)	295 (97.4)	75 (97.4)	83 (98.8)	32 (100)	23 (92.0)	103 (98.1)	110 (98.2)	151 (97.4)	160 (97.6)	144 (98.6)	131 (96.3)
Staphylococcus aureus	329 (81.0)	340 (82.5)	247 (83.2)	251 (82.8)	56 (72.7)	72 (85.7)	26 (81.3)	17 (68.0)	85 (81.0)	100 (89.3)	121 (78.1)	134 (81.7)	123 (84.2)	106 (77.9)
MRSA	141 (34.7)	145 (35.2)	138 (46.5)	140 (46.2)	0 (0.0)	3 (3.6)	3 (9.4)	2 (8.0)	32 (30.5)	37 (33.0)	46 (29.7)	43 (26.2)	63 (43.2)	65 (47.8)
MSSA	188 (46.3)	196 (47.6)	109 (36.7)	112 (37.0)	56 (72.7)	69 (82.1)	23 (71.9)	15 (60.0)	53 (50.5)	63 (56.3)	75 (48.4)	91 (55.5)	60 (41.1)	42 (30.9)
Streptococcus pyogenes	33 (8.1)	20 (4.9)	7 (2.4)	5 (1.7)	21 (27.3)	13 (15.5)	5 (15.6)	2 (8.0)	17 (16.2)	8 (7.1)	12 (7.7)	10 (6.1)	4 (2.7)	2 (1.5)
Streptococcus anginosus group	29 (7.1)	28 (6.8)	29 (9.8)	26 (8.6)	0 (0.0)	2 (2.4)	–	–	2 (1.9)	5 (4.5)	16 (10.3)	12 (7.3)	11 (7.5)	11 (8.1)
S. anginosus	5 (1.2)	3 (0.7)	5 (1.7)	3 (1.0)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	3 (2.1)	3 (2.2)
S. constellatus	14 (3.4)	10 (2.4)	14 (4.7)	9 (3.0)	0 (0.0)	1 (1.2)	–	–	0 (0.0)	4 (3.6)	9 (5.8)	4 (2.4)	5 (3.4)	2 (1.5)
S. intermedius	10 (2.5)	15 (3.6)	10 (3.4)	14 (4.6)	0 (0.0)	1 (1.2)	–	–	2 (1.9)	1 (0.9)	5 (3.2)	8 (4.9)	3 (2.1)	6 (4.4)
Enterococcus faecalis	10 (2.5)	4 (1.0)	5 (1.7)	1 (0.3)	2 (2.6)	2 (2.4)	3 (9.4)	1 (4.0)	3 (2.9)	3 (2.7)	3 (1.9)	1 (0.6)	4 (2.7)	0 (0.0)
E. faecium	1 (0.2)	2 (0.5)	1 (0.3)	1 (0.3)	0 (0.0)	1 (1.2)	–	–	0 (0.0)	1 (0.9)	1 (0.6)	1 (0.6)	–	–
Staphylococcus haemolyticus	5 (1.2)	8 (1.9)	1 (0.3)	1 (0.3)	4 (5.2)	3 (3.6)	0 (0.0)	4 (16.0)	4 (3.8)	1 (0.9)	1 (0.6)	4 (2.4)	0 (0.0)	3 (2.2)
Staphylococcus lugdunensis	4 (1.0)	7 (1.7)	3 (1.0)	6 (2.0)	0 (0.0)	0 (0.0)	1 (3.1)	1 (4.0)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	2 (1.4)	7 (5.1)
Streptococcus group C	3 (0.7)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.4)	0 (0.0)
Streptococcus group G	2 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
S. agalactiae	8 (2.0)	9 (2.2)	7 (2.4)	8 (2.6)	1 (1.3)	1 (1.2)	–	–	1 (1.0)	2 (1.8)	3 (1.9)	4 (2.4)	4 (2.7)	3 (2.2)
S. dysgalactiae	1(0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
S. mitis	2 (0.5)	7 (1.7)	2 (0.7)	7 (2.3)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	1 (0.9)	1 (0.6)	5 (3.0)	1 (0.7)	1 (0.7)
S. mutans	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)
S. oralis	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
S. salivarius	2 (0.5)	2 (0.5)	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.7)
S. sanguinis	4 (1.0)	2 (0.5)	4 (1.3)	2 (0.7)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	0 (0.0)	2 (1.3)	1 (0.6)	2 (1.4)	1 (0.7)
Viridans group streptococci	3 (0.7)	7 (1.7)	3 (1.0)	7 (2.3)	0 (0.0)	0 (0.0)	–	–	1 (1.0)	1 (0.9)	1 (0.6)	4 (2.4)	1 (0.7)	2 (1.5)
Mycobacterium fortuitum	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Gram-positive anaerobic organisms	10 (2.5)	13 (3.2)	9 (3.0)	11 (3.6)	1 (1.3)	1 (1.2)	0 (0.0)	1 (4.0)	1 (1.0)	2 (1.8)	5 (3.2)	5 (3.0)	4 (2.7)	6 (4.4)
Peptostreptococcus spp.	4 (1.0)	6 (1.5)	3 (1.0)	4 (1.3)	1 (1.3)	1 (1.2)	0 (0.0)	1 (4.0)	0 (0.0)	1 (0.9)	1 (0.6)	2 (1.2)	3 (2.1)	3 (2.2)
Actinomyces israelii	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
A. odontolyticus	1 (0.2)	2 (0.5)	1 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	–	–	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	2 (1.5)
Clostridium perfringens	4 (1.0)	2 (0.5)	4 (1.3)	2 (0.7)	–	–	–	–	1 (1.0)	0 (0.0)	2 (1.3)	1 (0.6)	1 (0.7)	1 (0.7)
Gram-negative aerobic organisms	9 (2.2)	7 (1.7)	6 (2.0)	5 (1.7)	2 (2.6)	2 (2.4)	1 (3.1)	0 (0.0)	1 (1.0)	0 (0.0)	7 (4.5)	6 (3.7)	1 (0.7)	1 (0.7)
Gram-negative anaerobic organisms	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.7)	–	–	–	–	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.6)	–	–
Positive blood culture	11 (2.7)	17 (4.1)	5 (1.7)	14 (4.6)	4(5.2)	2 (2.4)	–	–	3 (2.9)	7 (6.3)	5 (3.2)	6 (3.7)	3 (2.1)	4 (2.9)
Polymicrobial G+ infection	42 (10.3)	41 (10.0)	–	–	–	–	–	–	–	–	–	–	–	–
Mixed G+ and G– infection	9 (2.2)	9 (2.2)	–	–	–	–	–	–	–	–	–	–	–	–

micro-ITT = microbiological intent-to-treat; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.
[a] From the primary infection site.

pooled population, than from North American patients (3/161 [1.9%] vs. 278/600 [46.3%]), who made up 73.3% of the population. The prevalence of *S. pyogenes* was higher in European patients than in North American patients (34/161 [21.1%] vs. 12/600 [2.0%]). Of note, 7 patients from Europe had *S. haemolyticus* infections and 9 from North America had *S. lugdunensis* infections.

S. aureus was the predominant pathogen isolated from all ABSSSI types. The incidence of MRSA was highest in patients with major cutaneous abscesses (128/282 [45.4%]), and *S. anginosus* group organisms were more prevalent in patients with infected wounds (28/319 [8.8%]) and cutaneous abscesses (22/282 [7.8%]) than in those with cellulitis (7/217 [3.2%]). The key pathogens in patients with cellulitis were *S. aureus* (185/217 [85.3%]) and *S. pyogenes* (25/217 [11.5%]). *S. pyogenes* was also isolated from 22 of 319 patients with infected wounds (6.9%).

3.3. In vitro susceptibility of baseline pathogens

Table 2 shows the susceptibility of baseline pathogens to tedizolid and linezolid. All baseline isolates, including MRSA, had tedizolid MICs ≤0.5 mg/L, whereas linezolid MICs ranged from ≤0.06 to 2 mg/L; thus, all isolates for *Staphylococcus* spp., *S. pyogenes*, *S. anginosus* group, and *E. faecalis* were susceptible to tedizolid and linezolid as the range of MIC values for both antibiotics was below CLSI and EUCAST susceptibility breakpoints (CLSI, 2018; EUCAST, 2018). Based on MIC_{90} values, the in vitro potency of tedizolid was 4-fold higher than that of linezolid for all *S. aureus,* MSSA, *S. pyogenes*, and *S. anginosus* group isolates and 8-fold higher for MRSA. No geographic differences were observed in the activity of tedizolid and linezolid against target pathogens.

3.4. Microbiological response against pathogens

Microbiological response rates for pathogens were high with both tedizolid and linezolid at the EOT and PTE visits in both micro-ITT and ME analysis sets (Table 3, Table A.1 [see Appendix A]). In each treatment group, the microbiological response rate of *S. aureus* exceeded 88% at EOT and PTE in the micro-ITT analysis set and 95% in the ME analysis set. Response rates of MRSA were similarly high. In general, response rates for other key pathogens were similar between treatment groups at EOT and PTE, though the response rate of *S. anginosus* group pathogens in the micro-ITT analysis set was lower at both EOT and PTE with tedizolid (22/30 [73.3%]) than with linezolid (25/28 [89.3%]). Response rates, however, were similar between tedizolid and linezolid in the ME analysis set at both EOT (21/22 [95.5%] vs. 25/26 [96.2%]) and PTE (19/20 [95.0%] vs. 23/24 [95.8%]). Differences in favorable microbiological responses between micro-ITT and ME analysis sets were minimal: EOT, micro-ITT ≥96.9% (tedizolid) vs. ≥87.5% (linezolid), ME ≥96.8% vs. ≥87.5%; PTE, micro-ITT ≥95.5% vs. ≥94.7%, ME ≥100% vs. 94.4%. Most responses to tedizolid and linezolid were classified as favorable based on presumed eradication; cultures were performed in ≤5% of patients in both analysis groups at EOT and PTE.

Response rates were generally consistent across geographic regions and clinical syndromes (Table 3, Tables A.1–A.3 [see Appendix A]). In both treatment arms, the favorable response rate was slightly lower for MRSA than for MSSA across geographic regions and clinical syndromes at EOT and PTE.

3.5. Correlation of microbiological outcomes at PTE with MIC of tedizolid and linezolid for key pathogens

For tedizolid, a favorable microbiological response was observed at PTE in the ME population for staphylococci and streptococci at MIC values up to 0.5 mg/L and 0.25 mg/L, respectively (Table 4). For linezolid, favorable response was observed up to MIC values up to 4 mg/L and 1 mg/L, respectively. These findings for tedizolid and linezolid are consistent with 2018 CLSI and EUCAST susceptibility breakpoints (see Table 4 footnotes). Similar results were noted between positive clinical

Table 2
Activity of tedizolid and linezolid against baseline pathogens.[a]

Pathogen	Agent	No.	MIC range	MIC_{90}	MIC distribution (no. of isolates), mg/L							%S[b]
					≤0.06	0.12	0.25	0.5	1	2	4	
Staphylococcus aureus	Tedizolid	668	0.12–0.5	0.5	0	14	523	131	0	0	0	100
	Linezolid	668	1–4	2	0	0	0	0	78	551	39	100
MRSA	Tedizolid	285	0.12–0.5	0.25	0	13	254	18	0	0	0	100
	Linezolid	285	1–4	2	0	0	0	0	57	225	3	100
MSSA	Tedizolid	383	0.12–0.5	0.5	0	1	269	113	0	0	0	100
	Linezolid	383	1–4	2	0	0	0	0	21	326	36	100
Streptococcus pyogenes	Tedizolid	53	≤0.015–0.25	0.25	4	37	12	0	0	0	0	100
	Linezolid	53	0.5–1	1	0	0	0	35	18	0	0	100
S. anginosus group	Tedizolid	54	≤0.015–0.25	0.25	25	19	10	0	0	0	0	100
	Linezolid	54	≤0.06–1	1	4	11	11	12	16	0	0	100
S. anginosus	Tedizolid	7	0.12–0.25	NA	0	6	1	0	0	0	0	100
	Linezolid	7	0.25–1	NA	0	0	2	3	2	0	0	100
S. constellatus	Tedizolid	24	≤0.015–0.25	0.25	8	10	6	0	0	0	0	100
	Linezolid	24	≤0.06–1	1	2	2	3	7	10	0	0	100
S. intermedius	Tedizolid	23	≤0.015–0.25	0.25	17	3	3	0	0	0	0	100
	Linezolid	23	≤0.06–1	1	2	9	6	2	4	0	0	100
S. agalactiae	Tedizolid	16	0.12–0.25	NA	0	7	9	0	0	0	0	NA
	Linezolid	16	0.5–1	NA	0	0	0	7	9	0	0	NA
Enterococcus faecalis	Tedizolid	12	0.25–0.5	NA	0	0	8	4	0	0	0	100
	Linezolid	12	1–2	NA	0	0	0	0	3	9	0	100
Staphylococcus haemolyticus	Tedizolid	13	0.12–0.25	NA	0	6	7	0	0	0	0	NA
	Linezolid	13	0.5–1	NA	0	0	0	1	12	0	0	NA
Staphylococcus lugdunensis	Tedizolid	11	0.12–0.25	NA	0	6	5	0	0	0	0	100
	Linezolid	11	0.5–1	NA	0	0	0	4	7	0	0	100
Peptostreptococcus spp.	Tedizolid	11	≤0.3–0.25	NA	4	3	4	0	0	0	0	NA
	Linezolid	11	0.5–2	NA	0	0	0	2	7	2	0	NA

%S, percent susceptible; MIC_{90} = MIC required to inhibit the growth of 90% of isolates; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; NA = not available.

[a] From the primary infection site or blood cultures.

[b] Based on CLSI susceptibility breakpoints (tedizolid: ≤0.5 mg/L for *Staphylococcus* spp., *Streptococcus pyogenes*, and *Enterococcus faecalis*, and ≤0.25 mg/L for *Streptococcus anginosus* group; linezolid: ≤4 mg/L for *Staphylococcus* spp. and ≤ 2 mg/L for *Streptococcus pyogenes*, *Enterococcus faecalis*, and *Streptococcus anginosus* group) (CLSI, 2018). Isolates were also 100% susceptible based on EUCAST breakpoints (EUCAST, 2018).

Table 3
Favorable microbiological outcomes by pathogen[a] at EOT and PTE visits (micro-ITT and ME populations).

Pathogen	Visit	All patients (micro-ITT) *n*/*N*1 (%)		All patients (ME) *n*/*N*1 (%)		Clinical syndrome (micro-ITT), *n*/*N*1 (%)					
						Cellulitis		Infected wound		Major cutaneous abscess	
		Tedizolid	Linezolid	Tedizolid	Linezolid	Tedizolid	Linezolid	Tedizolid	Linezolid	Tedizolid	Linezolid
Staphylococcus aureus	EOT	299/329 (90.9)	310/342 (90.6)	280/293 (95.6)	300/306 (98.0)	76/85 (89.4)	92/101 (91.1)	113/121 (93.4)	121/134 (90.3)	110/123 (89.4)	97/107 (90.7)
	PTE	292/329 (88.8)	304/342 (88.9)	271/285 (95.1)	279/284 (98.2)	74/85 (87.1)	91/101 (90.1)	108/121 (89.3)	119/134 (88.8)	110/123 (89.4)	94/107 (87.9)
MRSA	EOT	121/141 (85.8)	124/146 (84.9)	112/121 (92.6)	121/125 (96.8)	27/32 (84.4)	30/37 (81.1)	42/46 (91.3)	37/44 (84.1)	52/63 (82.5)	57/65 (87.7)
	PTE	119/141 (84.4)	120/146 (82.2)	112/122 (91.8)	113/116 (97.4)	26/32 (81.3)	30/37 (81.1)	41/46 (89.1)	35/44 (79.5)	52/63 (82.5)	55/65 (84.6)
MSSA	EOT	178/188 (94.7)	188/198 (94.9)	168/172 (97.7)	181/183 (98.9)	49/53 (92.5)	62/64 (96.9)	71/75 (94.7)	85/91 (93.4)	58/60 (96.7)	41/43 (95.3)
	PTE	173/188 (92.0)	186/198 (93.9)	159/163 (97.5)	168/170 (98.8)	48/53 (90.6)	61/64 (95.3)	67/75 (89.3)	85/91 (93.4)	58/60 (96.7)	40/43 (93.0)
Streptococcus pyogenes	EOT	32/33 (97.0)	19/20 (95.0)	31/31 (100.0)	17/17 (100.0)	17/17 (100.0)	8/8 (100.0)	11/12 (91.7)	9/10 (90.0)	4/4 (100.0)	2/2 (100.0)
	PTE	30/33 (90.9)	19/20 (95.0)	28/30 (93.3)	18/18 (100.0)	16/17 (94.1)	8/8 (100.0)	10/12 (83.3)	9/10 (90.0)	4/4 (100.0)	2/2 (100.0)
S. agalactiae	EOT	8/9 (88.9)	8/10 (80.0)	8/9 (88.9)	8/9 (88.9)	1/2 (50.0)	3/3 (100.0)	3/3 (100.0)	4/4 (100.0)	4/4 (100.0)	1/3 (33.3)
	PTE	8/9 (88.9)	8/10 (80.0)	7/8 (87.5)	8/8 (100.0)	1/2 (50.0)	3/3 (100.0)	3/3 (100.0)	4/4 (100.0)	4/4 (100.0)	1/3 (33.3)
S. anginosus group	EOT	22/30 (73.3)	25/28 (89.3)	21/22 (95.5)	25/26 (96.2)	3/3 (100.0)	4/5 (80.0)	12/16 (75.0)	12/12 (100.0)	7/11 (63.6)	9/11 (81.8)
	PTE	22/30 (73.3)	25/28 (89.3)	19/20 (95.0)	23/24 (95.8)	3/3 (100.0)	4/5 (80.0)	12/16 (75.0)	12/12 (100.0)	7/11 (63.6)	9/11 (81.8)
Staphylococcus haemolyticus	EOT	5/5 (100.0)	8/8 (100.0)	5/5 (100.0)	8/8 (100.0)	4/4 (100.0)	1/1 (100.0)	1/1 (100.0)	4/4 (100.0)	0/0 (0.0)	3/3 (100.0)
	PTE	5/5 (100.0)	7/8 (87.5)	5/5 (100.0)	6/6 (100.0)	4/4 (100.0)	1/1 (100.0)	1/1 (100.0)	4/4 (100.0)	0/0 (0.0)	2/3 (66.7)
Staphylococcus lugdunensis	EOT	4/4 (100.0)	6/7 (85.7)	3/3 (100.0)	5/5 (100.0)	0/0 (0.0)	0/0 (0.0)	2/2 (100.0)	0/0 (0.0)	2/2 (100.0)	6/7 (85.7)
	PTE	4/4 (100.0)	6/7 (85.7)	4/4 (100.0)	6/6 (100.0)	0/0 (0.0)	0/0 (0.0)	2/2 (100.0)	0/0 (0.0)	2/2 (100.0)	6/7 (85.7)

EOT = end of therapy; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; *n* = number of patients with a favorable outcome; *N*1 = number of patients within pathogen and treatment assignment subgroup; PTE = posttherapy evaluation.
[a] From the primary infection site or blood cultures.

Table 4
Correlation of MIC and microbiological favorable response by pathogen[a] at PTE with tedizolid and linezolid (ME population).

MIC, mg/L	Microbiological favorable response (*n*/*N*) [%]) at MIC						
	Staphylococcus aureus	MRSA	MSSA	*Staphylococcus haemolyticus*	*Staphylococcus lugdunensis*	*Streptococcus pyogenes*	*Streptococcus anginosus* group
				Tedizolid			
≤0.015	–	–	–	–	–	1/1 (100.0)	2/2 (100.0)
0.015	–	–	–	–	–	–	–
0.03	–	–	–	–	–	–	2/2 (100.0)
0.06	–	–	–	–	–	2/2 (100.0)	3/3 (100.0)
0.12	4/5 (80)	4/5 (80)	–	2/2 (100.0)	3/3 (100.0)	19/20 (95.0)	7/7 (100.0)
0.25	212/225 (94.2)	100/109 (91.7)	112/116 (96.6)	3/3 (100.0)	1/1 (100.0)	5/7 (71.4)	4/4 (100.0)
0.5	54/55 (98.2)	6/6 (100.0)	48/49 (98.0)	–	–	–	–
1	–	–	–	–	–	–	–
Total	270/285 (94.7)	110/120 (91.7)	160/165 (96.9)	5/5 (100.0)	4/4 (100.0)	27/30 (90.0)	18/18 (100.0)
				Linezolid			
0.12	–	–	–	–	–	–	3/3 (100.0)
0.25	–	–	–	–	–	–	4/4 (100.0)
0.5	–	–	–	1/1 (100.0)	2/2 (100.0)	18/18 (100.0)	6/6 (100.0)
1	36/38 (94.7)	28/30 (93.3)	8/8 (100.0)	4/4 (100.0)	2/2 (100.0)	9/12 (75.0)	5/5 (100.0)
2	217/229 (94.8)	81/89 (91.0)	136/140 (97.1)	–	–	–	–
4	17/18 (94.4)	1/1 (100.0)	16/17 (94.1)	–	–	–	–
Total	270/285 (94.7)	110/120 (91.7)	160/165 (96.9)	5/5 (100.0)	4/4 (100.0)	27/30 (90.0)	18/18 (100.0)

MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; PTE = posttherapy evaluation.
CLSI and EUCAST susceptibility breakpoints for tedizolid are ≤0.5 mg/L for *Staphylococcus* spp. and *Streptococcus pyogenes*, and ≤0.25 mg/L for *Streptococcus anginosus* group. For linezolid, susceptibility breakpoints are ≤4 mg/L for *Staphylococcus* spp. and ≤2 mg/L for *Streptococcus pyogenes* and *Streptococcus anginosus* group (CLSI only) (CLSI, 2018; EUCAST, 2018).
[a] From the primary infection.

outcomes at PTE and the MIC of pathogens (data not shown). MIC values of tedizolid associated with microbiological failure were ≤0.5 mg/L in all cases; most were ≤0.25 mg/L. For linezolid, MIC values associated with microbiologic failure were ≤2 mg/L in all cases.

3.6. Activity of tedizolid against MRSA isolates

3.6.1. Epidemiological analysis of MRSA

At baseline, MRSA infection was confirmed in 287 patients (ESTABLISH-1, 178; ESTABLISH-2, 109), of whom 278 were from North America and 252 were available for PFGE analysis. Most analyzed isolates (316/341 [92.7%]) were the community-acquired USA300 genotype (Fig. 2). Most USA300 isolates (188/341, 55.1%) had the highly conserved USA300-0114 profile. The remaining isolates were classified as USA300-other, which included substrains other than USA300-0114 and USA300 isolates for which information on the specific substrain was not available. In total, 228 of 230 USA300 isolates were found to be PVL positive.

The remaining MRSA isolates were USA100 ($n = 3$), USA200 ($n = 1$), USA400 ($n = 2$), USA500 ($n = 1$), USA700 ($n = 1$), USA800 ($n = 4$), USA900 ($n = 1$), USA1000 ($n = 2$), USA1100 ($n = 5$), USA1200 ($n = 1$), and epidemic MRSA (EMRSA-15; $n = 3$) strains. One isolate was of mixed culture; another isolate did not match any known genetic patterns and was thus treated as an unknown strain. As expected from their pulsed-field type, additional testing at the central laboratory found all USA400, USA1100, and USA1200 isolates to be PVL positive; most other isolates (13/16) were PVL negative.

Table 5
In vitro activity of tedizolid and linezolid against MRSA isolates[a,b] by USA type and PVL status.

Isolate	Drug	Range, mg/L	MIC_{50}, mg/L	MIC_{90}, mg/L	% S[c]
MRSA	Tedizolid ($n = 139$)	0.12–0.5	0.25	0.25	100
	Linezolid ($n = 146$)	1–4	2	2	100
USA300-0114	Tedizolid ($n = 73$)	0.12–0.5	0.25	0.25	100
	Linezolid ($n = 63$)	1–2	2	2	100
USA300-other	Tedizolid ($n = 50$)	0.12–0.5	0.25	0.25	100
	Linezolid ($n = 44$)	1–2	2	2	100
PVL positive	Tedizolid ($n = 133$)	0.12–0.5	0.25	0.5	100
	Linezolid ($n = 132$)	1–4	2	2	100
PVL negative	Tedizolid ($n = 5$)	0.25–0.25	0.25	0.25	100
	Linezolid ($n = 10$)	1–4	2	2	100
EMRSA-15	Tedizolid ($n = 10$)	0.25–0.5	0.25	0.5	100
	Linezolid ($n = 10$)	1–2	2	2	100

%S, percent susceptible; EMRSA = epidemic methicillin-resistant *Staphylococcus aureus*; MIC = minimum inhibitory concentration; MIC_{50} = minimum inhibitory concentration against 50% of the isolates; MIC_{90} = minimum inhibitory concentration against 90% of the isolates; MRSA = methicillin-resistant *Staphylococcus aureus*; PVL = Panton-Valentine leucocidin.

[a] Susceptibility data were not obtained for a small number of isolates.

[b] From the primary infection site or blood cultures.

[c] Based on CLSI susceptibility breakpoints for *Staphylococcus* spp. which are ≤0.5 mg/L and ≤4 mg/l for tedizolid and linezolid, respectively. (CLSI, 2018). Isolates were also 100% susceptible based on EUCAST breakpoints (EUCAST, 2018).

3.6.2. In vitro activity of tedizolid and microbiological response of MRSA pulsed-field types

Tedizolid showed 8-fold higher in vitro activity than linezolid against USA300-0114 and USA300-other isolates, with MIC_{90} of 0.25 mg/L versus 2 mg/L (Table 5); tedizolid was also 4-fold to 8-fold more active than linezolid against all other USA pulsed-field types and against EMRSA-15. All isolates were susceptible to tedizolid and linezolid according to established breakpoint criteria, and PVL status did not affect the in vitro activity of either agent.

Tedizolid and linezolid showed excellent microbiological activity against both USA300 and non-USA300 PVL-positive MRSA isolates, including virulent strains associated with severe infection, such as USA300-0114 (Table 6). The activity of tedizolid against USA300 isolates exceeded 90% in the ME population at both EOT and PTE.

3.6.3. Correlation of PVL status with microbiological response for S. aureus

In the micro-ITT analysis set at EOT, microbiological response rates for PVL-positive isolates of *S. aureus* (MRSA and MSSA) were similar for tedizolid and linezolid (87.9% and 85.6%, respectively) (Table 7). Response rates for PVL-negative isolates were slightly higher for both agents because of a higher percentage of patients with indeterminate results for PVL-positive isolates. Results at PTE were similar to those at

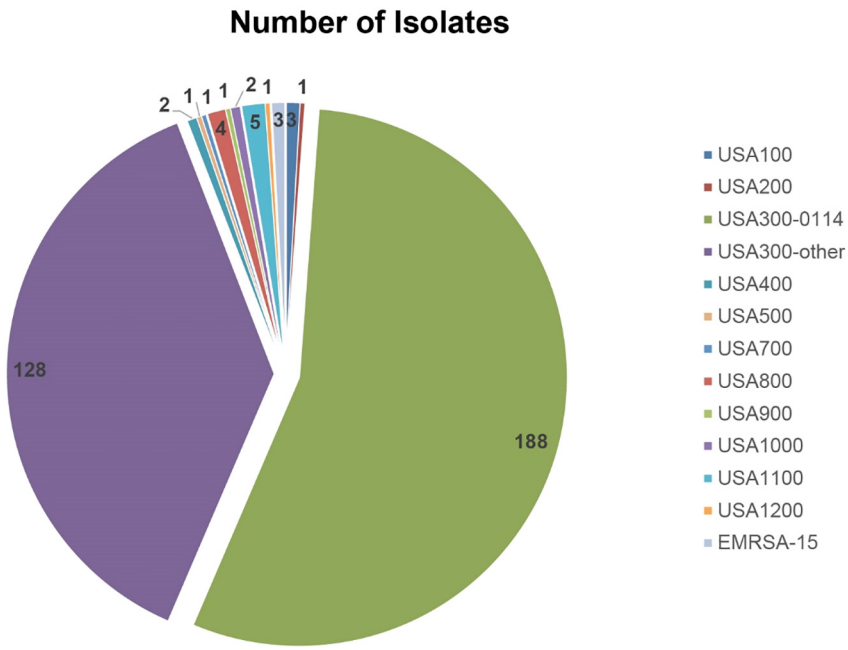

Fig. 2. Methicillin-resistant *Staphylococcus aureus* strain types in pooled phase 3 studies. This figure depicts the strains and substrains identified in the pooled analysis population. The majority of isolates were USA300 genotype. EMRSA = epidemic methicillin-resistant *Staphylococcus aureus*.

Table 6
Favorable microbiological response of tedizolid by MRSA pulsed-field types (PVL-positive isolates).

Pathogen	micro-ITT *n*/*N*1 (%)				ME *n*/*N*1 (%)			
	EOT		PTE		EOT		PTE	
	Tedizolid	Linezolid	Tedizolid	Linezolid	Tedizolid	Linezolid	Tedizolid	Linezolid
USA300	106/123 (86.2)	91/110 (82.7)	105/123 (85.4)	87/110 (79.1)	100/107 (93.5)	90/94 (95.7)	99/106 (93.4)	81/84 (96.4)
Non-USA300	5/5 (100.0)	6/6 (100.0)	4/5 (80.0)	6/6 (100.0)	6/6 (100.0)	4/4 (100.0)	3/4 (75.0)	6/6 (100.0)

EOT = end of therapy; ME = microbiologically evaluable; micro-ITT = microbiological intent to treat; MRSA = methicillin-resistant *Staphylococcus aureus*; *n* = number of patients with a favorable outcome; *N*1 = number of patients within pathogen and treatment assignment subgroup; PTE = posttherapy evaluation; PVL = Panton-Valentine leucocidin.

EOT. In the ME analysis set, which excluded patients with indeterminate results, favorable microbiological response rates were similar for PVL-positive and PVL-negative isolates and exceeded 94% with both agents.

3.7. Superinfection, new infection, and emergence of resistance during therapy

Superinfection was defined as isolation of a nonbaseline pathogen from the primary infection site while the patient was receiving study drug, together with worsening or new signs or symptoms of the primary ABSSSI. No superinfections occurred in the tedizolid group; in the linezolid group, 2 patients in the micro-ITT population and 1 in the ME population had a superinfection. The 2 patients in the micro-ITT group with superinfections were from North America, and each superinfection was detected at the 48- to 72-h visit. One patient had a baseline MRSA infection followed by superinfection with MSSA; symptoms reported at the 48- to 72-h visit included an increase in lesion size. The second patient had an *S. constellatus* infection at baseline, was superinfected with *Streptococcus* Group F, and reported a slightly elevated temperature (>37.6°C) at the 48- to 72-h visit. At PTE, each patient had a favorable microbiological response (categorized as presumed eradication).

New infection was defined as isolation of a nonbaseline pathogen from a posttreatment culture of the primary ABSSSI site in a patient with worsening or new signs or symptoms of the primary ABSSSI. Two tedizolid-treated patients with major cutaneous abscess each acquired a new infection. In 1 patient with baseline MSSA, *E. faecalis* was isolated after new signs and symptoms of infection appeared on days 20 and 35. This patient's microbiological response had been categorized as persistent at EOT and presumed eradicated at PTE. The other patient had baseline MRSA that was not present after day 1 and a favorable microbiological response at EOT and PTE based on presumed eradication. On day 39, a new MRSA infection was isolated (MIC 0.25 mg/L).

Emergence of resistance was defined as at least a 4-fold increase in MIC value of a baseline pathogen at EOT or PTE. No instances of decreased susceptibility to either agent were observed.

4. Discussion

As new antibiotics are often approved for marketing and used on the basis of clinical endpoints from noninferiority study designs, having objective microbiological outcomes and in vitro activity data can serve to support clinical efficacy data and provide context for appropriate use.

In this pooled microbiological analysis of the 2 ESTABLISH studies, a favorable microbiological response or outcome was defined by the rate of *eradication* of the baseline pathogen or presumed eradication (clinical success plus no specimen to isolate) at EOT or PTE. Overall, tedizolid and linezolid demonstrated favorable microbiological outcomes against the most frequently encountered Gram-positive pathogens, including MRSA. The microbiological response rate was high (>85%) and consistent, regardless of geographic region, clinical syndrome, or treatment arm. The high response rates for tedizolid and linezolid against key pathogens were observed across a relatively narrow MIC range for all target organisms and correlated with the observed MIC values of the isolates; however, tedizolid achieved these favorable response rates with a shorter treatment regimen (once daily for 6 days) compared with linezolid (twice daily for 10 days).The slightly higher eradication rates observed in the ME versus micro-ITT population were expected because of the exclusion of patients with indeterminate responses.

USA300 was the most common MRSA strain isolated in the clinical trials, consistent with the known prevalence of this strain in skin and skin structure infections (Tenover and Goering, 2009). In the ME analysis set, the differences between favorable microbiological response for PVL-positive and PVL-negative isolates were minimal; therefore, PVL status did not influence favorable microbiological outcomes to tedizolid or linezolid.

As stated earlier, MIC distributions for key target pathogens demonstrated susceptibility to both tedizolid and linezolid with a relatively narrow MIC range; however, both the MIC distributions and the MIC_{90} values for tedizolid were similar to or less than those reported in surveillance studies of patients with skin and skin structure infections (Benasci and Sahm, 2017). The in vitro potency of tedizolid against the clinical trial isolates from the 2 ESTABLISH trials was 4-fold to 8-fold

Table 7
Favorable microbiological response by PVL status for *Staphylococcus aureus*.

Analysis population	Visit	PVL positive		PVL negative	
		Tedizolid *n*/*N*1 (%)	Linezolid *n*/*N*1 (%)	Tedizolid *n*/*N*1 (%)	Linezolid *n*/*N*1 (%)
micro-ITT	EOT	167/190 (87.9)	154/180 (85.6)	128/135 (94.8)	149/155 (96.1)
	PTE	166/190 (87.4)	151/180 (83.9)	122/135 (90.4)	146/155 (94.2)
ME	EOT	157/167 (94.0)	148/152 (97.4)	122/125 (97.6)	145/147 (98.6)
	PTE	153/163 (93.9)	138/141 (97.9)	115/119 (96.6)	134/136 (98.5)

EOT = end of therapy; ME = microbiologically evaluable; micro-ITT = microbiological intent-to-treat; PTE = posttherapy evaluation; PVL = Panton-Valentine leucocidin.
n = number of patients with a favorable outcome; *N*1 = number of patients within pathogen and treatment assignment subgroup.

greater than that of linezolid, and the organisms found in these trials are those commonly observed in medical practice. All clinical trial isolates were susceptible to tedizolid and linezolid based on current CLSI/EUCAST breakpoints. (CLSI, 2018; EUCAST, 2018; Sivextro [prescribing information], 2016; Sivextro [summary of product characteristics], 2016).

A strength of the pooled analysis was that the predominant Gram-positive species isolated in the ESTABLISH-1 and -2 trials were consistent with those anticipated for ABSSSI trials (Boucher et al., 2014; Corey et al., 2010; Weigelt et al., 2005). Approximately one-third of patients with baseline Gram-positive isolates had MRSA infections, providing important comparative data on the microbiological efficacy of tedizolid and linezolid for these serious ABSSSI infections. In addition to *S. aureus* and *S. pyogenes*, less frequently encountered pathogens such as *S. anginosus* group, *S. haemolyticus*, and *S. lugdunensis* were also isolated. *S. haemolyticus* and *S. lugdunensis*, in particular, have been associated with multiple-drug resistance (Barros et al., 2012; Bocher et al., 2009; Frank et al., 2008; Shittu et al., 2004), and thus, our findings would help to inform treatment options in these less frequently encountered and difficult-to-treat infections.

A limitation of the study was that the microbiological efficacy results were driven by presumed eradication. As expected, because of the difficulty in obtaining a follow-up specimen from a healing lesion, the results are based primarily on clinical response and not on actual microbiological data. In addition, because several of the microbiological efficacy analyses in the tables are analyses of subgroups that have been further subcategorized, individual data points must be interpreted with caution.

Overall, this pooled analysis of phase 3 clinical trial data provides additional insight into the positive microbiological activity of tedizolid and linezolid beyond clinical response rates alone and supports the consideration of tedizolid phosphate 200 mg once daily for 6 days as an option for the successful treatment of patients with ABSSSI.

Ethics approval and consent to participate

Written informed consent was obtained from all participants, and the studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and with all relevant international, national, and local rules and legislation. The protocol was approved by the Copernicus Group Independent Review Board and by institutional review boards or ethics committees at each participating center; the study design and a list of study sites and investigators have been reported.

Consent for publication

Not applicable.

Availability of data and material

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's (MSD) data sharing policy, including restrictions, is available at http://engagezone.merck.com/ds_documentation.php. Requests for access to the study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Competing interests

RC has received consultancy fees from Achaogen, Actavis (Cerexa/Forest), Arsanis, Basilea, Bayer, Bio2Medical, Cempra, Contrafect, Medtronic, Melinta, Merck (Trius/Cubist), Motif, Nabriva, Paratek, Pfizer, Quintiles/Novella, SCPharma, Tetraphase, The Medicines Company, and Theravance. He has also received clinical trial support from Dr. Reddy's laboratory and The Medicines Company. GM has received clinical trial support from Allergan, AstraZeneca, Cempra, Cerexa, and Trius (now MSD). RG reports no conflicts of interest. MB, TS, CDA, and PP are all current or former employees of MSD.

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Authors' contributions

RC was involved in the conception of the study, interpretation of the results, and critical review and revision of the manuscript for important intellectual content. GM substantially contributed to the acquisition of data, interpretation of the results, and critical review and revision of the manuscript for important intellectual content. RG substantially contributed to the conception of the study, acquisition and analysis of the data, interpretation of the results, and critical review and revision of the manuscript for important intellectual content. MB substantially contributed to data analysis, interpretation of the results, and critical review and revision of the manuscript for important intellectual content. TS substantially contributed to the conception of the study, interpretation of the results, and critical review and revision of the manuscript for important intellectual content. CDA substantially contributed to the conception of the study, acquisition, and analysis of the data, interpretation of the results, and drafting, critical review, and revision of the manuscript for important intellectual content. PP contributed to the conception of the study, interpretation of the results, and critical review and revision of the manuscript for important intellectual content. All authors read and approved the final draft of the manuscript for submission and agree to be accountable for the accuracy of the data and the integrity of the work.

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Appendix A. Supplementary data

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