Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial

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Summary

Background New antibiotics are needed to treat infections caused by drug-resistant bacteria. Tedizolid is a novel oxazolidinone antibacterial drug designed to provide enhanced activity against Gram-positive pathogens. We aimed to assess the efficacy and safety of intravenous to oral tedizolid for treatment of patients with acute bacterial skin and skin-structure infections.

Methods ESTABLISH-2 was a randomised, double-blind, phase 3, non-inferiority trial done between Sept 28, 2011, and Jan 10, 2013, at 58 centres in nine countries. Patients (aged ≥12 years) with acute bacterial skin and skin-structure infections (cellulitis or erysipelas, major cutaneous abscess, or wound infection) that had a minimum lesion area of 75 cm² and were suspected or documented to be associated with a Gram-positive pathogen, were randomly assigned (1:1), via an interactive voice-response system with block randomisation, to receive intravenous once-daily tedizolid (200 mg for 6 days) or twice-daily linezolid (600 mg for 10 days), with optional oral step-down. Randomisation was stratified by geographic region and type of acute bacterial skin and skin-structure infection. The primary endpoint was early clinical response (≥20% reduction in lesion area at 48–72 h compared with baseline), with a non-inferiority margin of –10%. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT01421511.

Findings 666 patients were randomly assigned to receive tedizolid (n=332) or linezolid (n=334). 283 (85%) patients in the tedizolid group and 276 (83%) in the linezolid group achieved early clinical response (difference 2·6%, 95% CI –3·0 to 8·2), meeting the prespecified non-inferiority margin. Gastrointestinal adverse events were less frequent with tedizolid than linezolid, taking place in 52 (16%) of 331 patients and 67 (20%) of 327 patients in the safety population. Treatment-emergent adverse events leading to discontinuation of study drug were reported by one (<1%) patient in the tedizolid group and four (1%) patients in the linezolid group.

Interpretation Intravenous to oral once-daily tedizolid 200 mg for 6 days was non-inferior to twice-daily linezolid 600 mg for 10 days for treatment of patients with acute bacterial skin and skin-structure infections. Tedizolid could become a useful option for the treatment of acute bacterial skin and skin-structure infections in the hospital and outpatient settings.

Funding Cubist Pharmaceuticals.

Lancet Infect Dis 2014

Published Online
June 6, 2014
http://dx.doi.org/10.1016/S1473-3099(14)70737-6

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(14)70798-4

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Introduction

Acute bacterial skin and skin-structure infections are frequently encountered in clinical practice and can be devastating to patients.[1-3] These infections are among the most common of those treated in hospitals, and numbers of associated emergency department visits and hospital admissions have increased substantially.[4,5] Gram-positive bacteria, mainly *Staphylococcus aureus* (and also β-haemolytic streptococci), are the main causes,[1,6] with strains of meticillin-resistant *S aureus* (MRSA) now endemic in some European countries, the USA, and elsewhere.[7,8] Community-acquired MRSA has become a major cause of skin and soft-tissue infections,[1] for which it is associated with a high rate of treatment failure and recurrence.[9,10] These developments have led to MRSA being declared a serious threat to public health.[8,11] Although treatment options for MRSA are available, limitations or challenges exist, which include (but are not limited to) drug–drug interactions, need for dose adjustments, safety concerns, and the existence or development of resistance.[6] These issues emphasise the need for new antibiotics to treat acute bacterial skin and skin-structure infections.

Tedizolid phosphate is a novel oxazolidinone prodrug that is rapidly converted to its microbiologically active moiety tedizolid by endogenous phosphatases. Tedizolid binds to the bacterial 50S ribosomal subunit to inhibit protein synthesis, resulting in broad in-vitro activity against Gram-positive pathogens, including MRSA and strains resistant to vancomycin or linezolid.[12–14] Animal models suggest that tedizolid has bactericidal activity against *S aureus* in vivo.[15,16] Compared with other drugs of its class, tedizolid has additional target-site interactions with the peptidyl transferase binding region of 23S rRNA, which are thought to contribute to its potency.[12] Tedizolid's pharmacokinetic and pharmacodynamic properties allow for once-daily administration, either orally or intravenously at equivalent dosage,[17–19] with good penetration into skin and soft tissue.[20] Tedizolid is therefore a suitable candidate

for clinical investigation as a treatment for acute bacterial skin and skin-structure infections.

In the USA, regulatory requirements for clinical trials in this setting have undergone substantial changes (appendix). Treatment of patients with acute bacterial skin and skin-structure infections with oral tedizolid was assessed in the ESTABLISH-1 study—the first trial done according to draft guidance about evaluation of new treatments for such infections released by the US Food and Drug Administration (FDA) in 2010.[21] Findings from ESTABLISH-1 showed non-inferior efficacy of 200 mg oral tedizolid phosphate once daily given for 6 days compared with 600 mg oral linezolid twice daily given for 10 days.[18] However, the potential role of intravenous tedizolid in an overall strategy for management of acute bacterial skin and skin-structure infections has not yet been explored.

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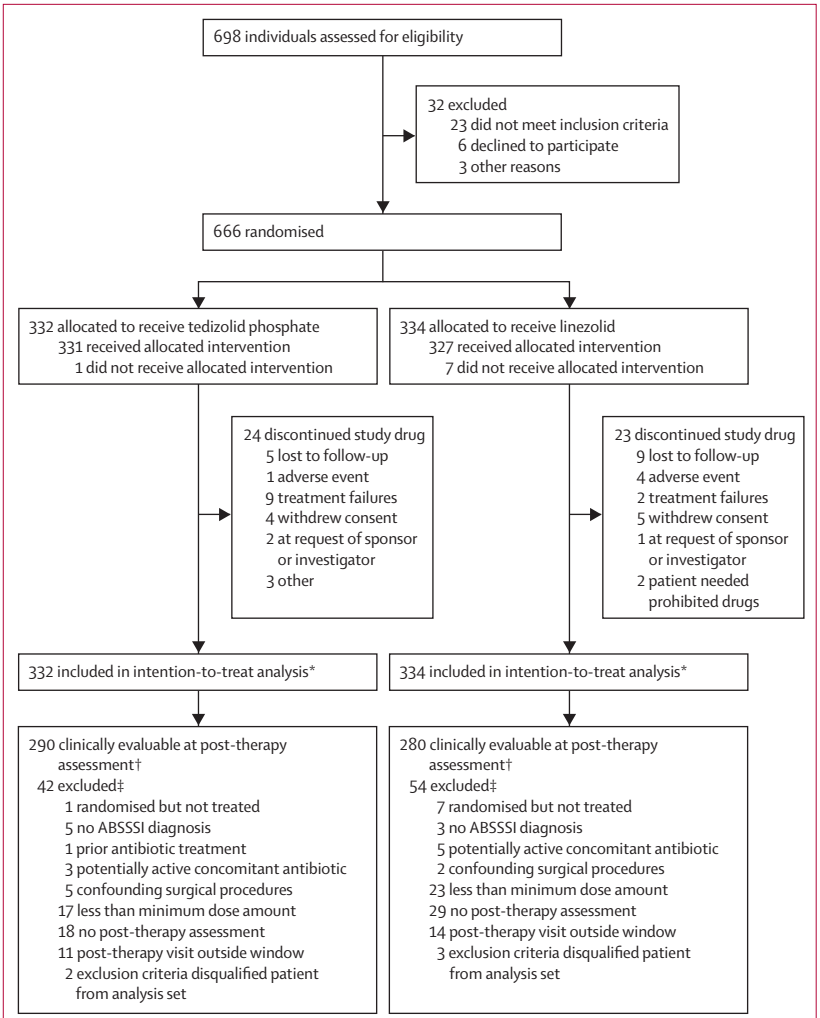

Figure 1: **Trial profile**
ABSSSI=acute bacterial skin and skin-structure infection. *Included all randomised patients. †Included all patients who had no major violations, had not received potentially effective concomitant antibiotics, and completed the post-therapy assessment. ‡Patients could have been excluded for more than one reason.

We undertook the ESTABLISH-2 study to assess the efficacy and safety of intravenous to oral tedizolid for treatment of patients with acute bacterial skin and skin-structure infections. This study is the first prospectively designed trial with a study design that is consistent with all the fundamental elements included in the final FDA guidance about development of drugs for acute bacterial skin and skin-structure infections from 2013.[22]

Methods

Study design and participants

We undertook this randomised, double-blind, multinational, phase 3, parallel-group, non-inferiority trial between Sept 28, 2011, and Jan 10, 2013, at 58 centres in nine countries (Argentina, Australia, Germany, New Zealand, Poland, Russia, South Africa, Spain, and the USA).

We enrolled patients aged 12 years or older with acute bacterial skin and skin-structure infections (cellulitis or erysipelas, major cutaneous abscess, or wound infection) that had a minimum lesion area of 75 cm² and were suspected or documented to be associated with a Gram-positive pathogen. Patients also had to have at least one systemic or regional sign of infection (lymphadenopathy, raised body temperature, white blood-cell count ≥10 000/μL or <4000/μL, or >10% immature neutrophils). In patients with abscesses and wounds, erythema, oedema, or induration had to extend 5 cm or further from the margin of the abscess or wound to the edge of the lesion to satisfy eligibility criteria. Ineligible patients had received systemic antibiotics with Gram-positive cocci activity in the previous 96 h or had failed antibiotic treatment for the primary site of acute bacterial skin and skin-structure infection. Additionally, we excluded patients with uncomplicated skin or skin-structure infections, infections associated with prosthetic devices or vascular catheter sites, thrombophlebitis, diabetic foot infections, infected burns, chronic skin ulcers, non-clean surgery, known bacteraemia at screening, septic shock or severe sepsis, a history of opportunistic infections with the underlying cause still active, receiving chronic systemic immunosuppressive treatment or antipyretic drugs (other than aspirin ≤200 mg a day), severe renal disease, or severe hepatic disease. The appendix provides full inclusion and exclusion criteria.

We undertook the study in accordance with the 2008 Declaration of Helsinki and all relevant international, European Union, national, and local rules and legislation. Institutional review board or ethics committee approval was obtained at each participating centre. All participants provided written informed consent. This trial is registered with ClinicalTrials.gov, number NCT01421511.

Randomisation and masking

Patients were randomly assigned (1:1), via an interactive voice-response system with block randomisation, to receive intravenous tedizolid phosphate 200 mg once daily for 6 days or intravenous linezolid 600 mg twice

daily for 10 days, with optional oral step-down. Randomisation was stratified by geographic region and type of acute bacterial skin and skin-structure infection. Patients, study investigators, study staff participating in direct patient care or clinical evaluations, and the study sponsor were masked to treatment assignment. We used a double-dummy design with placebo unique to each active treatment to maintain the blind.

Procedures

All patients received two or more intravenous doses of active treatment or placebo and could then be switched to oral drug if they met at least two of the following criteria: no increase from baseline in primary lesion area, length, or width; temperature less than 37·7°C; no worsening of local signs and symptoms at the primary infection site; or improvement of one or more local signs or symptoms since the previous visit. Patients could receive intravenous therapy for the entire study duration at the discretion of the investigator, even if switching criteria were met. For wound infections, either aztreonam or metronidazole, or both, could be added for Gram-negative or anaerobic coverage, as deemed appropriate by the investigator.

Other concomitant systemic antibiotics and topical antibiotics (except those associated with a surgical dressing) applied to the primary lesion were prohibited from 96 h before the first dose of study drug to the late follow-up visit (18–25 days after end of treatment). Incision and drainage of the primary infection site not planned before randomisation was discouraged after day 1 for wounds and abscesses, and after the 48–72 h visit for cellulitis. Non-steroidal anti-inflammatory drugs (NSAIDs; excluding aspirin ≤200 mg a day) and oral steroids were prohibited between enrolment and 72 h after first dose, and antipyretic drugs were discouraged during that time unless the patient's temperature exceeded 38°C.

The appendix describes various analysis populations.

Outcomes

The primary endpoint was early clinical response 48–72 h after start of treatment. We classed patients as responders if they had a 20% or greater reduction in area (length×width of erythema, oedema, and induration) of the primary lesion from baseline, did not receive any systemic concomitant antibiotics with Gram-positive activity, and did not die from any cause within 72 h of the first dose. Standardised measurement of lesion area (ie, erythema, oedema, or induration, whichever was largest) was done with a flexible plastic ruler, by multiplying the longest head-to-toe length of the lesion with the widest width perpendicular to that length. Patients with missing data for any component of the primary endpoint were classed as non-responders. Secondary endpoints were response at day 7 (investigator-assessed), end of treatment assessment (programmatic and investigator-assessed) and post-therapy assessment (7–14 days after end of treatment; investigator-assessed), and changes in patient-reported pain at prespecified time points throughout the study. We also report investigator-assessed response at late follow-up, defined as no clinical relapse from post-therapy assessment. Favourable microbiological response was defined as eradication (absence of original baseline pathogens) or presumed eradication (no specimen to culture in a patient assessed as a clinical success, based on programmatic determination of clinical response at end of treatment and investigator-assessed clinical

	Tedizolid phosphate (n=332)	Linezolid (n=334)
Age (years)	46 (17–86)	46 (15–89)
Men	225 (68%)	214 (64%)
Region of enrolment		
North America	156 (47%)	158 (47%)
Latin America	13 (4%)	13 (4%)
Europe	112 (34%)	111 (33%)
South Africa	48 (14%)	46 (14%)
Australia and New Zealand	3 (1%)	6 (2%)
Lymphadenopathy	235 (71%)	235 (70%)
Temperature ≥38°C (fever)	103 (31%)	97 (29%)
White blood-cell count (≥10 000 cells per μL or <4000 cells per μL)	176 (53%)	151 (45%)
Immature neutrophils (>10%)*	53/328 (16%)	40/327 (12%)
At least one Gram-positive ABSSSI identified at baseline	197 (59%)	202 (60%)
Staphylococcus aureus†	158 (80%)	167 (83%)
MRSA†	53 (27%)	56 (28%)
MSSA†	105 (53%)	111 (55%)
Panton-Valentine leucocidin-positive *S aureus*†	93 (47%)	78 (39%)
β-haemolytic streptococci†,‡	25 (13%)	20 (10%)
Streptococcus anginosus group†	15 (8%)	12 (6%)
Enterococcus faecalis†	5 (3%)	4 (2%)
Bacteraemia	7 (2%)	12 (4%)
Admitted to, or already in, hospital	140 (42%)	143 (43%)
Length of hospital stay (days)§	9·2 (4·60)	10·3 (5·08)
Comorbidities		
History of diabetes mellitus	32 (10%)	41 (12%)
Obesity¶	101 (30%)	118 (35%)
Renal impairment (moderate to severe)	14 (4%)	12 (4%)
Hepatic impairment/disease	9 (3%)	8 (2%)
Hepatitis C‖	65/322 (20%)	80/321 (25%)
HIV positive	8 (2%)	7 (2%)
Concurrent secondary ABSSSI lesion	48 (14%)	47 (14%)
Risk factors		
Present or recent intravenous drug use	66 (20%)	74 (22%)
Poor living conditions**	15 (5%)	18 (5%)
Previous ABSSSI lesion	71 (21%)	63 (19%)
Type of ABSSSI		
Cellulitis or erysipelas	166 (50%)	168 (50%)
Major cutaneous abscess	68 (20%)	68 (20%)
Infected wound	98 (30%)	98 (29%)

(Table 1 continues on next page)

	Tedizolid phosphate (n=332)	Linezolid (n=334)
(Continued from previous page)		
Anatomical location of ABSSSI		
Leg or foot	129 (39%)	135 (40%)
Groin, buttock, or back	37 (11%)	45 (13%)
Arm	131 (39%)	120 (36%)
Chest or abdomen	18 (5%)	15 (4%)
Head or neck	17 (5%)	19 (6%)

Data are median (range), n (%), n/N (%), or mean (SD) unless otherwise indicated. MRSA=meticillin-resistant *Staphylococcus areus*. MSSA=meticillin-susceptible *Staphylococcus areus*. ABSSSI=acute bacterial skin and skin-structure infection. *Data were not available for four (1%) patients in the tedizolid group and seven (2%) patients in the linezolid group. †Percentages for bacterial isolates were calculated with numbers of patients who had at least one Gram-positive ABSSSI identified at baseline. ‡Mostly *Streptococcus pyogenes*; the only other β-haemolytic *Streptococcus* species isolated was *S agalactiae* (n=5 in the linezolid group; one patient in the linezolid group had both *S pyogenes* and *S agalactiae* isolated). §The geographical heterogeneity among study sites affects data for hospital length-of-stay because of different health-care systems and medical practice patterns. We did not analyse whether all or part of hospital admission or stay was due to the primary ABSSSI or another, concurrent illness. ¶Defined as a BMI of 30 kg/m^2 or more. ||Data were not available for ten (3%) in the tedizolid group and 13 (4%) patients in the linezolid group. **Poor living conditions included homelessness and crowding.

***Table 1*: Demographic and clinical characteristics**

	Tedizolid phosphate (n=332)	Linezolid (n=334)	p value*
Mean time to oral switch (days)	1·7 (1·18)	1·8 (1·35)	0·99
Mean duration of intravenous treatment (days)†			
Patients in the USA	2·2 (2·17)	2·0 (2·03)	0·20
Patients outside the USA	4·6 (3·74)	4·7 (3·63)	0·62
Median duration of intravenous treatment (days)			
Patients in the USA	2 (1–10)	2 (1–8)	0·19
Patients outside the USA	3 (1–11)	3 (1–11)	0·62
Patients receiving 2 or more days of intravenous treatment	240 (72%)	232 (69%)	0·44
Patients receiving only intravenous study drug for entire prespecified treatment duration‡	64 (19%)	58 (17%)	0·62

Data are mean (SD), median (range), or n (%), unless otherwise indicated. *Calculated with Fisher's exact test for categorical data and the Wilcoxon rank-sum test for continuous data. †Reasons for step-down from intravenous to oral study drug were not collected. ‡All but one of these patients were enrolled in Russia.

***Table 2*: Exposure to intravenous study drug**

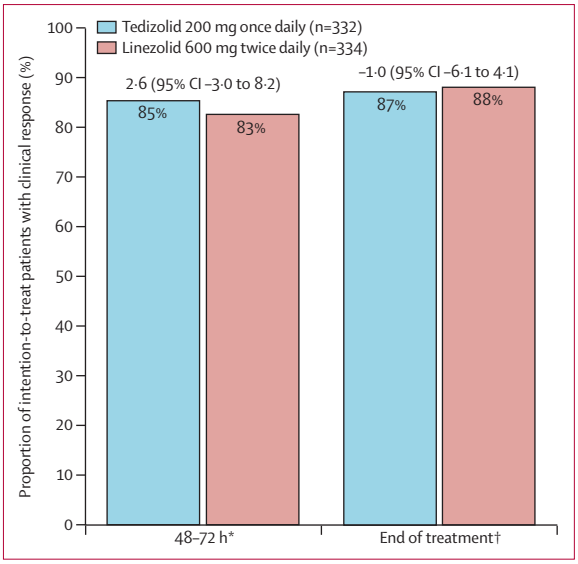

***Figure 2*: Clinical response rates based on objective assessments incorporating changes in lesion area, at 48–72 h (primary efficacy endpoint) and at end of treatment (secondary efficacy endpoint) in the intention-to-treat population**

*Primary endpoint: 20% or more decrease in lesion area from baseline at 48–72 h after first dose, measured as total area erythema, induration, or oedema (whichever is largest), and patients who had no systemic concomitant antibiotics with Gram-positive activity and did not die from any cause within 72 h of first dose. †Secondary endpoint: programmatic clinical response, defined as decreased lesion area from baseline, absence, or near resolution of prespecified signs and symptoms (fever, tenderness, purulent drainage), no treatment discontinuation due to adverse events, and no major protocol violations that would prohibit accurate determination of response (ie, no concomitant antibiotics other than metronidazole or aztreonam, no unplanned surgical interventions, no osteomyelitis) at the end of treatment (day 11).

response at the post-therapy assessment); all patients with persistence or presumed persistence at end of treatment were deemed to have had an unfavourable microbiological response at the post-therapy assessment. The appendix shows detailed endpoint definitions.

We assessed patient-reported pain with two different pain scales (appendix). Collection of adverse events, physical examinations (including neurological examinations and visual acuity assessments), assessment of haematological and chemistry laboratory parameters, and electrocardiograms were done in the safety population (ie, patients who received any amount of active drug).

Baseline pathogens isolated from lesions by aspirate, biopsy, incision, or deep swab, or isolated from blood samples were sent to a central laboratory (Eurofins Medinet, Chantilly, VA, USA) for pathogen identification and antibiotic susceptibility testing.

Statistical analysis

Sample size was calculated with standard methods.[23] With an assumption of an 81% point estimate in both treatment groups for the primary outcome (on the basis of results from a phase 2 dose-ranging study[17]), 90% power, a one-sided α level of 0·025, and a 10% non-inferiority margin, a total sample size of 329 patients in each treatment group was needed. In total, 30% or fewer patients were to be enrolled with cutaneous abscess, and patients from the USA could not represent more than 50% of this group.

We concluded non-inferiority of tedizolid to linezolid if the lower limit of the 95% CI for the difference in the primary endpoint, calculated with the Miettienen and Nurminen method without stratification, was more than –10%. This non-inferiority margin was based on historical data and current guidance from the US FDA.[22,24] For secondary endpoints, two-sided 95% CIs were constructed for recorded differences in response rates without stratification with the Miettienen and Nurminen method. Post-hoc exploratory analyses of treatment differences in haematological parameters were done with Fisher's exact test, with two-sided p-values reported as descriptive statistics. We identified

differences in baseline characteristics between treatment groups with Fisher's exact test or the Wilcoxon rank sum test. We did statistical analyses with SAS (version 9.2).

Role of the funding source

Employees of the study sponsor had a role in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 666 patients were randomly assigned to receive tedizolid (n=332) or linezolid (n=334).

Baseline and demographic characteristics were similar between groups (table 1). Median lesion area of acute bacterial skin and skin-structure infections was 231·3 cm² (IQR 120·9–473·1) in the tedizolid group and 238·6 cm² (IQR 120·9–483·0) in the linezolid group. Median area of abscesses was 155·1 cm² (IQR 94·7–262·0) versus 178·8 cm² (119·4–287·0), of which more than 80% underwent incision and drainage procedures (appendix). At least one Gram-positive pathogen was isolated in 60% of patients at baseline; MRSA was identified in about 27% of these patients (table 1). All baseline isolates of *S aureus* (and *Enterococcus faecalis*) had a tedizolid minimum inhibitory concentration (MIC) of 0·5 mg/L or lower, and all other isolates had an MIC of 0·25 mg/L or lower; no official susceptibility breakpoints for tedizolid are defined. All isolates were linezolid susceptible. In the tedizolid group, tedizolid MICs for MRSA ranged from 0·12 to 0·5 mg/L (MIC_{50} 0·25 mg/L; MIC_{90} 0·5 mg/L). In the linezolid group, linezolid MICs for MRSA ranged from 1 to 2 mg/L (MIC_{50} 2 mg/L; MIC_{90} 2 mg/L). All baseline pathogens were vancomycin susceptible, but we did not test for heterogeneous vancomycin-intermediate *S aureus*.

92% of patients in the safety population received either five to six doses of tedizolid (313 of 331 patients) or 19 to 20 doses of linezolid (295 of 327 patients). Table 2 shows data for exposure to intravenous study drug. 17 patients (nine in the tedizolid group and eight in the linezolid group) received concomitant aztreonam and 12 patients received concomitant metronidazole (six in each treatment group). The differences in mean duration of intravenous treatment between patients outside the USA and patients in the USA (table 2) probably suggest differences in standard practice, and administrative and reimbursement patterns of infection management, mainly the preference to avoid hospital admission in the USA.

283 (85%) participants in the tedizolid group and 276 (83%) of those in the linezolid group achieved early clinical

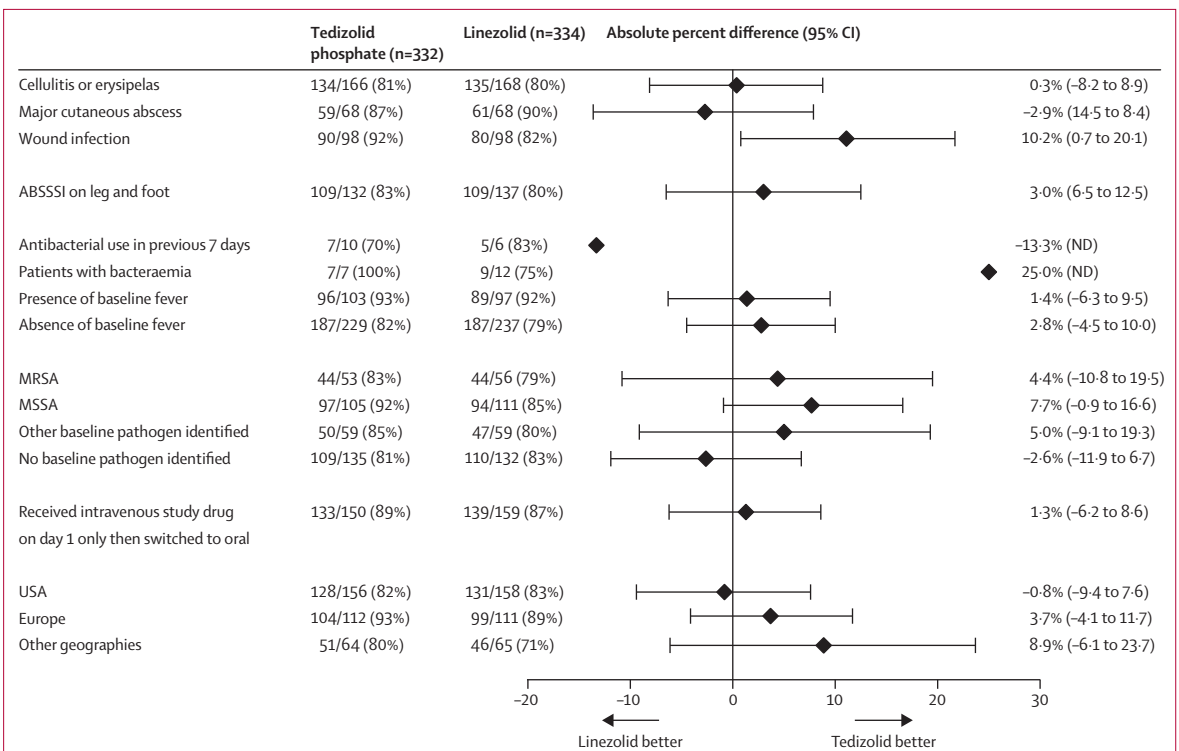

***Figure 3*: Early clinical response at the 48–72 h visit by subgroup in the intention-to-treat population**

Data are n/N (%), unless otherwise indicated. Percent difference is response rate for the tedizolid group minus linezolid group. Some patients had more than one baseline pathogen identified. ABSSSI= acute bacterial skin and skin-structure infection. MRSA=meticillin-resistant *Staphylococcus aureus*. MSSA=meticillin-susceptible *Staphylococcus aureus*. ND=not determinable.

response (figure 2), showing non-inferiority of tedizolid to linezolid. Patients were classified as non-responders if they had a reduction of less than 20% in lesion area (40 [12%] in the tedizolid group *vs* 41 [12%] in the linezolid group), missing lesion measurements at the 48–72 h visit (five [2%] *vs* 14 [4%]), or if they had received concomitant systemic antibiotics (seven [2%] *vs* six [2%]). Missing data did not affect the non-inferiority findings: a tipping point analysis showed that if all patients with missing data in the linezolid group were considered to be responders, and all those in the tedizolid group with missing data non-responders, non-inferiority was preserved (95% CI –6·9 to 3·7). A multiple imputation analysis further confirmed these results (95% CI –4·7 to 6·3). We recorded no meaningful differences between groups in rates of early clinical response, irrespective of type of acute bacterial skin or skin-structure infection, geographic region, baseline pathogen, and timing of oral step-down (day 2 *vs* later; figure 3). Of note, some of the clinically relevant subgroups were small in size, restricting conclusions that can be drawn from these post-hoc analyses. Results for secondary endpoints in the intention-to-treat population were consistent with those for the primary outcome (figure 2, table 3), as were microbiological responses in the microbiological intention-to-treat population (table 4). Improvements in patient-reported pain were similar between treatment groups (appendix). We noted high concordance (>80%) between treatment outcomes recorded at the 48–72 h and post-therapy assessment visits (appendix).

Of patients who were clinically evaluable at the end-of-treatment visit, 272 (90%) of 304 in the tedizolid group and 280 (94%) of 299 in the linezolid group had a programmatically determined clinical response (difference –4·1%, 95% CI –8·8% to 0·3%) and 281 (95%) of 296 versus 284 (97%) of 293 patients had investigator-assessed clinical success (–2·0%, –5·7% to 1·2%) at that timepoint. Of patients who were clinically evaluable at the post-therapy assessment, 268 (92%) of 290 in the tedizolid group and 269 (96%) of 280 in the linezolid group had investigator-assessed clinical success (–3·7%, –7·7 to 0·2). Microbiological responses in microbiologically evaluable patients showed a similar pattern to those in the microbiological intention-to-treat population (appendix).

Overall, the incidence of treatment-emergent adverse events was similar between study groups (table 5). However, gastrointestinal disorders (mostly consisting of diarrhoea, nausea, and vomiting) were less common in the tedizolid group than in the linezolid group (52 [16%] of 331 patients *vs* 67 [20%] of 327 patients). Treatment-emergent adverse events were mostly mild to moderate, with the most common in either treatment group noted as nausea, headache, secondary abscesses, diarrhoea (none associated with *Clostridium difficile* toxin), and vomiting; very few patients had infusion-site reactions (table 5). Treatment-emergent adverse events leading to discontinuation of study drug were reported by one (<1%) patient in the tedizolid group (abdominal discomfort) and four (1%) patients in the linezolid group (reduced visual acuity, nausea, vomiting, pain, pyrexia, anaphylactic reaction, headache, and restlessness); all these events resolved after discontinuation of study drug. Comparisons of the worst haematological parameters at any post-baseline assessment through last dose of active drug showed that 27 (9%) of 314 patients in the tedizolid group and 41 (13%) of 305 patients in the linezolid group (p=0·071) had platelet counts less than the lower limit-of-normal (<150×10⁹/L) and nine (3%) of 305 patients versus 21 (7%) of 299 patients (p=0·024), had absolute neutrophil counts less than the lower limit-of-normal (<1·6×10⁹/L). Post-baseline haemoglobin values below the lower limit-of-normal were similar between both groups (data not shown). One patient in each treatment group died; neither death was regarded as related to study treatment.

	Tedizolid phosphate (n=332)	Linezolid (n=334)	Difference (95% CI)
48–72 hours*	304 (92%)	302 (90%)	1·2% (–3·3 to 5·6)
Day 7*	309 (93%)	308 (92%)	0·9% (–3·2 to 4·9)
End of treatment (day 11)†	304 (92%)	301 (90%)	1·4% (–3·0 to 5·9)
Post-therapy assessment (7–14 days after end of treatment)†	292 (88%)	293 (88%)	0·3% (–4·8 to 5·3)
Late follow-up (18–25 days after end of treatment)‡	262/268 (98%)	266/269 (99%)	–1·1% (–3·8 to 1·3)

Data are n (%), unless otherwise indicated. ABSSSI=acute bacterial skin and skin-structure infection. *Clinical success defined as improvement in overall clinical status of ABSSSI compatible with continuation of study drug. †Clinical success defined as resolution or near resolution of disease-specific signs and symptoms, absence or near resolution of baseline systemic signs of infection, and no further antibiotic treatment required for treatment of primary ABSSSI lesion. ‡Clinical success defined as no new signs or symptoms of primary ABSSSI after post-therapy assessment. Only assessed in patients who were clinically evaluable and deemed clinical successes at post-therapy assessment.

***Table 3*: Investigator-assessed clinical success rates**

	Tedizolid phosphate (n=197)	Linezolid (n=202)	Difference (95% CI)
Gram-positive pathogens (aerobes)	168/192* (88%)	177/199* (89%)	–1·4 (–8·.0 to 5·1)
Staphylococcus aureus	143/158 (91%)	147/167 (88%)	2·5 (–4·5 to 9·4)
Meticillin-resistant *S aureus*	43/53 (81%)	43/56 (77%)	4·3 (–11·4 to 19·8)
Meticillin-susceptible *S aureus*	100/105 (95%)	104/111 (94%)	1·5 (–5·2 to 8·4)
β-haemolytic streptococci	23/25 (92%)	19/20 (95%)	–3·0 (–21·2 to 17·0)
Streptococcus anginosus group	10/15 (67%)	12/12 (100%)	–33·3 (–58·7 to –4·8)

Data are n/N (%), unless otherwise indicated. Favourable responses include eradication (absence of baseline pathogen) and presumed eradication (no source specimen to culture and patient assessed as clinical success by investigator). An indeterminate response denotes a patient with an indeterminate clinical response or with another circumstance that precluded a microbiological evaluation. Unfavourable responses include persistence (continued presence of baseline pathogen) and presumed eradication (no source specimen to culture and patient assessed as clinical failure by investigator). All patients with persistence or presumed persistence at end of treatment were assigned an unfavourable microbiological response at the post-therapy assessment. Some patients had multiple Gram-positive pathogens at baseline. *The other five patients in the tedizolid phosphate group and the other three patients in the linezolid group had anaerobic pathogens isolated.

***Table 4*: Favourable microbiological response at the post-therapy assessment visit (7–14 days after end of treatment) in the microbiological intention-to-treat population (patients with a Gram-positive pathogen isolated at baseline)**

Discussion

Our findings show that once-daily tedizolid 200 mg for 6 days, given intravenously with an option to switch to oral drug, was non-inferior to twice-daily linezolid 600 mg for 10 days for the treatment of acute bacterial skin and skin-structure infections, on the basis of the primary endpoint of objective early clinical response at 48–72 h. Furthermore, clinical success rates were similar between treatment groups at all subsequent time points, including investigator-assessed clinical responses 7–14 days after end of treatment and at late follow-up—the primary and secondary efficacy endpoints recommended by European regulatory authorities. Microbiological outcomes were likewise similar between groups. Enrolled patients presented with severe skin infections at baseline, with large lesions, adjacent lymphadenopathy or systemic signs of infection, and moderate to high average pain levels. Of note, more than a quarter of patients with confirmed Gram-positive pathogens had MRSA infections, and outcomes in these patients matched the overall results. Both drugs were generally well tolerated, with patients in the tedizolid group reporting gastrointestinal adverse events and adversely affected haematological parameters less frequently than those in the linezolid group.

The results were consistent with those of a previous trial (ESTABLISH-1), in which tedizolid and linezolid were given orally only.[18] ESTABLISH-1 followed draft 2010 US FDA guidance for clinical trials for treatment of acute bacterial skin and skin-structure infections and consequently used a different definition of early clinical response as the primary endpoint—ie, cessation of lesion area spread and the absence of fever (in addition to the patient being alive and not having received systemic concomitant antibiotics). In a predefined sensitivity analysis using the same definition of early clinical response as the present study (≥20% decrease in lesion area with no fever criteria), 78% of patients given tedizolid and 76% of those given linezolid in ESTABLISH-1 had an early clinical response. Notably, ESTABLISH-2 enrolled substantially more European patients, more patients with cellulitis, more febrile patients, and patients with larger lesions than did ESTABLISH-1. These differences in lesion areas might partly be attributable to minor differences in measurement methodology. Defining of lesion area as the total area of erythema or induration or oedema, whichever was largest (the method used in ESTABLISH-2), has been shown to result in median baseline measurements that are roughly 8% greater than when the area is defined as erythema alone (the method used in ESTABLISH-1);[25] however, this factor would not explain all the differences in lesion area between these studies.

Because placebo-controlled trials would be unethical, and in view of the high rates of treatment response with antibacterial drugs, clinical trials assessing novel antibiotics for treatment of acute bacterial skin and skin-structure infections should use a non-inferiority design.[22,24,26] We chose linezolid as the comparator because, like tedizolid, it can also be given both intravenously and orally and is approved for treatment of complicated skin and skin-structure infections.[27] Comparisons of our results with those of previous clinical trials of linezolid for complicated skin and skin-structure infections are not feasible because of substantial differences in study design and patient populations.

A potential limitation of our study concerns the reliability of lesion measurements. Manual measurement of lesion size of acute bacterial skin and skin-structure infections could introduce variability; however, this variability would be expected to be of similar size and direction between treatment groups. The measurement method used in our trial has previously been shown to be reliable: in a non-comparative phase 2 study (clinicaltrials.gov NCT01519778) of tedizolid done in 200 patients to assess different approaches to measurement of lesion area of acute bacterial skin and skin-structure infections with use of a flexible plastic ruler, response rates were consistent between all measurement methods and observers, and interobserver variability was low.[25,28] Another potential limitation is that our study population, most of whom originated from the community setting, had a somewhat lower incidence of comorbidities than reported for patients admitted to or already in the hospital treated for complicated skin and skin-structure infections in clinical practice.[29] Reasons include differences in how these patient populations have traditionally been defined, and the ethical requirement to exclude some highly comorbid patients

	Tedizolid phosphate (n=331)	Linezolid (n=327)	Difference (95% CI)
Patients with at least one serious treatment-emergent adverse event*	7 (2%)	9 (3%)	−0·6 (−3·3 to 1·9)
Any treatment-emergent adverse event†	148 (45%)	141 (43%)	1·6 (−6·0 to 9·2)
Nausea	26 (8%)	36 (11%)	−3·2 (−7·8 to 1·3)
Headache	20 (6%)	22 (7%)	−0·7 (−4·6 to 3·2)
Abscess	14 (4%)	10 (3%)	1·2 (−1·8 to 4·3)
Diarrhoea	11 (3%)	17 (5%)	−1·9 (−5·2 to 1·3)
Vomiting	10 (3%)	17 (5%)	−2·2 (−5·5 to 0·9)
Cellulitis	9 (3%)	6 (2%)	0·9 (−1·6 to 3·5)
Fatigue	8 (2%)	7 (2%)	0·3 (−2·2 to 2·8)
Dizziness	4 (1%)	7 (2%)	−0·9 (−3·3 to 1·2)
Vulvovaginal mycotic infection	2 (<1%)	7 (2%)	−1·5 (−3·8 to 0·3)
Infusion-site reactions	5 (2%)	7 (2%)	−0·6 (−3·0 to 1·6)
Any drug-related treatment-emergent adverse event‡	68 (21%)	81 (25%)	−4·2 (−10·6 to 2·2)

Data are n (%), unless otherwise indicated. *Serious treatment-emergent adverse events in the tedizolid group (n=1 patient each; none deemed related to study drug): myocardial infarction leading to death (in an elderly man with extensive medical history of coronary heart disease), *Escherichia* sp urinary tract infection, pneumonia and staphylococcal bacteraemia, septic shock, diabetes mellitus, hypertension, nephrolithiasis. Serious treatment-emergent adverse events in the linezolid group (n=1 patient each, unless otherwise indicated): tuberculous meningitis leading to death (in a 33-year old woman on day 14 of the study), anaphylactic reaction (deemed related to study drug), acute coronary syndrome, acute myocardial infarction, cellulitis (n=2), bacterial urinary tract infection, increased blood glucose, superficial thrombophlebitis. †Only treatment-emergent adverse events taking place in 2% or more of patients in either treatment group are shown. ‡Possibly, probably, or definitely related to study treatment.

Table 5: **Treatment-emergent adverse events in the safety population**

from initial phase 3 studies. Because we showed the non-inferiority of tedizolid to linezolid for treatment of acute bacterial skin and skin-structure infections, the results might be applicable to a broad range of patients with these infections, including patients with renal or hepatic impairment. Further investigation is warranted to confirm this assumption. Data suggest that severe hepatic or renal insufficiency, even the need for haemodialysis, do not affect the pharmacokinetics of tedizolid.[30,31]

Our results have potential implications for the care of patients with acute bacterial skin and skin-structure infections (panel). This study further confirms that a short 6 day course of tedizolid might offer an alternative to longer treatment durations recommended with linezolid or with other antibacterial drugs to which linezolid is non-inferior.[33] Moreover, a clinical response noted within 48–72 h seems to be indicative of sustained treatment success 1–2 weeks after the end of antibacterial therapy, as shown by the good concordance between early and late responses recorded in both this trial and in ESTABLISH-1.[18] Our results support the value of a step-down strategy with tedizolid, whereby patients treated for acute bacterial skin and skin-structure infections in an emergency department are given one intravenous dose before being discharged with oral drug after a fairly short period of observation (ie, up to 24 h). This approach is supported by the good response rates reported in patients who received only their initial dose intravenously, and by safety results suggesting that intravenous tedizolid was generally well tolerated. Many patients would probably benefit from outpatient oral tedizolid treatment only, in view of tedizolid's high bioavailability (>90%, with little interpatient variability);[19] this was shown in ESTABLISH-1, in which patients had similar baseline characteristics and disease severity, and treatment outcomes, as those enrolled in the present study.[18] Moreover, in patients needing hospital admission, the relatively short treatment duration with tedizolid might allow shorter hospital lengths-of-stay and could therefore also reduce the risk for various complications associated with exposure to health-care facilities.

Unlike other serious infections, such as pneumonia, no validated criteria are available to help clinicians identify patients with acute bacterial skin and skin-structure infections who are more likely to need hospital admission, and patterns of clinical practice that affect admission rates can vary widely between different countries. Related to this issue is our observation that patients from the USA received intravenous study drug for an average of about 2 days, whereas mean intravenous treatment outside the USA was about twice that long. In view of the multinational nature of this trial, varying practice patterns between countries (and even study sites)—which might be affected by administrative and reimbursement rather than clinical factors—probably contributed substantially to this difference. However, the study was not designed to assess this possibility, and the scarcity of available data about the reasons for de-escalation is a limitation of our trial. Future studies should aim to identify patient subsets that are likely to need sequential intravenous to oral or exclusively intravenous tedizolid treatment, rather than merely oral drug, to achieve successful treatment outcomes. Studies comparing other intravenous to oral regimens used in clinical practice (eg, vancomycin step-down to oral cephalosporins) with tedizolid might also be of interest. On the basis of our results and tedizolid's favourable pharmacological properties, clinical trials assessing tedizolid for the treatment of other types of infections,

***Panel:* Research in context**

Systematic review

As part of the ongoing tedizolid clinical development programme, EF, CDA, and PP undertook a systematic literature review in July, 2013, searching PubMed, Medline, Embase, and the open internet with the ProQuest Dialog platform and Google. Systematic searches included various predefined search strings relating to skin infections in general, meticilin-resistant *Staphylococcus aureus*, antibacterial drug resistance in Gram-positive pathogens, and safety events or concerns related to the use of tedizolid and other antibacterials. Results of this search suggested that: (1) acute bacterial skin and skin-structure infections, which are mainly caused by Gram-positive pathogens, are a significant cause of morbidity and hospital admissions; (2) resistance to antibacterials commonly used to treat acute bacterial skin and skin-structure infections (eg, β-lactam antibiotics) is an important health-care concern in various regions of the world, including the USA and parts of Europe, Latin America, and Asia; (3) resistance to and changing minimum inhibitory concentrations of other antibiotics used to treat meticillin-resistant strains (eg, vancomycin and linezolid) have been reported; and (4) antibacterial drugs approved for the treatment of meticillin-resistant strains can be associated with substantial safety (eg, thrombocytopenia and nephrotoxic effects) and dosing issues (even needing therapeutic drug monitoring in specific situations[32]). These search results emphasise the need for novel antibacterial drugs to treat acute bacterial skin and skin-structure infections. Tedizolid has a number of promising pharmacologic properties that make it a suitable candidate for clinical development in this setting.

Interpretation

ESTABLISH-2 is the first prospectively designed phase 3 trial using a study design consistent with all the fundamental elements included in the October, 2013, final guidance from the US Food and Drug Administration on the undertaking of clinical trials for antibacterial treatment of acute bacterial skin and skin-structure infections. Our results show that a 6-day course of tedizolid phosphate 200 mg once daily is a viable alternative to 10 days of linezolid 600 mg twice daily for the treatment of patients with acute bacterial skin and skin-structure infections, with non-inferior efficacy and better gastrointestinal tolerability. Furthermore, our data suggest that tedizolid can be started as an intravenous infusion and the subsequent treatment course completed with oral drug at equivalent dosage. In view of the similarities between patient populations and outcomes in this study and another phase 3 trial[18] in which tedizolid was given orally only, most patients with acute bacterial skin and skin-structure infections could be treated exclusively with oral drug. Additional research is needed to help clinicians readily identify patients who could be successfully treated as outpatients as early as possible in the course of treatment. This trial adds to prospectively collected evidence showing that early, objective treatment response assessed at 48–72 h is highly indicative of clinical success at later time points.

including those needing longer-term dosing, seem to be warranted.

Tedizolid could become a useful option for the treatment of acute bacterial skin and skin-structure infections in both the hospital and outpatient settings.

Contributors

PP, CDA, AFD, GRC, and GJM contributed to study conception and design. EF and CDA were responsible for running the trial. GJM participated in data collection and enrolment of patients. AFD was responsible for data analysis. GJM, GRC, EF, AFD, CDA, and PP participated in interpretation of the results. EF and PP prepared the first draft of the manuscript. All authors participated in further development of the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interests

GJM has received speaker honoraria from Cubist Pharmaceuticals and Forest Laboratories and has received research support from Cubist Pharmaceuticals (for participation in this trial) and from Cerexa. EF, CDA, and PP are employees of Cubist Pharmaceuticals. GRC has been a clinical trial adjudicator for Cubist Pharmaceuticals and Pfizer; a scientific advisor to Achaogen, Cempra, Forest Laboratories/Cerexa, Rib-X, The Medicines Company, Theravance, and Trius Therapeutics (a subsidiary of Cubist Pharmaceuticals); a consultant to Achaogen, Cempra, Contrafect, Cubist Pharmaceuticals, Forest Laboratories/Cerexa, Furiex, GlaxoSmithKline, Rib-X, The Medicines Company, and Theravance; and a principal investigator for Cempra, Forest Laboratories/Cerexa, GlaxoSmithKline, The Medicines Company, and Theravance. AFD is a consultant to Cubist Pharmaceuticals and was compensated for supporting this research and is also a consultant to Cempra, Cerexa, Durata, Nabriva, and Paratek.

Acknowledgments

This study was funded by Cubist Pharmaceuticals. We thank the study participants and the investigators and study coordinators involved in this clinical trial, and Dominik Wolf (Cubist Pharmaceuticals) for medical writing support. These data have been previously presented in part at the 23rd European Congress of Clinical Microbiology and Infectious Diseases; Berlin, Germany; April 27–30, 2013. LB 2964.

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