Advancing mRSA Management:
A New Force for the Clinicians

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- Co-founder and Past President of the International Society of Anti-infective Pharmacology (ISAP)
- Member of General Assembly (2006-) and of the Steering Committee (2008-2010) of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Singapore
Kuala-Lumpur
Malaysia

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Disclosures

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  – the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
  – The European Union for applied research on optimisation of β-lactams treatments through on-line monitoring of free serum levels
  – *Université catholique de Louvain* for past personal support

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  – AstraZeneca, GSK, Sanofi-Aventis, Bayer, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …

Other past and present relationships in relation to this talk

– Belgian Antibiotic Policy Coordination Committee (BAPCOC)
– European Committee for Antibiotic Susceptibility Testing (EUCAST)
– European Medicines Agency (EMA)
– Drive-AB (a EU programme for a new economical framework for antibiotics)

Slides: http://www.facm.ucl.ac.be → Lectures
The programme…

• A very short view of Belgium and of where I work…

• Brief overview of tedizolid as a new anti-MRSA agent

• Tedizolid vs. linezolid: PK/PD – resistance – safety

• How tedizolid fits into an antibiotic stewardship program (shortening antibiotic courses)

• Areas of planned future studies and enlarged published clinical experience *

• Questions, objections, suggestions …

* may include off-label usages
Belgium
The Catholic University of Louvain in brief

- Created in 1425, it was one of the major University of the so-called "Low Countries" in the 1500 – 1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy, …). Teaching was in Latin, Greek, and Hebrew (College of the 3 languages…)

The University in the 1500's
Erasmus
Vesalius
The Catholic University of Louvain in brief

- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities...

- in 1968, the University was divided into
  - a French-speaking Université catholique de Louvain
  - a Flemish-speaking Katholieke Universiteit Leuven...

Professor C. de Duve, Professor of Biochemistry, obtained the Nobel Prize (Physiology and Medicine) in 1974 for his work on intracellular organelles (lysosomes, peroxisomes…) (here in front of a centrifuge)
The Catholic University of Louvain in brief (4 of 4)

- The Flemish-speaking *Katholieke Universiteit Leuven* has remained in Louvain (Leuven) and is named in English "Catholic University Leuven".

- The French-speaking *Université catholique de Louvain* has moved about 25 km South in a place called "Louvain-la-Neuve, with the "Health Sciences Sector" located in Brussels (Woluwe).

- Together, the two sister Universities have about **60,000 students**
What do we do?

- Teaching of pharmacology and pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective pharmacology
- 30 graduating students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

- Toxicity, medicinal chemistry, and improved schedules of aminoglycosides
- novel antibiotics
  - beta-lactams (ceftaroline...)
  - fluoroquinolones (delafloxacin *...)
  - Fab inhibitors (Debio1462 ** ...
  - oxazolidinones (tedizolid ...)
  * recently approved; ** in development

- re-assessment of older antibiotics

www.facm.ucl.ac.be

- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

www.isap.org

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), with the Institute (framed), located in then the outskirts of Brussels, Belgium
Why should a Belgian come so far to speak about tedizolid?
Why should a Belgian come so far to speak about tedizolid?

to find a better environment?

to leave this?
Because we have been working on tedizolid since 2007 …

called "torezolid"
or TR-700
at that time…

doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009

Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

Sandrine Lemaire¹, Françoise Van Bambeke¹, Peter C. Appelbaum² and Paul M. Tulkens¹∗

¹Unité de Pharmacologie cellulaire et moléculaire & Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; ²Hershey Medical Center, Hershey, PA 17033, USA
The programme…

• A very short view of Belgium and of where I work…

• **Brief overview of tedizolid as a new anti-MRSA agent**

  • Tedizolid vs. linezolid: PK/PD – resistance – safety

  • How tedizolid fits into an antibiotic stewardship program (shortening antibiotic courses)

• Areas of planned future studies and enlarged published clinical experience *

• Questions, objections, suggestions …

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Where does tedizolid come from?

Now Dong-A ST
From linezolid to tedizolid: the basics

Linezolid (LZD)

Tedizolid (TR-700)

Substantial differences that DO impact on
- intrinsic activity *(more potent)*
- activity against LZD-resistant strains
- half-life *(longer)*
Tedizolid is systematically 3-4-x more active than linezolid against LSDS strains

Tedizolid is systematically 3-4-x more active than linezolid against LSDS strains.

Table 1. Susceptibility of the strains of *S. aureus*, *L. monocytogenes* and *L. pneumophila* used in this study to linezolid and torezolid

<table>
<thead>
<tr>
<th>Species, phenotype and strain no.</th>
<th>linezolid</th>
<th>torezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA ATCC 25923&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>HA-MRSA ATCC 33591&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
<td>0.125–0.25</td>
</tr>
<tr>
<td>SA 238&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>CM 05&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>CA-MRSA NRS 192&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2</td>
<td>0.125–0.25</td>
</tr>
<tr>
<td>NRS 384 (US300)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>VISA NRS 52&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>VRSA VRS 1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1–2</td>
<td>0.125–0.25</td>
</tr>
<tr>
<td>VRS 2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1–2</td>
<td>0.25</td>
</tr>
<tr>
<td>animal MRSA N7112046&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td><strong>Listeria monocytogenes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGD&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1–2</td>
<td>0.125</td>
</tr>
<tr>
<td><strong>Legionella pneumophila</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATCC 33153&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4–8</td>
<td>0.25–0.5</td>
</tr>
</tbody>
</table>

LZD<sup>r</sup>, resistant to linezolid.
<sup>a</sup>Representative values of at least two determinations.
<sup>b</sup>From the American Tissue Culture Collection (Manassas, VA, USA).
<sup>c</sup>Provided by P. C. Appelbaum.<sup>36</sup>
<sup>d</sup>Provided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.
<sup>e</sup>From the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARS)<sub>8</sub> programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN27220070005C); details on each strain are available at http://www.narsa.net/content/home.jsp.
<sup>f</sup>Provided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.
<sup>g</sup>Provided by P. Berche, Hôpital Necker, Paris, France.<sup>28</sup>

And also for a large-scale survey of different Gram-positive organisms from multiple US and European sites

- **S. aureus** (n=4499)
  - % of isolates at MC
  - MIC (µg/mL): 0.0, 0.2, 0.3, 0.5, 1, 2, 4, >4

- **Coagulase (-) staphylococci** (n=537)
  - % of isolates at MC
  - MIC (µg/mL): 0.0, 0.25, 0.5, 1, 2, 4, >4

- **Enterococci** (n=873)
  - % of isolates at MC
  - MIC (µg/mL): 0.0, 0.2, 0.3, 0.5, 1, 2, 4, >4

- **β-haemolytic streptococci** (n=975)
  - % of isolates at MC
  - MIC (µg/mL): 0.0, 0.125, 0.25, 0.5, 1

And also for another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

Activities of Tedizolid and Linezolid Determined by the Reference Broth Microdilution Method against 3,032 Gram-Positive Bacterial Isolates Collected in Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

Michael A. Pfaller, a,b Robert K. Flamm, a Ronald N. Jones, a David J. Farrell, a Rodrigo E. Mendes a
JMI Laboratories, North Liberty, Iowa, USA; University of Iowa College of Medicine, Iowa City, Iowa, USA b

And also for another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

Activities of Tedizolid Broth Microdilution Isolates Collected in Countries in 2014

Michael A. Pfaller, a,b Robert K. Flamm
JMI Laboratories, North Liberty, Iowa, USA; University of Illinois, Chicago, Illinois, USA

S. aureus (all; n=2382)

Cumulative percentage

m g/L

0 0.015625 0.03125 0.0625 0.1 0.25 0.5 1 2 4 8

Tedizolid
Linezolid

And also for another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014.

Activities of Tedizolid Broth Microdilution Isolates Collected in Countries in 2014

Michael A. Pfaller,¹ b Robert K. Flamm
JMI Laboratories, North Liberty, Iowa, USA; University of Kentucky, Lexington, Kentucky, USA

E. faecalis (n=193)

0.03 0.0625 0.125 0.25 0.5 1 2 4 8 m g/L

cumulative percentage

100 75 50 25 0

tedizolid
linezolid

Tedizolid is also active against resistant blood stream infection (BSI) isolates

Broad In Vitro Activity Analysis of Tedizolid Compared with Other Agents against a Global Collection of Gram-Positive Isolates Causing Bloodstream Infections (2014–2016)

Sites of origin: USA (31), Europe (40), Turkey (2), Latin America (8), Asia-Pacific (16)


Tedizolid and MSSA/MRSA

Tedizolid and *E. faecium* Van S/Van R

Sites of origin: USA (31), Europe (40), Turkey (2), Latin America (8), Asia-Pacific (16)
The programme…

• A very short view of Belgium and of where I work…

• Brief overview of tedizolid as a new anti-MRSA agent

• **Tedizolid vs. linezolid: PK/PD – resistance – safety**

• How tedizolid fits into an antibiotic stewardship program (shortening antibiotic courses)

• **Areas of planned future studies and enlarged published clinical experience** *

• Questions, objections, suggestions …

* may include off-label usages
Tedizolid clinical presentations

Tedizolid phosphate

- Active pharmaceutical ingredient: stable at room temp for >2 yrs
- 2 formulations:
  - IV Lyophile: TR-701 FA Lyophilised Vial for Injection, 200 mg
  - Oral Tablet: TR-701 FA Immediate Release Tablet, 200 mg

Tablets can be crushed in water and tedizolid phosphate remains stable for at least 4h

Tedizolid: key PK/PD parameters and breakpoints

- excellent oral bioavailability (IV ~ oral)

- long half-life (~12 h)
  (with concentrations > 0.5 mg/L for ~18 h)

- activity dependent from the AUC$_{24h}$ (total daily dose/clearance) irrespective of the dosing scheme (Q8, Q12, Q24)

  ✓ ONCE daily dosing (oral or IV) @ 200 mg
  ✓ breakpoint: S ≤ 0.5 mg/L – R > 0.5 (EUCAST) or ≥ 2 (FDA)

- elimination mainly by the faeces

  ✓ no need of dose adjustment in patients with renal impairment or in hemodialysis
Tedizolid has a longer half-life than linezolid → once-daily dosing is possible

Tedizolid:
- mean $t_{1/2} \sim 2 \times$ that of linezolid
- $18h$ presence > breakpoint (0.5 mg/L) vs. $12h$ for linezolid (4 mg/L).

This allows for a once-a-day dosing

Muñoz et al. ECCMID 2010 P1594
AUC$_{24h}$ and activity tedizolid

TZD activity depends on actual $f$ AUC$_{24h}$/MIC value, and is independent of the dosing schedule (in the limits investigated)

Tedizolid elimination is largely not through the kidney …

- When using $^{14}$C-labelled tedizolid phosphate, in humans, most of the radioactivity is excreted in faeces

Impact of variations in excretory functions on tedizolid pharmacokinetics

Tedizolid has also been shown to have predictable PKs in the following patient groups:

- **Moderate hepatic impairment**
  (Child-Pugh score 7–9)
- **Severe hepatic impairment**
  (Child-Pugh score 10–15)
- **Elderly** (age 66–78)
- **Obese and morbidly obese**
- **Ethnic populations**
- **No exposure difference between fasted and fed conditions**

Tedizolid pharmacokinetics for patients with severe renal impairment
(eGFR < 30 mL/min/1.73 m²)

Tedizolid distributes equally in muscle and adipose tissue (microdialysis) compared to plasma

- Subjects administered a single oral dose of 600 mg tedizolid phosphate (prodrug)
- Microdialysis probes into the subcutaneous adipose tissue and into the muscle
- Analysis by high-performance liquid chromatography with UV detection

Tedizolid accumulates in lung macrophages (and fluid) of healthy adults volunteers (200 mg dose)

Tedizolid is active in neutropenic mice

Use Of Translational PK/PD Infection Models to Understand Impact of Neutropenia on Efficacy of Tedizolid Phosphate

Tedizolid is also active against linezolid-resistant isolates (cfr+)
Oxazolidinones: the cfr+ mechanism of resistance

- plasmid-mediated ¹
- First identified in animals and then in clinical isolates ²,³
- acting through C-8 methylation of the a ribosomal adenine (A2503) ⁴,⁵
- causes cross-resistance to linezolid and 5 drug classes (phenicols, lincasamides, pleuromutilins, streptogramins and 16-membered macrolides) ⁶,⁷
- present now in Europe ⁸,⁹ and in China ¹⁰

¹ Toh et al. Mol Microbiol 2007;64:1506-14 - PMID 17555436
⁵ Giessing et al. RNA 2009;15:327-36 - PMID 19144912
⁷ Smith & Mankin. Antimicrob Agents Chemother 2008;52:1703-12 - PMID 18299405
¹⁰ Bi et al. J Glob Antimicrob Resist 2017;pii:S2213-7165(17)30205-9 - PMID 29101082
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1. Toh et al. Mol Microbiol 2007;64:1506-14 - PMID 17555436
5. Giessing et al. RNA 2009;15:327-36 - PMID 19144912

FIG. 1. Binding of the phenicol, lincosamide, pleuromutilin, and streptogramin A classes of antimicrobials to overlapping sites at the ribosomal peptidyl transferase center. (A) The structure of the bacterial 50S ribosomal subunit showing the slice plane used in panel B. (B) An expanded view showing the structures of four drugs bound at the peptidyl transferase center. The structural data can be found in reference 22 and references therein. The names and chemical structures of the four antimicrobial agents are shown at the bottom on background colors that correspond to the bound structures (depicted in stick representation). The target of the Cfr methyltransferase, nucleotide A2503, is shown in red. The surrounding RNA is shown in light gray. (C) The Cfr-mediated resistance patterns with S. aureus for chloramphenicol, clindamycin, tiamulin, and virginiamycin M1. The data are from Table 1. The MICs are depicted on a logarithmic scale with strains lacking Cfr shown in the left column of each pair of bars (marked −), whereas those of strains containing Cfr are shown in the right column of each pair of bars (marked +). The numbers above the +Cfr columns are the n-fold differences in MICs between −Cfr and +Cfr strains. Details on the visualization of the 50S ribosomal subunit and antibiotic-50S subunit complexes are provided in Materials and Methods.
Oxazolidinones: the \textit{cfr}+ mechanism of resistance

• plasmid-mediated \textsuperscript{1}
• First identified in animals and then in clinical isolates \textsuperscript{2,3}
• acting through C-8 methylation of the a ribosomal adenine (A2503) \textsuperscript{4,5}
• causes cross-resistance to linezolid and 5 drug classes (phenicols, lincasamides, pleuromutilins, streptogramins and 16-membered macrolides) \textsuperscript{6,7}
• present now in Europe \textsuperscript{8,9} and in China \textsuperscript{10}

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5  Giessing et al. RNA 2009;15:327-36 - PMID 19144912
7  Smith & Mankin. Antimicrob Agents Chemother 2008;52:1703-12 - PMID 18299405
10 Bi et al. J Glob Antimicrob Resist 2017;pii:S2213-7165(17)30205-9 - PMID 29101082

• Tedizolid retains full potency against \textit{cfr}+ strains and we know why… (see next slides)

1  Shaw et al. Antimicrob Agents Chemother. 2008;52:4442-7 - PMID 18838596
Why is tedizolid active against LZD<sup>R</sup> strains (cfr)?

LZD

TR700

FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound <i>H. marismortui</i> 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome. Substantial steric hindrance between the LZD C-5 acetamide group and the 23S rRNA base A2503 carbon-8 methyl (bonds shown in brown) likely contributes to reduced binding affinity (B). As modeled, the TR-700 hydroxymethyl substituent does not display this steric clash with the A2503 methyl group (D), explaining its retained activity against cfr strains. A group of PTC bases were removed from the images to improve clarity. Images were generated with PyMOL (16).

Why is tedizolid active against LZDr strains (cfr)?

How to report tedizolid susceptibility?

SPECIAL REPORT
For reprint orders, please contact: reprints@futuremedicine.com

Susceptibility testing and reporting of new antibiotics with a focus on tedizolid: an international working group report

Mark H Wilcox¹, Natalia Dmitrieva², Ana Cristina Gales³, Irina Petukhova³, Suleiman Al-Obeidi⁴, Flavia Rossi⁵ & Joseph M Blondeau⁶

How to report tedizolid susceptibility?

Susceptibility testing and new antibiotics with a new international working group.

Mark H Wilcox¹, Natalia Dmitrieva², Ana Cristina Suleiman Al-Obeid³, Flavia Rossi⁴ & Joseph Marrie⁵.

Figure 1. Recommended approach for routine reporting of susceptibility of new antibiotics, for example, tedizolid.

¹Use of broth microdilution is also applicable.  
As recommended by published evidence/according to susceptibility testing guidance [42,47].  
NS: Nonsusceptible; S: Susceptible.

A summary for tedizolid at this point?

Chemistry and microbiology

- 3-4 x more potent than linezolid across all Gram-positive pathogens *
- active against cfr+ linezolid-resistant strains
- active against intracellular *S. aureus* and other intracellular bacteria **

Pharmacokinetics, breakpoints, tissue distribution…

- longer half-life than linezolid → once daily dosing
- No need of dose readjustment (renal or hepatic failure, weight…)
- 200 mg/day covers for MICs up to 0.5 mg/L (EU) or 1 mg/L (USA)
- penetrate in muscle and adipose tissue, and in lung macrophages ***

---

* MICs are 4-8 mg/L for *Moraxella, Pasteurella* and *Bacteroides* spp. but other Gram-negative bacteria are resistant as a result of endogenous efflux activity (Livermore DM J Antimicrob Chemother 2003;51(Suppl 2):ii9-16 - PMID 12730138)


*** Linezolid penetrates the central nervous system (Tsona et al. J Chemother 2010;22:17-9 - PMID 20227987); see slides 80-84 for tedizolid activity against intracerebral nocardiosis
A summary for tedizolid at this point?

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- penetrate in muscle and adipose tissue, and in lung macrophages

* Legonella pneumophila and Listeria monocytogenes (Lemaire et al. JAC 2010; 64:1035–1043)

but what about safety?

Linezolid adverse effects

• Drug interactions:
  – cytochrome P450: no special effect
  – antibiotics: rifampin causes a 21 % ↓ in LZD serum levels
  – **Monoamine Oxidase Inhibition** (reversible, nonselective inhibitor):
    ↩ adrenergic and serotonergic agents (PRECAUTIONS)
• **Myelosuppression** (including anaemia, leukopenia, pancytopenia, and thrombocytopenia) (WARNING)
• Hypoglycaemia
• **Lactic acidosis** (PRECAUTION – Immediate medical attention)
• **Peripheral and Optic Neuropathy** (> 28 days)
• Convulsions

From: ZYVOX® prescribing information – Pfizer Inc., NY, NY - 1/2017
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From: ZYVOX® prescribing information – Pfizer Inc., NY, NY - 1/2017
Monoamine Oxidase (MAO) Substrate Specificity *

Consequences of MAO-A Inhibition

Serotonin Syndrome

Hypertensive crisis

MAO-A

Serotonin

Noradrenaline

Adrenaline

Octopamine

Dopamine

Tyramina

Tryptamine

Kynuramine

3-methoxytyramine

MAO-B

Benzylamine

Phenylethylamine

N-phenylamine

Octylamine

N-acetylputrescine

Milacemide

N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

* Linezolid inhibits both enzymes, causing increased concentration of these bioamines ...

* MAO-A is the predominant form for oxidation of tyramine

Is serotonergic syndrome an important problem?

Spectrum of Clinical Findings

Manifestations of the serotonin syndrome range from mild to life-threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single patient with the serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia.

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No effect of tedizolid on monoamine oxidase in experimental and human studies

In Vitro, In Vivo, and Clinical Studies of Tedizolid To Assess the Potential for Peripheral or Central Monoamine Oxidase Interactions

S. Flanagan,* K. Bartzik,* S. L. Minassian,* E. Fang,* P. Prokocimer*
Trius Therapeutics, Inc., San Diego, California, USA; Minassian Biostatistics, Inc., San Diego, California, USA

5-HTP Mouse Head Twitch *(Model of Serotonergic Effects)

* The head-twitch response (HTR) is a rapid side-to-side head movement that occurs in mice and rats after the serotonin 5-HT2A receptor is activated (Nakagawasai et al. Neurotoxicology. 2004;25:223-32 - PMID: 14697897)

FIG 3  Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD (n = 8 mice/group). Tedizolid refers to tedizolid phosphate. *, P < 0.05 versus the control group.

Human data for blood pressure response to pseudoephedrine (60 mg) vs placebo in tedizolid-pretreated patients

FIG 2 Blood pressure response to 60 mg pseudoephedrine in placebo- and tedizolid phosphate-pretreated study populations. Patients (n = 18) were randomized to oral placebo or oral tedizolid phosphate doses of 200 mg per day for 4 days; on the fifth day, 60 mg pseudoephedrine was administered with the morning dose of placebo or tedizolid phosphate, and blood pressure was recorded over the subsequent 24 h. Blood pressure was measured within 15 min prior to drug administration (Pre), every hour for 8 h after study drug administration, and at 10, 12, and 24 h.

Linezolid adverse effects

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From: ZYVOX® prescribing information – Pfizer Inc., NY, NY - 1/2017
Linezolid adverse effects

- Drug interactions:
  - cytochrome P450: no special effect
  - antibiotics: rifampin causes a 21% decrease in LZD serum levels
  - Monoamine Oxidase Inhibition (reversible, nonselective inhibitor):
    - adrenergic and serotonergic agents (PRECAUTIONS)

- Myelosuppression (including anaemia, leukopenia, pancytopenia, and thrombocytopenia) (WARNING)

- Hypoglycaemia

- Lactic acidosis (PRECAUTION – Immediate medical attention)

- Peripheral and Optic Neuropathy (> 28 days)

- Convulsions

No effect of tedizolid on platelet counts in phase I (21 days) study

Characterization of the haematological profile of 21 days of tedizolid in healthy subjects

Thomas P. Lodise1*, Monique R. Bidell1, Shawn D. Flanagan2, Evan J. Zasowski1, Sonia L. Minassian3 and Philippe Prokocimer2
Linezolid adverse effects

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- Hypoglycaemia

- Lactic acidosis (PRECAUTION – Immediate medical attention)

- Peripheral and Optic Neuropathy (> 28 days)

- Convulsions

A long-term (9 months) animal study showed no evidence of neurotoxic effects of tedizolid
A summary of tedizolid preclinical safety attributes…

- **Drug-Drug Interactions**
  - No inhibition or induction of human hepatic cytochrome P450 activities at high concentrations *
  - No tyramine or noradrenergic "Pressor potentiation Effect" (vs significant effect for linezolid) (see previous slides)
  - No serotonergic effect in head twitch model (see previous slides)

- **Other potential pharmacological issues**
  - No effects in pivotal cardiovascular, neurobehavioral, respiratory, or gastrointestinal systems *
  - No IKr or QTc signal with TR-700 at highest soluble dose *
  - No non-clinical genetic toxicology signals: Ames, Chrom Ab, Micronucleus, UDS *
  - No genotoxicity or reprotoxicity issues *
  - No effect on spermatogenesis *

* not shown here but see registration data (FDA / EMA)
The programme…

• A very short view of Belgium and of where I work…

• Brief overview of tedizolid as a new anti-MRSA agent

• Tedizolid vs. linezolid: PK/PD – resistance – safety

• **How tedizolid fits into an antibiotic stewardship program (shortening antibiotic courses)**

• Areas of planned future studies and enlarged published clinical experience *

• Questions, objections, suggestions …

* may include off-label usages
Do we need short antibiotic courses?

Managing skin and soft-tissue infection and nosocomial pneumonia caused by MRSA: a 2014 follow-up survey

Matthew Dryden a,⁎, Arjana Tambic Andrasevic b, Matteo Bassetti c, Emilio Bouza d, Jean Chastre e,f, Mo Baguneid g, Silvano Esposito h, Helen Giamarellou i, Inge Gyssens j,k,l, Dilip Nathwani m, Serhat Unal n, Andreas Voss o, Mark Wilcox p

Treatment duration can be obtained when early switch/early discharge is implemented

Antibiotic treatment patterns across Europe in patients with complicated skin and soft-tissue infections due to meticillin-resistant Staphylococcus aureus: A plea for implementation of early switch and early discharge criteria

Christian Eckmann, Wendy Lawson, Dilip Nathwani, Caitlyn T. Solem, Jennifer M. Stephens, Cynthia Macahilig, Damien Simoneau, Petr Hajek, Claudie Carbonneau, Richard Chambers, Jim Z. Li, Seema Haider

Do we have criteria? Back to future!

Desai et al. BMC Infect Dis. 2006;6:94 - PMID 16762061

Criteria for Early Switch / Early Discharge

**Table 1: IV to oral switch inclusion criteria used**

1. Clinical status
   - Temperature less than 38°C for 24 hours
   - White cell count normalising
   - No unexplained tachycardia (Heart rate less than 100 beats per minute)
   - Sensitivity received (if microbiology positive)

2. Oral absorption
   - Patient tolerates oral fluids
   - No medical problems leading to reduced oral absorption (e.g. vomiting, diarrhoea, and gastrointestinal surgery)
   - No surgical operation scheduled within next 36 hours

**Table 2: IV to oral switch exclusion criteria used**

1. Continuing sepsis
   - Temperature less than 36°C or more than 38°C
   - White cell count less than $4 \times 10^9/L$ or more than $12 \times 10^9/L$
   - Unexplained tachycardia (Heart rate greater than 100 beats per minute in last 12 hours)

2. Oral route compromised
   - Vomiting or severe diarrhoea
   - Other ongoing or potential absorption problem
Early Switch should be part of a policy

Adapted from:
Can we do it with a new drug?

Am I OK to go home?
Tedizolid phase III studies

**ORIGINAL CONTRIBUTION**

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections
The ESTABLISH-1 Randomized Trial

Philipe Prokocimer, MD
Carisa De Anda, PharmD
Edward Fang, MD
Purvi Mehta, MD
Anita Das, PhD

Importance  Acute bacterial skin and skin structure infections (ABSSSIs), including cellulitis or erysipelas, major cutaneous abscesses, and wound infections, can be life-threatening and may require surgical and hospitalization. Increasingly, ABSSSIs are associated with drug-resistant pathogens, and many antimicrobial regimens have adverse effects restricting their use. Tedizolid phosphate is a novel oxazolidinone in development for the treatment of ABSSSIs.


**Articles**

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

Gregory J Moran, Edward Fang, G Ralph Corey, Anita F Das, Carisa De Anda, Philippe Prokocimer

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.

Tedizolid phase III studies

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections
The ESTABLISH-1 Randomized

- **tedizolid**: 200 mg **once daily** for 6 days
- **linezolid**: 600 mg **twice daily** for 10 days (as per label)

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

**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.

ESTABLISH-1 and -2 Integrated Efficacy: All Efficacy Endpoints Achieved

ITT Analysis Set*

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Tedizolid N=664</th>
<th>Linezolid N=669</th>
</tr>
</thead>
<tbody>
<tr>
<td>48-72 hours (≥20% lesion area reduction)</td>
<td>81.6</td>
<td>79.4</td>
</tr>
<tr>
<td>Day 11 (End of therapy)</td>
<td>87.0</td>
<td>87.9</td>
</tr>
<tr>
<td>Days 7-14 post-EOT (Investigator assessed response)</td>
<td>86.7</td>
<td>86.8</td>
</tr>
</tbody>
</table>

- 2.2 (-2.0; 6.5)
- 0.8 (-4.4; 2.7)
- 0.1 (-3.8; 3.6)

* Pooled data

ESTABLISH-1 and -2 Integrated Efficacy: Non-inferiority Achieved in Each Infection Type

Early Clinical Response Rate at 48–72 h. ITT Analysis Set*

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Tedizolid N=664</th>
<th>Linezolid N=669</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis/erysipelas</td>
<td>75.7</td>
<td>74.3</td>
</tr>
<tr>
<td>Major cutaneous abscess</td>
<td>85.7</td>
<td>86.7</td>
</tr>
<tr>
<td>Wound infection</td>
<td>87.2</td>
<td>81.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample Size</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n=301</td>
<td>n=307</td>
</tr>
<tr>
<td>n=168</td>
<td>n=166</td>
</tr>
<tr>
<td>n=195</td>
<td>n=196</td>
</tr>
</tbody>
</table>

* Pooled data

ESTABLISH-1 and -2 Integrated Efficacy
(by relevant host and disease factors (A) and baseline severity measures (B) in the ITT population)

MRSA and MSSA eradication rates are equivalent for tedizolid 200 mg 6 days vs linezolid 600 mg 10 days

* Pooled data

Tedizolid Use was Associated with Overall Reduced Risk of Myelosuppression

Patients with reduced platelet counts during the entire study period

Tedizolid was associated with a significantly lower risk of developing thrombocytopenia. Tedizolid is not known to increase the risk of anaemia, leukopenia, or pancytopenia.


FIG 3 Patients with platelet counts below the lower limit of normal (LLN) (<150,000 cells/mm³) over time. *, P < 0.05. EOT, end-of-therapy.

LLN = lower limit of normal.
What about comparisons with other anti-MRSA drugs?

Systematic review and network meta-analysis of tedizolid for the treatment of acute bacterial skin and skin structure infections caused by MRSA

Rachael McCool¹, Ian M. Gould², Jacqui Eales¹, Teresa Barata³, Mick Arber¹, Kelly Fleetwood³, Julie Glanville¹ and Teresa L. Kauf¹

BMC Infect Dis. 2017 Jan 7;17(1):39 – PMID: 28061827
What about comparisons with other anti-MRSA drugs?

Systematic review and network meta-analysis of teicoplanin for the treatment of acute infections

Rachael McCord and Teresa L.

Fig. 2  Network diagram of studies of ABSSSI treatment

BMC Infect Dis. 2017 Jan 7;17(1):39 – PMID: 28061827
What about comparisons with other anti-MRSA drugs?

Fig. 3  Clinical response at the end of treatment: all trials. Odds ratios (fixed-effects model)
What about comparisons with other anti-MRSA drugs?

**Fig. 5** Discontinuation due to adverse events: all trials. Odds ratios (fixed-effects model)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds Ratio (95% CI/CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tedizolid v Linezolid</td>
<td>0.2 [0.0, 2.2]</td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td>0.5 [0.1, 1.9]</td>
</tr>
<tr>
<td>Tedizolid v Ceftaroline</td>
<td>0.3 [0.0, 7.1]</td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td>0.8 [0.0, 45.8]</td>
</tr>
<tr>
<td>Tedizolid v Daptomycin</td>
<td>0.3 [0.0, 1.3]</td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td>0.3 [0.0, 1.3]</td>
</tr>
<tr>
<td>Tedizolid v TelaVanCin</td>
<td>0.3 [0.0, 1.3]</td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td>0.3 [0.0, 1.3]</td>
</tr>
<tr>
<td>Tedizolid v Vancomycin</td>
<td>0.4 [0.1, 1.8]</td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td>0.4 [0.1, 1.8]</td>
</tr>
</tbody>
</table>
Summary – clinical data * and perspectives

- Non-inferior to linezolid overall and in all infection types tested (ABSSSIs)
  - with a shorter duration of therapy (6 days vs 10 days)
  - a lower daily dose (200 mg/day vs 1200 mg/day)
  - a simplified schedule of administration (once daily)

- High eradication rates against Gram-positive pathogens

- Well tolerated with no serious AE occurring related to tedizolid **

- Significantly lower incidence of gastrointestinal adverse events vs linezolid; irrespective of treatment duration **

- Significantly lower risk of developing thrombocytopenia vs linezolid

* as shown in this presentation; ** ask for back-up slides
Summary – clinical data and perspectives

- Non-inferior to linezolid overall and in all infection types tested (ABSSSIs)
  - with a shorter duration of therapy (6 days vs 10 days)
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- Significantly lower incidence of gastrointestinal adverse events vs linezolid; irrespective of treatment duration
- Significantly lower risk of developing thrombocytopenia vs linezolid

Compare also with the other available antibiotics that you have used so far …
A recent expert opinion …

Tedizolid in skin and skin structure infections: brave new world?
Periklis Panagopoulos\textsuperscript{a}, Nikolaos Papanas\textsuperscript{b} and Efstratios Maltezos\textsuperscript{a}

\textsuperscript{a}Unit of Infectious Diseases, Second Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis, Greece; \textsuperscript{b}Diabetic Foot Clinic, Diabetes Centre, Second Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis, Greece

"Tedizolid has demonstrated excellent activity against broad spectrum aerobic and facultative anaerobic gram-positive bacteria.

Other advantages include the availability of both oral and intravenous routes of administration, the short course of therapy, the convenient dosing scheme, and the trend toward less hematological toxicity.

Taken these advantages into consideration, tedizolid appears increasingly preferable to linezolid in ABSSSIs."

The programme…

• A very short view of Belgium and of where I work…

• Brief overview of tedizolid as a new anti-MRSA agent

• Tedizolid vs. linezolid: PK/PD – resistance – safety

• How tedizolid fits into an antibiotic stewardship program (shortening antibiotic courses)

• **Areas of planned future studies and enlarged published clinical experience** *

• Questions, objections, suggestions …

_______

* may include off-label usages
New expected data on tedizolid from the company

Tedizolid Phosphate (TR-701 FA) vs Linezolid for the Treatment of Nosocomial Pneumonia (MK-1986-002)

This study is currently recruiting participants.

See [Contacts and Locations](https://clinicaltrials.gov/ct2/show/record/NCT02019420) - Last visited: 14 Nov 2017

Verified November 2017 by Cubist Pharmaceuticals LLC

Sponsor:
Cubist Pharmaceuticals LLC

ClinicalTrials.gov Identifier:
NCT02019420

First Posted: December 24, 2013
Last Update Posted: November 8, 2017

35 centres worldwide
1. Microbiology (1 of 2)

Tedizolid possessed a potent *in vitro* activity against most of the BJI Gram-positive pathogens with 95% of them exhibiting a MIC ≤0.5 mg/L.

PJ I S. *epidermidis* were fully susceptible ...(MIC$_{50}$ and MIC$_{90}$ 2 to 4 dilution than linezolid).

Results may warrant evaluation of *tedizolid* as a potential treatment option for *Nocardia* infections.
The CARTM regimen promises to have kill rates better than standard therapy.

Tedizolid, at standard clinical doses, achieved an unprecedented $2.0 \log_{10} \text{cfu/mL}$ kill of MAC as monotherapy.

- MIC$_{50/90}$ lower (1-8x) than linezolid (MIC$_{90}$ [mh/L]: M. abscessus: 4-8; M. fortuitum: 2; M. chelonae: 2; M. marinum: $\leq 1$; MIC$_{50}$ [mg/L]: M. avium complex 8; M. arupense: 4).
- Evaluation of tedizolid as a potential treatment is warranted.
2. New applications

Tedizolid alone or tedizolid combined with rifampin was active in a rat model of MRSA foreign body-associated osteomyelitis.

Tedizolid combined with rifampin was active in a rat model of MRSE foreign body-associated osteomyelitis.

We describe a case involving the safe and successful use of tedizolid, a new oxazolidinone, to treat VRE prosthetic joint infection.
3. Safety

In long-term therapeutic use of oxazolidinones, tedizolid is a good alternative to linezolid in cases of inadequate clinical tolerance, myelotoxicity or renal failure secondary to increased toxicity.
3. Efficacy and Safety

Short Communication

Myelosuppression-sparing treatment of central nervous system nocardiosis in a multiple myeloma patient utilizing a tedizolid-based regimen: a case report

Aasiya Matin a, Smriti Sharma b, Pankaj Mathur a, Senu K. Apewokin c,∗

a Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR, USA
b Department of Veterans Affairs, University of Arkansas for Medical Sciences, Little Rock, AR, USA
c Division of Infectious Diseases, Department of Medicine, University of Cincinnati, 231 Albert Sabin Way, MSB 61538, Cincinnati, OH 45267, USA


Hints:

• **Linezolid has recently been widely employed for the treatment of multidrug-resistant Gram positive CNS infections with remarkable success and has become a prominent agent in contemporary treatment strategies…**

• **This patient was at high risk of anemia, and neutropenia because of myelosuppression related to its antimyeloma chemotherapy (bortezomib, thalidomide and dexamethasone)**
3. Efficacy and Safety

Fig. 1. White blood cell counts during treatment of central nervous system nocardiosis. IV, intravenous; PO, oral; TMP-SMX, trimethoprim/sulfamethoxazole; ANC, absolute neutrophil count; MRI, magnetic resonance imaging; afib, atrial fibrillation; UTI, urinary tract infection.
Post-marketing experience: a survey of selected published data

3. Efficacy and Safety

![Diagram showing treatment course and MRI images with captions:]

**Fig. 1.** White blood cell counts during treatment of central nervous system nocardiosis. IV, intravenous; PO, oral; TMP-SMX, trimethoprim/sulfamethoxazole; ANC, absolute neutrophil count; MRI, magnetic resonance imaging; a/fib, atrial fibrillation; UTI, urinary tract infection.

**Fig. 2.** Serial MRIs during the treatment course.

---

3. Efficacy and Safety

WBC count and absolute neutrophil count remained stable despite her concurrent chemotherapy, with absolute CD4 counts actually showing an improvement.
3. Efficacy and Safety

Tedizolid-based treatment of nocardiosis may provide a safe myelosuppression-sparing option for patients with an exhausted bone marrow who require prolonged antibiotic therapy for CNS nocardiosis or require concurrent institution of chemotherapy.

WBC count and absolute neutrophil count remained stable despite her concurrent chemotherapy, with absolute CD4 counts actually showing an improvement.


Please, ask questions …

be critical, ask for facts!

Vesalius - anatomy

All slide are available on http://www.facom.ucl.ac.be → Lectures
Back up slides
Belgium
Belgium

10 millions inhabitants …

10 Nobel prizes (10/850) for activities in Belgium

- **Peace**
  - [Institute of International Law](http://www.nobelprize.org), Ghent (1904)
  - [Auguste Beernaert](http://www.nobelprize.org), (1909)
  - [Henri Lafontaine](http://www.nobelprize.org), (1913)
  - [Father Dominique Pire](http://www.nobelprize.org), (1958)

- **Literature**
  - [Maurice Maeterlinck](http://www.nobelprize.org), Ghent (1911)

- **Medicine**
  - [Jules Bordet](http://www.nobelprize.org), Brussels (1919)
  - [Corneille Heymans](http://www.nobelprize.org), Ghent (1938)
  - [Christian de Duve](http://www.nobelprize.org), Louvain (1974)
  - [Albert Claude](http://www.nobelprize.org), Brussels (1974)

- **Chemistry**
  - [Ilya Prigogine](http://www.nobelprize.org), Brussels (1977)

- **Physics**
  - [François Englert](http://www.nobelprize.org), Brussels (2013)

source: [http://www.nobelprize.org](http://www.nobelprize.org)

Last accessed: 10 May 2016
Discovery and Microbiology
New antibiotics: what is your own view of the pipeline?
New antibiotics: where are we?

Approvals by FDA/EMA – systemic antibiotics


bacteria cartoons fro:

telavancin

ceftaroline
New antibiotics: where are we?

Approvals by FDA/EMA – systemic antibiotics

16
14
10
7
4
2
5

1983-1987
1988-1992
1993-1997
1998-2002
2003-2007
2008-2012
2013-

dalbavancin/oritavancin
→ tedizolid
→ delafloxacin
→ ceftazidime/avibactam
→ ceftolozane/tazobactam
→ meropenem/vaborbactam
→

bacteria cartoons fro:
Novel anti-MRSA antibiotics acting on resistant isolates *

• already approved
  – 2 β-lactams (ceftaroline / ceftobiprole a)
  – 3 lipoglycopeptides (telavancin, dalbavancin, oritavancin)
  – 1 fluoroquinolone: delafloxacin b,f
  – 1 oxazolidinone: tedizolid c

• in clinical development
  – an old friend: fusidic acid d
  – another oxazolidinone: radezolid e
  – a revamped aminoglycoside: plazomycin
  – new fluoroquinolones (nadifloxacin, …) f
  – new topoisomerase type II inhibitors (gepotidacin, …)
  – fatty acid synthesis inhibitors (AFN-1252/Debio 1452, …) g

a approved in Europe and other countries for pneumonia (CAP/HAP) - In discussion with FDA for ABSSSI and SAB
b approved in the USA (FDA) – to be submitted to the EMA in 2018
c active against cfr+ linezolid resistant isolates
d development for use in the US
e currently in development for topical applications
f very low MICs (overcoming current mutation and efflux-mediated resistance mechanisms)
g very low MICs (typically 0.008 mg/L) and S. aureus-specific

* not an exhaustive list ...
Novel anti-MRSA antibiotics acting on resistant isolates *

- already approved
  - 2 β-lactams (ceftaroline / ceftobiprole)
  - 3 lipoglypopeptides (telavancin, dalbavancin, oritavancin)
  - 1 fluoroquinolone: delafloxacin
  - 1 oxazolidinone: tedizolid

- In late stage of clinical development
  - fusidic acid
  - radezolid
  - plazomycin
  - new fluoroquinolones (nadifloxacin, …)
  - new topoisomerase type II inhibitors (gepotidacin, …)
  - fatty acid synthesis inhibitors (AFN-1252/Debio 1452, …)

This was predicted a few years ago

In comparison with other infectious agents, the antimicrobial pipeline for MRSA is potentiated with a number of agents under pre-clinical and clinical development. This is a hopeful sign that the IDSA’s target might possibly be met by 2020.


---

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b approved in the USA (FDA) – to be submitted to the EMA in 2018
c active against cfr+ linezolid resistant isolates
d development for use in the US
e currently in development for topical applications
f very low MICs (overcoming current mutation and efflux-mediated resistance mechanisms)
g very low MICs (typically 0.008 mg/L)
## Anti-MRSA antibiotics: pros and cons...

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
</table>
| vancomycin    | 15 mg/kg every 12 h or continuous infusion | • long first choice for IV treatment of MRSA  
• IV only and requires drug monitoring  
• may cause nephrotoxicity  
• beware of MICs ≥ 1 mg/L |
| linezolid     | 600 mg every 12 h IV or PO    | • allows for efficient IV → oral switch  
• toxicities (⚠️ if renal insufficiency) |
| daptomycin    | 4 – 6 mg/kg Q24h IV           | • bactericidal  
• doses uncertain (myopathies if ⚠️) |
| ceftaroline   | 600 mg every 12 h IV          | • bactericidal  
• IV only and requires compliance |
| oritavancin   | 1200 mg once  
1000 mg + 500 mg at day 7 | • bactericidal (VISA and VRSA not susceptible !)  
• convenient use but long infusion time (3h)  
• prolonged tissue accumulation (risk ?) |
| dalbavancin   | * approved after publication of the IDSA guidelines (notes based on analysis of the official US and EU labels [no EU label for delafloxacin]) |
| delafloxacin  | 300 mg every 12h IV  
450 mg every 12h PO | • bactericidal  
• efficient IV → oral switch  
• many severe toxicities in label (black box) |


* approved after publication of the IDSA guidelines (notes based on analysis of the official US and EU labels [no EU label for delafloxacin])
Vancomycin MIC >1µg/mL as a predictor for treatment failure in MRSA bloodstream infections

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>High MIC 1.5 µg/mL</th>
<th>Low MIC &lt;1.5 µg/mL</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>163</td>
<td>188</td>
<td>OR 2.69 (1.60, 4.51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>$\tau^2 = 0.38$;</td>
<td>$c^2 = 22.59$, df 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$I^2 = 56%$. Test</td>
<td>$P = 0.01$;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>for overall effect:</td>
<td>$Z = 3.75 (P = 0.0002)$</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; df: degrees of freedom; MIC: minimum inhibitory concentration; MRSA: methicillin-resistant Staphylococcus aureus; OR: odds ratio


an example of the problems with vancomycin
Vancomycin MIC >1µg/mL as a predictor for treatment failure in MRSA bloodstream infections

Forest plot using Mantel–Haenszel analysis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>High MIC ≥1.5 µg/mL</th>
<th>Low MIC &lt;1.5 µg/mL</th>
<th>Weight</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Bae et al.</td>
<td>14</td>
<td>37</td>
<td>12</td>
<td>28</td>
</tr>
<tr>
<td>Choi et al.</td>
<td>12</td>
<td>34</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>Ferry et al.</td>
<td>9</td>
<td>24</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>Hidayat et al.</td>
<td>20</td>
<td>51</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>Hsu et al.</td>
<td>17</td>
<td>45</td>
<td>4</td>
<td>38</td>
</tr>
<tr>
<td>Lalueza et al.</td>
<td>3</td>
<td>13</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>Lodise et al.</td>
<td>6</td>
<td>66</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Moise et al.</td>
<td>11</td>
<td>14</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Moise-Broder et al.</td>
<td>23</td>
<td>25</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>Takesue et al.</td>
<td>34</td>
<td>97</td>
<td>85</td>
<td>662</td>
</tr>
<tr>
<td>Yoon et al.</td>
<td>14</td>
<td>18</td>
<td>17</td>
<td>45</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>163</td>
<td>424</td>
<td>1015</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.38$; $c^2 = 22.59$, df 10 ($P = 0.01$); $I^2 = 56\%$. Test for overall effect: $Z = 3.75$ ($P = 0.0002$)

CI: confidence interval; df: degrees of freedom; MIC: minimum inhibitory concentration; MRSA: methicillin-resistant *Staphylococcus aureus*; OR: odds ratio

## Potency of tedizolid against key Gram-positive species in the US and Europe (recent data) *

<table>
<thead>
<tr>
<th>Species</th>
<th>n</th>
<th>MIC$_{50}$ (µg/mL)</th>
<th>MIC$_{90}$ (µg/mL)</th>
<th>% S CLSI / EUCAST</th>
<th>% I CLSI / EUCAST</th>
<th>% R CLSI / EUCAST</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>7813</td>
<td>0.25</td>
<td>0.5</td>
<td>99.8 / 99.8</td>
<td>0.2 / NA</td>
<td>0.0 / 0.2</td>
</tr>
<tr>
<td>MRSA</td>
<td>3234</td>
<td>0.25</td>
<td>0.5</td>
<td>99.6 / 99.6</td>
<td>0.3 / NA</td>
<td>0.1 / 0.4</td>
</tr>
<tr>
<td>MSSA</td>
<td>4579</td>
<td>0.25</td>
<td>0.5</td>
<td>99.9 / 99.9</td>
<td>0.1 / NA</td>
<td>0.0 / 0.1</td>
</tr>
<tr>
<td><em>S. pyogenes</em></td>
<td>684</td>
<td>0.12</td>
<td>0.25</td>
<td>100.0 / 100.0</td>
<td>NA / NA</td>
<td>0.0 / 0.0</td>
</tr>
<tr>
<td><em>S. agalactiae</em></td>
<td>715</td>
<td>0.25</td>
<td>0.25</td>
<td>100.0 / 100.0</td>
<td>NA / NA</td>
<td>0.0 / 0.0</td>
</tr>
<tr>
<td><em>E. faecalis</em> (VR)</td>
<td>37</td>
<td>0.25</td>
<td>0.5</td>
<td>100.00 / NA</td>
<td>NA / NA</td>
<td>NA / NA</td>
</tr>
<tr>
<td><em>E. faecalis</em> (VS)</td>
<td>829</td>
<td>0.25</td>
<td>0.5</td>
<td>99.39 / NA</td>
<td>NA / NA</td>
<td>NA / NA</td>
</tr>
<tr>
<td><em>E. faecium</em> (VR)</td>
<td>202</td>
<td>0.25</td>
<td>0.5</td>
<td>NA / NA</td>
<td>NA / NA</td>
<td>NA / NA</td>
</tr>
<tr>
<td><em>E. faecium</em> (VS)</td>
<td>168</td>
<td>0.25</td>
<td>0.5</td>
<td>NA / NA</td>
<td>NA / NA</td>
<td>NA / NA</td>
</tr>
</tbody>
</table>

N=11,231 isolates (2009-2013)

*STAR Global Surveillance Programme

CLSI: The Clinical & Laboratory Standards Institute; EUCAST: The European Committee on Antimicrobial Susceptibility Testing; I: intermediate; MIC: minimum inhibitory concentration; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *S. aureus*; NA: not available; R: resistant; S: susceptible; VR: vancomycin resistant; VS, vancomycin susceptible

Tedizolid is more potent because of more interactions with the target …

*W.B. Im et al. / European Journal of Medicinal Chemistry 46 (2011) 1027–1039*  
PMID: [21392356](https://doi.org/10.1016/j.ejmech.2011.06.066)

Fig. 2. Models of 11 (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.
## Strains from Europe

### Table 2. Activity of Tedizolid and Comparators against *S. aureus*, MRSA, and MSSA Isolated from Skin Infections (2009–2013) in European Patients

<table>
<thead>
<tr>
<th>Pathogen (No.)</th>
<th>Drug</th>
<th>MIC Range</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>%S</th>
<th>%I</th>
<th>%R</th>
</tr>
</thead>
<tbody>
<tr>
<td>All <em>S. aureus</em> (592)</td>
<td>Tedizolid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.06 to 1</td>
<td>0.25</td>
<td>0.5</td>
<td>99.8</td>
<td>0</td>
<td>0.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>≤0.25 to 4</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MRSA (125)</td>
<td>Tedizolid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.06 to 0.5</td>
<td>0.25</td>
<td>0.5</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>≤0.25 to 4</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MSSA (467)</td>
<td>Tedizolid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.12 to 1</td>
<td>0.25</td>
<td>0.5</td>
<td>99.8</td>
<td>0</td>
<td>0.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>≤0.25 to 4</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

592 non-duplicate, non-consecutive isolates of *S. aureus* collected between 2009 and 2013 from patients with skin infections from 19 European countries (Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Russia, Spain, Sweden, Turkey, and the United Kingdom)
And also for a another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

### TABLE 1 Numbers of organisms included in this study stratified by site of infection

<table>
<thead>
<tr>
<th>Organism or group</th>
<th>BSI</th>
<th>PIHP</th>
<th>SSSI</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>263</td>
<td>208</td>
<td>484</td>
<td>1,427</td>
<td>2,382</td>
</tr>
<tr>
<td>MSSA</td>
<td>193</td>
<td>134</td>
<td>372</td>
<td>982</td>
<td>1,681</td>
</tr>
<tr>
<td>MRSA</td>
<td>70</td>
<td>74</td>
<td>112</td>
<td>445</td>
<td>701</td>
</tr>
<tr>
<td><em>S. pyogenes</em></td>
<td>16</td>
<td>5</td>
<td>62</td>
<td>175</td>
<td>258</td>
</tr>
<tr>
<td><em>S. agalactiae</em></td>
<td>25</td>
<td>2</td>
<td>8</td>
<td>110</td>
<td>145</td>
</tr>
<tr>
<td><em>S. anginosus</em> group&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>37</td>
<td>54</td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>60</td>
<td>0</td>
<td>52</td>
<td>81</td>
<td>193</td>
</tr>
</tbody>
</table>

<sup>a</sup> *S. constellatus* (23 isolates), *S. anginosus* group not otherwise specified (4 isolates), *S. anginosus* (26 isolates), *S. intermedius* (1 isolate).

BSI: bloodstream infections  
PIHP: pneumonia in hospitalized patients  
SSSI: skin and skin structures infection  

Activity of tedizolid against staphylococci from difficult-to-treat infections

Antimicrobial Susceptibility Studies

In vitro activity of tedizolid against staphylococci isolated from prosthetic joint infections

Suzannah M. Schmidt-Malan b, Kerryl E. Greenwood Quaintance b, Melissa J. Karau b, Robin Patel a, b, *

a Division of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, MN 55905, USA
b Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, USA

Activity of tedizolid against contemporary *S. aureus* and *Enterococci* resistant to other antibiotics

Table 1. Tedizolid MIC distribution and MIC₉₀ values for tested isolates

<table>
<thead>
<tr>
<th>Strain</th>
<th>TZD—number (cumulative percentage) inhibited at MIC (mg/L)</th>
<th>TZD</th>
<th>TZD MIC range (mg/L)</th>
<th>Lzd</th>
<th>Lzd MIC range (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤0.063 0.125 0.25 0.5 1 2 4</td>
<td>MIC₉₀</td>
<td>(mg/L)</td>
<td>MIC₉₀</td>
<td>(mg/L)</td>
</tr>
<tr>
<td>MRSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 hVISA (n=120)</td>
<td>7 (5.8) 18 (20.8) 55 (66.7) 38 (98.3) 2⁹ (100) — (100) — (100)</td>
<td>0.5</td>
<td>0.03–1</td>
<td>4</td>
<td>0.25–8</td>
</tr>
<tr>
<td>2 VISA (n=100)</td>
<td>7 (7) 52 (59) 25 (84) 16 (100) — (100) — (100) — (100)</td>
<td>0.5</td>
<td>0.03–0.5</td>
<td>4</td>
<td>0.125–4</td>
</tr>
<tr>
<td>3 DNS (n=75)</td>
<td>— (0) 23 (30.7) 38 (81.3) 14 (100) — (100) — (100) — (100)</td>
<td>0.5</td>
<td>0.125–0.5</td>
<td>2</td>
<td>1–4</td>
</tr>
<tr>
<td>4 LRᵇ (n=7)</td>
<td>1 (14.3) 1 (28.6) 2 (57.1) — (57.1) 3 (100) — (100) — (100)</td>
<td>NA</td>
<td>0.063–1</td>
<td>NA</td>
<td>8–16</td>
</tr>
<tr>
<td>VRE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. faecium (n=120)</td>
<td>— (0) 6 (5) 51 (47.5) 32 (74.2) 25 (95) 3 (97.5) 3 (100)</td>
<td>1</td>
<td>0.125–4</td>
<td>4</td>
<td>1–32</td>
</tr>
<tr>
<td>E. faecalis (n=100)</td>
<td>1 (1) 29 (30) 69 (99) 1 (100) — (100) — (100) — (100)</td>
<td>0.25</td>
<td>0.063–0.5</td>
<td>2</td>
<td>0.25–2</td>
</tr>
<tr>
<td>LR E. faecium (n=10)</td>
<td>— (0) — (0) — (0) — (0) 4 (40) 3 (70) 3 (100)</td>
<td>NA</td>
<td>1–4</td>
<td>NA</td>
<td>8–32</td>
</tr>
<tr>
<td>DNS E. faecium (n=25)</td>
<td>— (0) — (0) 11 (44) 3 (56) 8 (88) 2 (96) 1 (100)</td>
<td>NA</td>
<td>0.25–4</td>
<td>NA</td>
<td>1–32</td>
</tr>
</tbody>
</table>

TZD, tedizolid; Lzd, linezolid; NA, not applicable.

⁹These two hVISA isolates were LR, with linezolid MIC values of 8 mg/L.

ᵇThe three isolates with tedizolid MICs of 1 mg/L did not possess the *cfr* gene.

1 hetero-vancomycin intermediate (MIC₉₀=2 mg/L) → associated with an increased risk of clinical failures
2 vancomycin-intermediate (MIC₉₀=8) → categorized as resistant by EUCAST
3 daptomycin-resistant (MIC₉₀=8) →
4 linezolid-resistant (MIC=8-16 mg/L)

Tedizolid and Penicillin-resistant S. pneumoniae

Activity of Tedizolid Phosphate (TR-701) in Murine Models of Infection with Penicillin-Resistant and Penicillin-Sensitive Streptococcus pneumoniae

Sunghak Choi, Weonbin Im, and Ken Bartiza
Dong-A Pharmaceutical Co., Yongin-Si, South Korea,* and Trius Therapeutics, Inc., San Diego, California, USA*

TABLE 1 MICs for tedizolid and linezolid against PRSPa

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (µg/ml)</th>
<th>Range</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tedizolid</td>
<td>0.125–0.25</td>
<td>0.25</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>0.125–1</td>
<td>0.5</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*a Twenty-eight isolates were tested. Penicillin resistance was determined on the basis of the oral penicillin resistance MIC breakpoint for nonmenigitis pneumococcal isolates (≥2 µg/ml). For penicillin G tested against these isolates, the MIC range was 2 to 4 µg/ml, the MIC50 was 2 µg/ml, and the MIC90 was 4 µg/ml.

FIG 1 Pneumococcal clearance from lungs of S. pneumoniae-infected mice by tedizolid phosphate. Oral antimicrobial treatment was started at 4 h postinfection. * P < 0.05 versus untreated control at the same time point; #, P < 0.001 versus uninfected control at the same time point.
Activity against *cfr*\(^+\) resistant strains …

<table>
<thead>
<tr>
<th>Strain</th>
<th>Reference</th>
<th>Presence of <em>cfr</em></th>
<th>MIC ((\mu\text{g/ml}))(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LVD</td>
</tr>
<tr>
<td>RN4220(pLI50)</td>
<td>68</td>
<td>−</td>
<td>2</td>
</tr>
<tr>
<td>RN4220(pLXM1)(^b)</td>
<td>68</td>
<td>+</td>
<td>8</td>
</tr>
<tr>
<td>CM05(^c)</td>
<td>44</td>
<td>−</td>
<td>2</td>
</tr>
<tr>
<td>CM05(^c)</td>
<td>68</td>
<td>+</td>
<td>8</td>
</tr>
<tr>
<td>29213</td>
<td>ATCC</td>
<td>−</td>
<td>2</td>
</tr>
<tr>
<td>29213(p42262)(^d)</td>
<td>45</td>
<td>+</td>
<td>16</td>
</tr>
<tr>
<td>42262(^e)</td>
<td>51</td>
<td>+</td>
<td>16</td>
</tr>
</tbody>
</table>

\(^a\) MICs (broth microdilution: CLSI)

\(^b\) The pLXM1 *cfr*-containing plasmid is isogenic to the empty pLI50 vector.

\(^c\) CM05\(^\Delta\) is isogenic to the CM05 clinical *cfr*-positive strain but lacks *cfr* and one copy of *ermB*.

\(^d\) 29213(p42262) was generated through transformation of ATCC 29213.

\(^e\) 42262 is a clinical *cfr*-positive isolate from a 2008 hospital outbreak in Madrid, Spain.

Accumulation and activity of tedizolid in macrophages

doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009

Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

Sandrine Lemaire¹, Françoise Van Bambeke¹, Peter C. Appelbaum² and Paul M. Tulkens¹*

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Accumulation and activity of tedizolid in eukaryotic cells

Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

Sandrine Lemaire¹, Françoise Van Bambeke¹, Paul van Opdenbosch⁴, Delphine Vanhoutte⁵, Daniel Criquet⁶, Jean-Marc Desreumaux³, Jacques H. Oger²

¹Unité de Pharmacologie cellulaire et moléculaire & Louvain, Brussels, Belgium; ²Hershey Medical Center, Hershey, USA; ³Hôpital universitaire de passy, Paris, France; ⁴Institut de recherche pour le développement, Toulouse, France; ⁵Vrije Universiteit Brussel, Brussels, Belgium; ⁶Bacterial Genomics Group, European cardiology network, Brussels, Belgium
Tedizolid is more active (3 – 4 x) than linezolid against intracellular *S. aureus*

Concentration-dependent effects of linezolid (LZD) and torezolid (TR-700) towards *S. aureus* ATCC 25923 after phagocytosis by THP-1 macrophages or HUVECs (endothelial cells)

Lemaire et al. JAC 2010; 64:1035–1043
Tedizolid is active intracellularly against MRSA disregarding resistance phenotypes

Concentration-dependent effects of tedizolid (TR-700) towards S. aureus with different resistance phenotypes after phagocytosis by THP-1 macrophages

Lemaire et al. JAC 2010; 64:1035–1043
Other antibiotics (competitors)
What are the problems with available anti-Gram-positive antibiotics?

1. The emergence of MRSA…
   ➔ what is the situation in your country?
What are the problems with available anti-Gram-positive antibiotics?

1. The emergence of MRSA…
   → what is the situation in your country?

2. Vancomycin is an old and "difficult" drug
   – IV only, at least twice daily, and 10 days or more…
   – monitoring is essential to avoid toxicity…
   – beware of MICs > 2 mg/L risk of failures!
What are the problems with available anti-Gram-positive antibiotics?

1. The emergence of MRSA…
   → what is the situation in your country?

2. Vancomycin is an old and "difficult" drug
   – IV only, at least twice daily, and 10 days or more…
   – monitoring is essential to avoid toxicity…
   – beware of MICs > 2 mg/L \(\text{risk of failures!}\)

3. Linezolid is fraught with toxicities
   – drug interactions (MAO inhibition)
   – myelosuppression, lactic acidosis…
   \(\text{more frequent than originally reported!}\)
Important limits of vancomycin: 1. MIC-related failures

Relationship of MIC to treatment failures

Important limits of vancomycin: 2. poor tissue penetration

CNS: <10%

Sternal bone\textsuperscript{1}: 57%
Heart valve\textsuperscript{4}: 12%

Bone\textsuperscript{5}: 7\%–13%

Epithelial lining fluid\textsuperscript{3}: 18%

Lung tissue\textsuperscript{2}: 17\%–24%

Fat\textsuperscript{4}: 14%
Muscle\textsuperscript{4}: 9%

Important limits of vancomycin: 3. unpredictable serum levels (at the level of individual patients and over time)

Continuous infusion of vancomycin: target value: 27.5 mg/L

![Graph showing total vancomycin concentrations over time in all patients with > 3 measures at any time (n=91)](image)

It looks fine, but…

Important limits of vancomycin: 3. unpredictable serum levels (at the level of individual patients and over time)

Continuous infusion of vancomycin:
target value: 27.5 mg/L

successive vancomycin serum levels values in individual patients with > 3 determinations after the first 96h of treatment (n = 52)

Ampe et al Intern J Antimicrob Agents 2013;41:439-446 – PMID 23523733
Important limits of vancomycin: 4. nephrotoxicity

Incidence of nephrotoxicity as a function of the trough serum levels

Pharmacokinetics/Pharmacodynamics
Tedizolid human pharmacokinetics: ascending doses

TR-700 has a PK profile allowing for once-a-day administration of TR-701.

Pharmacokinetics of TR-700 at steady state well predicted from single dose data and showed minimal accumulation.

The key pharmacodynamic driver for the efficacy of oxazolidinones is AUC/MIC. The value for TR-701 at 200 mg QD is 22.5/0.5=45.
Human pharmacokinetics: linearity over increasing doses: single and multiple doses

Pharmacokinetics of Tedizolid Following Oral Administration: Single and Multiple Dose, Effect of Food, and Comparison of Two Solid Forms of the Prodrug

Shawn D. Flanagan,¹ Paul A. Bien,¹ Kelly A. Muñoz,¹ Sonia L. Minassian,² and Philippe G. Prokocimer¹
¹Trius Therapeutics, San Diego, California; ²Minassian Biostatistics, San Diego, California

Tedizolid: Impact of renal and hepatic dysfunction

**renal dysfunction**

![Graph showing plasma tedizolid concentrations over time in subjects with severe renal impairment and matched controls, shown on a semi-logarithmic scale.]

**hepatic dysfunction**

![Graph showing plasma tedizolid concentrations over time in subjects with impaired hepatic function and matched controls, shown on a semilogarithmic scale.]

Tedizolid: Impact of renal (incl. dialysis and CCRT) and hepatic dysfunction

1. renal dysfunction

**TABLE 1** Mean tedizolid pharmacokinetics in the renal-impairment study

<table>
<thead>
<tr>
<th>Study group</th>
<th>( C_{\text{max}} ) (( \mu \text{g/ml} ))</th>
<th>( T_{\text{max}} ) (h)</th>
<th>( AUC_{0-\text{t}} ) (( \mu \text{g} \cdot \text{h/ml} ))</th>
<th>( AUC_{0-\infty} ) (( \mu \text{g} \cdot \text{h/ml} ))</th>
<th>( t_{1/2} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control ((n = 8))</td>
<td>3.11 (0.75)</td>
<td>1.00 (1.00–2.50)</td>
<td>32.02 (9.32)</td>
<td>32.43 (9.53)</td>
<td>12.25 (2.04)</td>
</tr>
<tr>
<td>Severe renal impairment ((n = 8))</td>
<td>3.12 (0.85)</td>
<td>1.26 (1.00–2.00)</td>
<td>29.69 (8.93)</td>
<td>29.99 (8.97)</td>
<td>12.85 (2.28)</td>
</tr>
<tr>
<td>Predialysis infusion ((n = 7))</td>
<td>2.53 (0.95)</td>
<td>1.00 (0.50–1.50)</td>
<td>22.97 (8.02)</td>
<td>23.15 (8.10)</td>
<td>11.41 (1.78)</td>
</tr>
<tr>
<td>Postdiagnosis infusion ((n = 8))</td>
<td>2.86 (1.01)</td>
<td>1.50 (1.00–1.50)</td>
<td>20.81 (4.65)</td>
<td>21.01 (4.71)</td>
<td>11.73 (2.33)</td>
</tr>
</tbody>
</table>

\( AUC_{0-\text{t}} \) integrated area under the curve based on samples from time zero to the time of the last collected sample; \( AUC_{0-\infty} \) area under the curve based on the terminal rate constant; \( C_{\text{max}} \) maximum concentration observed with a 200-mg dose; \( t_{1/2} \), tedizolid half-life; \( T_{\text{max}} \), time to reach the maximum concentration. Pharmacokinetic parameters are presented as means (standard deviations), except for \( T_{\text{max}} \) values, which are presented as medians (ranges).


**Additional information:** at conventional Continuous Renal Replacement Therapy (CRRT) rates, tedizolid transmembrane clearance appears modest relative to total body clearance and is unlikely to require dose adjustments.

2. hepatic dysfunction

**TABLE 2** Mean tedizolid pharmacokinetic parameters of the hepatic-impairment group

<table>
<thead>
<tr>
<th>Study group</th>
<th>( C_{\text{max}} ) (( \mu \text{g/ml} ))</th>
<th>( T_{\text{max}} ) (h)</th>
<th>( AUC_{0-\text{t}} ) (( \mu \text{g} \cdot \text{h/ml} ))</th>
<th>( AUC_{0-\infty} ) (( \mu \text{g} \cdot \text{h/ml} ))</th>
<th>( t_{1/2} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate impairment ((n = 8))</td>
<td>2.08 (0.74)</td>
<td>1.75 (0.50–3.00)</td>
<td>29.89 (16.76)</td>
<td>30.47 (17.50)</td>
<td>14.94 (3.49)</td>
</tr>
<tr>
<td>Matched controls ((n = 8))</td>
<td>1.85 (0.49)</td>
<td>2.00 (1.00–4.00)</td>
<td>22.80 (5.63)</td>
<td>23.00 (5.70)</td>
<td>13.42 (3.93)</td>
</tr>
<tr>
<td>Severe impairment ((n = 8))</td>
<td>2.20 (1.07)</td>
<td>2.00 (0.50–3.00)</td>
<td>34.80 (20.72)</td>
<td>35.23 (21.13)</td>
<td>14.19 (2.92)</td>
</tr>
<tr>
<td>Matched controls ((n = 8))</td>
<td>2.12 (0.80)</td>
<td>3.00 (1.00–8.00)</td>
<td>24.37 (8.03)</td>
<td>24.56 (8.05)</td>
<td>13.68 (3.71)</td>
</tr>
</tbody>
</table>

\( AUC_{0-\text{t}} \) integrated area under the curve based on samples from time zero to the time of the last collected sample; \( AUC_{0-\infty} \) area under the curve based on the terminal rate constant; \( C_{\text{max}} \) maximum concentration observed with a 200-mg dose; \( t_{1/2} \), tedizolid half-life; \( T_{\text{max}} \), time to reach the maximum concentration. Pharmacokinetic parameters are presented as means (standard deviations), except for \( T_{\text{max}} \) values, which are presented as medians (ranges).

## Similar pharmacokinetics in adolescents vs. adults

<table>
<thead>
<tr>
<th>Route</th>
<th>PK parameter</th>
<th>Geometric mean</th>
<th>Geometric mean ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>adolescents</td>
<td>adults *</td>
</tr>
<tr>
<td>IV</td>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>3.66 (10)</td>
<td>2.55 (34)</td>
</tr>
<tr>
<td></td>
<td>$\text{AUC}_{0-\infty}$ (µg x h/mL)</td>
<td>26.95 (10)</td>
<td>29.11 (33)</td>
</tr>
<tr>
<td>oral</td>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>2.17 (10)</td>
<td>2.23 (37)</td>
</tr>
<tr>
<td></td>
<td>$\text{AUC}_{0-\infty}$ (µg x h/mL)</td>
<td>23.94 (10)</td>
<td>28.3 (32)</td>
</tr>
</tbody>
</table>

* Historical data for adult PK parameters after IV dosing were pooled from studies TR701-107 ¹ and TR701-123 ². Oral dosing data for adults were obtained from study TR701-115 ³.

1 Flanagan et al. Pharmacotherapy 2014;34:891-900. PMID: 24989138

PK parameters governing the activity of antibiotics

- Maximum Concentration ($C_{max}$)
- Time ($T$) such that $T > MIC$
- Area Under the Curve (AUC) for 24 hours ($AUC_{24h}$)

$C_{max} / MIC$
$fT > MIC$
$AUC_{24h} / MIC$
How to determine which PK parameter is critical?

- If you fractionate the daily dose, you change $C_{\text{max}}$ without changing $\text{AUC}_{24\text{h}}$.
How to determine which PK parameter is critical?

- If you increase the dose without change of schedule, you increase BOTH $C_{\text{max}}$ and $\text{AUC}_{24h}$

\[
\text{AUC}_{24h} = \frac{\text{Dose}_{24h}}{\text{Clearance}}
\]

$\text{AUC}_{24h}$ is proportional to the dose.
What do you see?

The correlation with $f_{C_{\text{max}}}$ is not excellent.

The correlation with $f_{T > \text{MIC}}$ is worse!

Louie et al. AAC 2011; 55:3453-3460
How do you do this with tedizolid?

<table>
<thead>
<tr>
<th>Total dosage (mg/kg/24 h)</th>
<th>Regimen&lt;sup&gt;a&lt;/sup&gt;</th>
<th>$fC_{\text{max}}$/MIC ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>fAUC/MIC ratio&lt;sup&gt;c&lt;/sup&gt;</th>
<th>$fT&gt;\text{MIC}$ (%)&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10 mg/kg q24h</td>
<td>2.62</td>
<td>13.19</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg q12h</td>
<td>1.29</td>
<td>12.82</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>2.5 mg/kg q6h</td>
<td>0.64</td>
<td>12.26</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>20 mg/kg q24h</td>
<td>5.16</td>
<td>26.03</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg q12h</td>
<td>2.62</td>
<td>25.63</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg q6h</td>
<td>1.29</td>
<td>24.51</td>
<td>50</td>
</tr>
<tr>
<td>36</td>
<td>36 mg/kg q24h</td>
<td>9.29</td>
<td>46.88</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>18 mg/kg q12h</td>
<td>4.65</td>
<td>46.14</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>9 mg/kg q6h</td>
<td>2.32</td>
<td>44.12</td>
<td>87</td>
</tr>
<tr>
<td>72</td>
<td>72 mg/kg q24h</td>
<td>18.59</td>
<td>93.76</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>36 mg/kg q12h</td>
<td>9.29</td>
<td>92.28</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>18 mg/kg q6h</td>
<td>4.65</td>
<td>88.24</td>
<td>100</td>
</tr>
</tbody>
</table>

<sup>a</sup> The first dose was administered 2 h after infection. All doses of TR-701 are provided as dose equivalents (mg/kg/day) of TR-700. Doses were given every 24 h (q24h), every 12 h (q12h), or every 6 h (q6h).

<sup>b</sup> $fC_{\text{max}}$/MIC ratio, maximum concentration of free drug in serum divided by the MIC. The MICs for the MRSA strain were 0.5 mg/liter in CA-MHB and 1 mg/liter in 80% mouse serum.

<sup>c</sup> fAUC/MIC ratio, area under the concentration-time curve over 24 h for the free, unbound fraction of a drug divided by the MIC.

<sup>d</sup> $fT>\text{MIC}$, calculated cumulative percentage of a 24-h period that the concentration of the free drug exceeded the MIC under steady-state pharmacokinetic conditions (expressed as a percentage of the dosing interval).

Louie et al. AAC 2011; 55:3453-3460
Preclinical studies: definition of the "sufficient dose" in infected animals

Tedizolid maximal effect is obtained at the equivalent of 200 mg (human dose)

Drusano et al. AAC 2011; 55-5300-5305
Tedizolid cooperates with granulocytes *in vivo*

Drusano et al. AAC 2011; 55-5300-5305

Tedizolid becomes cidal at low doses (equivalent to human 200 mg dose) in the presence of PMN
Tedizolid is cidal *in vivo* ...
Tedizolid and granulocytes cooperate *in vivo* upon each administration

TR701/700 200 mg-Equivalent Dose
With Granulocytes

Killing progresses over time at each administration of tedizolid…

AUC$_{24}$h = 20.1 (equivalent to humans for a dose of 200 mg)

MIC = 0.5 mg/L

Drusano et al. AAC 2011; 55-5300-5305
Tedizolid vs daptomycin *in vivo*

Dose-Ranging Studies

- Tedizolid has daptomycin-like "*in vivo bactericidal*" activity
- Linezolid at 160 mg/kg/day → did not achieve stasis in this model

Louie et al. Antimicrob Agents Chemother. 2011;;55::3453-60 (tedizolid) and data on file (daptomycin)
Towards a breakpoint (FDA / EUCAST)

- A tedizolid $\text{AUC}_{0-24h}/\text{MIC}$ ratio of 15 was determined as the PK/PD target associated with the activity of tedizolid against *S. aureus* in the non-neutropenic mouse thigh model of infection…¹

Calculation of the probability of reaching the necessary AUC/MIC ratio for increasing MICs in humans…

¹ FDA briefing document: anti-infective drug advisory committee meeting
March 31, 2014
Last accessed: May 17, 2015
Tedizolid breakpoints (200 mg/once daily)...

Table 5 Susceptibility Test Interpretive Criteria for SIVEXTRO

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin-resistant and methicillin-susceptible isolates)</td>
<td>≤0.5</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>≤0.5</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>≤0.5</td>
</tr>
<tr>
<td><em>Streptococcus anginosus Group</em></td>
<td>≤0.25</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>≤0.5</td>
</tr>
</tbody>
</table>

S=susceptible, I=intermediate, R=resistant
* Includes *S. anginosus, S. intermedius, S. constellatus*
Safety
A short overview of phase I studies: impact of ascending doses (global)

INCIDENCE OF ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall Placebo (N = 10)</th>
<th>TR-701 200 mg (N = 6)</th>
<th>TR-701 400 mg (N = 6)</th>
<th>TR-701 600 mg (N = 6)</th>
<th>TR-701 800 mg (N = 6)</th>
<th>TR-701 1200 mg (N = 6)</th>
<th>TR-701 Overall (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event (AE)</td>
<td>-</td>
<td>10 (n=4)</td>
<td>4 (n=2)</td>
<td>7 (n=3)</td>
<td>2 (n=1)</td>
<td>5 (n=3)</td>
<td>28 (n=13)</td>
</tr>
<tr>
<td>Mild</td>
<td>-</td>
<td>10 (n=4)</td>
<td>4 (n=2)</td>
<td>7 (n=3)</td>
<td>2 (n=1)</td>
<td>5 (n=3)</td>
<td>28 (n=13)</td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Severe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Related AE</td>
<td>-</td>
<td>7 (n=3)</td>
<td>-</td>
<td>6 (n=3)</td>
<td>2 (n=1)</td>
<td>4 (n=3)</td>
<td>19 (n=10)</td>
</tr>
<tr>
<td>AE leading to Study Discontinuation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serious AE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

No dose effect up to 1200 mg/day

Presently proposed dosage
A short overview of phase I studies: impact of ascending doses (details)

ADVERSE EVENTS REPORTED BY AT LEAST 2 SUBJECTS IN TR-701 OVERALL

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>Overall Placebo (N = 10)</th>
<th>TR-701 200 mg (N = 6)</th>
<th>TR-701 400 mg (N = 6)</th>
<th>TR-701 600 mg (N = 6)</th>
<th>TR-701 800 mg (N = 6)</th>
<th>TR-701 1200 mg (N = 6)</th>
<th>TR-701 Overall (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All System Organ Classes</td>
<td>-</td>
<td>4 (66.7%)</td>
<td>2 (33.3%)</td>
<td>3 (50.0%)</td>
<td>1 (16.7%)</td>
<td>3 (50.0%)</td>
<td>13 (43.3%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>2 (33.3%)</td>
<td>-</td>
<td>3 (50.0%)</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>-</td>
<td>2 (33.3%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>-</td>
<td>2 (33.3%)</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>General Disorders</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>2 (6.7%)</td>
</tr>
</tbody>
</table>

- There were no deaths, Serious AEs, or discontinuations due to AEs.
- No clinically significant changes or findings were noted in clinical laboratory evaluations, vital sign measurements, 12-lead ECGs, and physical examinations.
- There was no dose-response relationship to the number of AEs and, overall, changes in safety evaluations were unremarkable.
Linezolid vs tedizolid effects on platelets (21 days [phase I trials]) *

* treatment duration of tedizolid in phase III is limited to 6 days

Prokocimer et al. ICAAC IDSA 2008; Poster F1-2069a.
Phase I: specific investigations: platelets (increasing doses)

Phase 1 MAD Study - Platelet Counts

- upper limit of normal values
- lower limit of normal values
- presently proposed dosage
# Tyramine Sensitivity in humans

<table>
<thead>
<tr>
<th></th>
<th>Linezolid&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Tedizolid&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) Tyr&lt;sub&gt;30&lt;/sub&gt; dose (mg)</td>
<td>136 (42)</td>
<td>339 (69)</td>
</tr>
<tr>
<td>Mean; Max Tyramine Sensitivity Factor (TSF)</td>
<td>3.48; 5.0</td>
<td>1.28; 2.1</td>
</tr>
<tr>
<td>Subjects with ≥2-fold TSF/total subjects</td>
<td>8/10</td>
<td>1/7</td>
</tr>
</tbody>
</table>

TSF = Tyramine Sensitivity Factor = (Tyr<sub>30</sub> following Placebo or pretreatment)/(Tyr<sub>30</sub> following TZD or LZD).

Note: 2-fold increase in TSF is threshold for clinically meaningful change in response to tyramine.  

2. Study TR701-105
### Vasopressor (Pseudoephedrine) Interaction in humans

<table>
<thead>
<tr>
<th></th>
<th>Linezolid&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Tedizolid&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Maximum SBP Change</td>
<td>Max SBP Value</td>
</tr>
<tr>
<td></td>
<td>Mean Maximum SBP Change</td>
<td>Mean Maximum SBP Change</td>
</tr>
<tr>
<td>Pseudoephedrine alone/+ placebo</td>
<td>18 (9)</td>
<td>133 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 (6)</td>
</tr>
<tr>
<td>Pseudoephedrine + drug</td>
<td>32 (10)</td>
<td>151 (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 (5)</td>
</tr>
<tr>
<td>Difference</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>1</td>
</tr>
</tbody>
</table>

4. Study TR701-114
Linezolid and tedizolid impairment of mitochondrial protein synthesis

1. Impairment of mitochondrial protein synthesis may explain linezolid-induced lactic acidosis and neuropathies

2. Both linezolid and tedizolid impair mitochondrial protein synthesis …. but this is reversible…¹

3. For linezolid, plasma concentrations of linezolid remain always > IC₅₀ → permanent inhibition ²

4. For tedizolid, free through concentrations fall < IC₅₀ → partial daily recovery ²

Linezolid adverse effects

- Drug interactions:
  - cytochrome P450: no special effect
  - antibiotics: rifampin causes a 21% reduction in LZD serum levels
  - Monoamine Oxidase Inhibition (reversible, nonselective inhibitor): adrenergic and serotonergic agents (PRECAUTIONS)

- Myelosuppression (including anaemia, leukopenia, pancytopenia, and thrombocytopenia) (WARNING)

- Hypoglycaemia

- Lactic acidosis (PRECAUTION – Immediate medical attention)

- Peripheral and Optic Neuropathy (> 28 days)

- Convulsions

In two phase I studies (n=72 and 40) with tedizolid up to 400mg/day, there was no evidence of clinical or subclinical neurologic or ophthalmologic changes

Characterization of Neurologic and Ophthalmologic Safety of Oral Administration of Tedizolid for Up to 21 Days in Healthy Volunteers

Edward Fang, MD, Kelly A. Muñoz, MS, and Philippe Prokocimer, MD*
Tedizolid and cardiac safety

Effects of therapeutic and supratherapeutic doses of oral tedizolid phosphate on cardiac repolarisation in healthy volunteers: a randomised controlled study

Shawn Flanagan a, Jeffrey Litwin b, Edward Fang c, Philippe Prokocimer a,*

a Merck & Co., Inc, Kenilworth, NJ 07033, USA
b eResearch Technology, Inc, 1818 Market Street, Philadelphia, PA 19103, USA

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b eResearch Technology, Inc., 1818 Market Street, Philadelphia, PA 19103, USA

Tedizolid and cardiac safety

Effects of therapeutic and rescue dosing of tedizolid phosphate on cardiac repolarization in healthy volunteers: a randomised controlled study

Shawn Flanagan a, Jeffrey Litwin b, c

a Merck & Co., Inc., Kenilworth, NJ 07033, USA
b eResearch Technology, Inc., 1818 Market Street, Philadelphia

tedizolid: two-sided 90% CI; Moxifloxacin: 98% CI
QTcF: QT interval corrected with Fridericia's formula

Placebo-adjusted change from baseline QTcF over time. Tedizolid: two-sided 90% CI; Moxifloxacin: 98% CI

Tedizolid and cardiac safety

PQTcF placebo-corrected change from baseline versus tedizolid plasma concentration. \( \Delta\Delta\text{QTcF} \), QTcF at each post-administration time point to baseline using the delta delta approach; QTcF, QT interval corrected with Fridericia’s formula.

\[ \Delta\Delta\text{QTcF} = 2.9141741 + (0.3164) \times (\text{tedizolid plasma concentration}) \]

Acute Bacterial Skin and Skin Structures Infections:
The new paradigms and the current situation
Typical examples of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in FDA guidance \(^1,^2\)

- Skin infections (lesions) as shown on the right with a minimum lesion surface area of approximately 75 cm\(^2\)

Examples include:
- Major cutaneous abscesses
- Wound infection
- Cellulitis
- Erysipelas

Clinical characteristics
- Early clinical response assessment at 48‒72 hours
- Acute infections
- Size requirement: ≥75 cm\(^2\)

Causative pathogens: Gram-positive bacteria (including MRSA) and Gram-negative bacteria

MRSA: methicillin-resistant *Staphylococcus aureus*

Complicated skin and skin structure infections are very common

- Complicated SSSIs (and ABSSSIs) are among the most common infections seen in clinical practice.\(^1\)
- *S. aureus* SSTI-associated hospitalisations in the US increased 123% between 2001 and 2009 and represented an increasing share of *S. aureus*-associated hospitalisations (39% to 51%).\(^2\)
- Healthcare costs increased significantly (by 34%).\(^2\)

![Graph showing the increase in *S. aureus*-SSTIs and their share of all *S. aureus* hospitalisations between 2001 and 2009.](image)

Adapted from Suaya et al. 2014.

ABSSSI: acute bacterial skin and skin structure infection; SSSI: skin and skin structure infection; SSTI: skin and soft tissue infection

MRSA rates in different countries

MRSA is highly prevalent in the Middle East

MRSA infections are a frequent cause of hospitalisations worldwide

IBSC: International Bacteremia Surveillance Collaborative (Finland, Australia, Canada, Denmark and Sweden); MRSA: methicillin-resistant *Staphylococcus aureus*; SSTI: skin and soft tissue infection

Patients with skin infections frequently have comorbidities

* Patients could have ≥1 comorbidity. Retrospective study: 2008–2011 with a cSSSI diagnosis (N=460)

cSSSI: complicated skin and skin structure infection; CHF: congestive heart failure; HIV: human immunodeficiency virus; IV: intravenous; PVD: peripheral vascular disease

Inappropriate antibiotic treatment in patients with surgical site infections resulted in worse clinical outcomes.

- Mortality rate after hospital admission:
  - Appropriate: 0.2%
  - Inappropriate: 1.2%
  - *P* < 0.01

- Hospital length of stay:
  - Appropriate: 4.6 days
  - Inappropriate: 10.4 days

Inappropriate antibiotic therapy increased mortality rate and hospital stay length.

Initial treatment failure due to inappropriate antibiotic therapy was defined as those hospitalised patients who received a new antibiotic after >24 hours, or underwent drainage/debridement/amputation >72 hours after hospital admission.

Do we need antibiotics for ABSSSIs?
Some say that antibiotics are not needed for "minor skin infections"…

**Skin Abscess**

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

**CASE VIGNETTE**

**A Woman with an Abscess**

MaryAnn B. Wilbur, M.D., M.P.H.

- one area of fluctuance (2 cm diameter, with tenderness, on the left anterior thigh…

- Erythema up to 2 cm beyond the edges of the fluctuance.

- No spontaneous drainage and no associated lymphadenopathy.

**TREATMENT OPTION 1**

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Robert S. Daum, M.D.

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Evidence-based medicine...

Trimethoprim–Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess


BACKGROUND
U.S. emergency department visits for cutaneous abscess have increased with the emergence of methicillin-resistant Staphylococcus aureus (MRSA). The role of antibiotics for patients with a drained abscess is unclear.

CONCLUSIONS
In settings in which MRSA was prevalent, trimethoprim–sulfamethoxazole treatment resulted in a higher cure rate among patients with a drained cutaneous abscess than placebo. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00729937.)
## MSSA SSTI: Available treatments

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(di/flu)cloxacillin</td>
<td>500 mg every 6 h</td>
<td>• IV and oral agents (but low bioavailability !)</td>
</tr>
<tr>
<td>oxacillin</td>
<td></td>
<td>• short half life (must be compliant !)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• allergies</td>
</tr>
<tr>
<td>nafcillin</td>
<td>1-2 g every 4 h</td>
<td>• IV only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• best choice but must be compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• allergies</td>
</tr>
<tr>
<td>clindamycin *</td>
<td>600 mg every 8 h IV</td>
<td>• Bacteriostatic</td>
</tr>
<tr>
<td></td>
<td>450 mg every 6 h PO</td>
<td>• active against MRSA but emergence of resistance (inducible)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• knowledge of local susceptibility is a must</td>
</tr>
<tr>
<td>doxycycline *</td>
<td>100 mg BID PO</td>
<td>• Bacteriostatic</td>
</tr>
<tr>
<td>minocycline *</td>
<td></td>
<td>• limited recent clinical experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• knowledge of local susceptibility is a must</td>
</tr>
<tr>
<td>TMP/SMX *</td>
<td>160/800 mg BID PO</td>
<td>• Bactericidal</td>
</tr>
<tr>
<td>(or more …)</td>
<td></td>
<td>• limited recent clinical experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• knowledge of local susceptibility is a must</td>
</tr>
</tbody>
</table>

* may also work on MRSA but requires documentation

Properties of the ideal antibiotic

- Adapted spectrum of activity
- Short treatment duration
- Available in IV and oral formulations
- Low toxicity
- Low potential for resistance development
- Good tissue penetration
- Minimal need for dose adjustment in special populations

Treatment duration can be obtained when early switch/early discharge is implemented

- **1502 patients with confirmed MRSA typical cSSTI** (cellulitis, abscess, wound or ulcer, …[requiring substantial surgical intervention]; exclud. diabetic foot, osteomyelitis, endocarditis, meningitis, joint infection, necrotising fasciitis, gangrene, prosthetic joint infection or prosthetic implant/device infection…)

- **across 12 EU countries**

- **Early switch (ES) criteria:**
  - afebrile ( < 38°C for 24h)
  - normalized WBC (not > 4 x 10⁹ and not > 12 x 10⁹ /L)
  - no unexplained tachycardia
  - SBP ≥ 100 mm Hg
  - oral fluids and medication tolerated

- **Early discharge (ED)**
  - all of the ES criteria
  - no reason to stay in hospital except infection treatment
  - 1ˢᵗ line antibiotic: vancomycin (IV)
  - Switch to oral: mainly with linezolid (main reason for ED)

Criteria for Early Switch / Early discharge

Implementing criteria-based early switch/early discharge programmes: a European perspective

D. Nathwani\textsuperscript{1}, W. Lawson\textsuperscript{2}, M. Dryden\textsuperscript{3}, J. Stephens\textsuperscript{4}, S. Corman\textsuperscript{4}, C. Solem\textsuperscript{5}, J. Li\textsuperscript{5}, C. Charbonneau\textsuperscript{6}, N. Baillon-Plot\textsuperscript{6}, S. Haider\textsuperscript{7} and C. Eckmann\textsuperscript{8}

1) Ninewells Hospital and Medical School, Dundee, 2) Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, 3) Hampshire Hospitals NHS Foundation Trust, Winchester, Hampshire, UK, 4) Pharmen International, Bethesda, MD, 5) Pfizer Inc., San Diego, CA, USA, 6) Pfizer Inc., Paris, France, 7) Pfizer Inc., Groton, CT, USA and 8) Klinikum Peine, Academic Hospital of Medical University Hannover, Peine, Germany

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D. Nathwani1, W. Lavell1, A. Teo2, S. Haider7 and C. Ecker, D. Nathwani, S. Holt3,4,5,1 and S. Boulton6

1 Ninewells Hospital and Medical School, Ninewells Medical Education and Research Centre, Ninewells, Dundee DD1 9SY, UK
2 Foundation Trust, Winchester, Hampshire, UK
3 Massachusetts Institute of Technology, Cambridge, MA, USA
4 AstraZeneca, Wilmington, DE, USA
5 Novartis Institutes for BioMedical Research Inc., Groton, CT, USA and Nature Reviews Nephrology

Table 1. Criteria used to determine patient eligibility for intravenous to oral antimicrobial switch therapy

<table>
<thead>
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<tr>
<td>Temperature &lt;38°C or &gt;36°C for 24–48 h; normalizing body temperature; afebrile for at least 8–24 h [5,9,12,14,16–18,20,21,23,25]</td>
</tr>
<tr>
<td>No unexplained tachycardia, haemodynamic instability [7,9,14,16,21,23,25]</td>
</tr>
<tr>
<td>Clinical improvement, no clinical indication for intravenous therapy [5,7,9,12,17–20,23,25]</td>
</tr>
<tr>
<td>Oral fluids/food tolerated, no reason to believe oral absorption of antimicrobials may be poor; may be by nasogastric/gastric feeding tube [5,7,9,12,14–20,22,23,25]</td>
</tr>
<tr>
<td>Improving white blood cell count [5,9,12,14,16,17,20,23,25]</td>
</tr>
<tr>
<td>Improving C-reactive protein [5,9]</td>
</tr>
<tr>
<td>Suitable oral antimicrobial therapy [9,12,23,24,33]</td>
</tr>
<tr>
<td>No surgery scheduled within next 24–36 h [16,25]</td>
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Do we need antibiotics for ABSSSIs?
Some say that antibiotics are not needed for "minor skin infections"…

Skin Abscess

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we do need antibiotics…
Tedizolid clinical development
What do you wish to see for tedizolid clinically?

- What is the human safety profile?
  ➔ **Phase I studies** (ascending doses)

- What is the useful dose?
  ➔ **PK/PD** (infected animal)
  ➔ **Phase II studies** (patients)

- What are the efficacy and safety profiles against "standard of care" in a large meaningful population?
  ➔ **Phase III studies**
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Tedizolid phase II study

Phase 2, Randomized, Double-Blind, Dose-Ranging Study Evaluating the Safety, Tolerability, Population Pharmacokinetics, and Efficacy of Oral Torezolid Phosphate in Patients with Complicated Skin and Skin Structure Infections


Trius Therapeutics, Inc., 6310 Nancy Ridge Road, Suite 105, San Diego, California 92121; SERRG, Inc., 5210 Armour Road Suite 400, Columbus, Georgia 31904; eStudy Site, 752 Medical Center Court, Suite 105, Chula Vista, California 91911; Ordway Research Institute, 150 New Scotland Avenue, Albany, New York 12208; and Duke Clinical Research Institute, 2400 Pratt Street, Durham, North Carolina 27705
Tedizolid phase II study

Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Oral Torezolid Phosphate in the Treatment of Skin and Skin Structure Infections

P. Prokocimer, P. Bien, J. Surber, Trius Therapeutics, Inc., 6310 Nancy Ridge Drive, San Diego, CA 92121

FIG. 1. Populations analyzed.
TABLE 3. Clinical cure rates with torezolid phosphate at TOC in the CE population, by lesion type and size

<table>
<thead>
<tr>
<th>Lesion type or size</th>
<th>Cure rate by torezolid phosphate dose (no. of patients cured/total no. of patients in group [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg</td>
</tr>
<tr>
<td>Abscess</td>
<td>43/43 (100)</td>
</tr>
<tr>
<td>Wound</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>11/12 (91.7)</td>
</tr>
<tr>
<td>Lesion size</td>
<td></td>
</tr>
<tr>
<td>5 &lt; 10 cm</td>
<td>21/21 (100)</td>
</tr>
<tr>
<td>10 &lt; 20 cm</td>
<td>21/21 (100)</td>
</tr>
<tr>
<td>≥20 cm</td>
<td>13/14 (92.9)</td>
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## Tedizolid phase II study

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<td></td>
<td>300 mg</td>
</tr>
<tr>
<td></td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion type Abscess</td>
<td>43/43 (100)</td>
</tr>
<tr>
<td></td>
<td>36/38 (94.7)</td>
</tr>
<tr>
<td></td>
<td>39/42 (92.9)</td>
</tr>
<tr>
<td>Wound</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td></td>
<td>3/4 (75)</td>
</tr>
<tr>
<td></td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>11/12 (91.7)</td>
</tr>
<tr>
<td></td>
<td>12/12 (100)</td>
</tr>
<tr>
<td></td>
<td>7/7 (100)</td>
</tr>
<tr>
<td>Lesion size 5 &lt; 10 cm</td>
<td>21/21 (100)</td>
</tr>
<tr>
<td></td>
<td>14/15 (93.3)</td>
</tr>
<tr>
<td></td>
<td>15/17 (88.2)</td>
</tr>
<tr>
<td>10 &lt; 20 cm</td>
<td>21/21 (100)</td>
</tr>
<tr>
<td></td>
<td>26/28 (92.9)</td>
</tr>
<tr>
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<td>11/11 (100)</td>
</tr>
<tr>
<td></td>
<td>8/9 (88.9)</td>
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</table>

This IS the effective dose!
Tedizolid phase III studies: why two non-inferiority trials?

1. For most indications, both FDA and EMA usually require two independent studies demonstrating efficacy and safety

- It is preferred that two major (pivotal) studies of efficacy are performed for each clinical indication sought… (EMA)

- … Two adequate and well-controlled trials generally are recommended to provide evidence of effectiveness … (FDA)

- General Considerations for Clinical Trials (EMEA - March 1998 -- CPMP/ICH/291/95)

- Evaluation of medicinal products indicated for treatment of bacterial infections - Adopted guideline (EMA - 2011 -- CPMP/EWP/558/95 rev 2)

- Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (FDA - CDER -- October 2013)
2. Appropriate **comparators** should be utilized and adequate numbers of subjects included to achieve the study objectives

- Comparisons may be made with **placebo, no treatment, active controls** or of different doses of the drug under investigation

- The choice of the comparator depends, among other things, on the **objective of the trial**

- The regimen selected [for comparison] should be considered **one of the best available treatments based on** one or more of previous studies, medical opinion, indication specific treatment guidelines… and **anticipated prevalence of resistance to the comparative agent at the investigative sites** … (EMA)

- For ABSSSI, there were **no placebo-controlled trials** reported in the historical literature… (FDA)

---

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<table>
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<tr>
<th></th>
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<th></th>
</tr>
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<tbody>
<tr>
<td>cSSSI</td>
<td>ABSSSI</td>
<td></td>
</tr>
<tr>
<td>Infection Type</td>
<td>Large abscess, wound, cellulitis, DFI, chronic ulcer</td>
<td>Large abscess, wound, cellulitis/erysipelas – min. 75 cm²</td>
</tr>
<tr>
<td>Infection Severity</td>
<td>Intermediate/Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Primary Endpoints</td>
<td>Subjective Clinicians assessment at 7–14 days after EOT</td>
<td>Objective ≥20% reduction in lesion size at 48–72 hours</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>Varied Low Potential for Differentiation</td>
<td>Higher Potential for differentiation</td>
</tr>
</tbody>
</table>

- **ABSSSI** = acute bacterial skin and skin structure infections
- **cSSSI** = complicated skin and skin structure infections; including chronic ulcers, diabetic foot infections, and burns – very different in nature, treated differently (polymicrobial) and chronic

* The 2010 FDA Guidance primary endpoint: "Cessation of lesion spread & fever at 48-72 h" was updated in 2013

# FDA new clinical guidance (2013)

<table>
<thead>
<tr>
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## Cellulitis/erysipelas
- Diffuse skin infection characterised by spreading of oedema, redness, and heat \(^1,2\)
- May be accompanied by lymphangitis and regional lymph node inflammation \(^2\)
- Erysipelas may be differentiated with raised skin lesions and clear demarcation line of affected and unaffected areas \(^2\)

## Wound infection
- Purulent drainage with oedema, redness, and/or induration of the surrounding wound \(^1\)

## Cutaneous abscess
- Involves the dermis and deeper skin tissues in the presence of pus collections \(^1,2\)

1 see note * in the bottom of the slide

* Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (FDA - CDER -- October 2013)  
Clinical presentations of skin infections

Types of skin and soft tissue infections

- **cSSTIs:** Necrotising fasciitis, Pyomyositis
- **cSSSIs:** Infected ulcer, Diabetic foot infections
- **ABSSSIs:** Wound infections, Cellulitis and erysipelas, Cutaneous abscess
- **uSSSIs:** Impetigo, Furuncles and carbuncles

ABSSSIs: acute bacterial skin and skin structure infections; cSSSIs: complicated skin and skin structure infections; cSSTIs: complicated skin and soft tissue infections; uSSSIs: uncomplicated skin and skin structure infections

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Measurement of Lesions

**Measurement for All Lesions**
Head-to-toe vs largest perpendicular width

**Additional Measurement for Abscesses and Wounds***
(at screening only)
Abscess/wound margin to perimeter of erythema, oedema, and/or induration/cellulitis

*Erythema extending at least 5cm in the shortest distance from the peripheral margin of the abscess or wound

Two Methods to Measure the Lesion Size
Ruler Technique (RT) and Digital Planimetry (DP)

- RT: the longest head-to-toe length and the greatest perpendicular width of a lesion; accurate for rectangular or square lesions
- DP: outline the edge of erythema with a surgical marker, then take photographic images of the lesions with digital camera.

ESTABLISH-1 (PO) and -2 (IV/PO)
Primary & Secondary Efficacy Endpoints

**ESTABLISH-1 (PO)**

**Primary Endpoint**
- ✓ Cessation of spread and afebrile at 48–72 hours after first dose of drug

**Key Secondary Endpoint**
- ✓ ≥ 20% Reduction in lesion area at 48–72 hours after first dose of drug
- ✓ Programmatic clinical response at EOT
- ✓ Investigator’s assessment of clinical response at PTE

**ESTABLISH-2 (IV/PO)**

**Primary Endpoint**
- ✓ ≥ 20% Reduction in lesion area at 48–72 hours after first dose of drug

**Key Secondary Endpoint**
- ✓ Cessation of spread and afebrile at 48–72 hours after first dose of drug
- ✓ Programmatic clinical response at EOT
- ✓ Investigator’s assessment of clinical response at PTE

EOT: end of therapy;  
PTE: post-treatment evaluation  
IV: intravenous;  
PO: oral

ESTABLISH-1 (PO) and -2 (IV/PO) Phase 3 Trial Design: combining FDA and EMA endpoints

(double-blind, double-dummy)

Day 1
48–72 hours after initial dose

End of Therapy Day 11

Post-Therapy Evaluation Day 18–25

Late Follow-Up Day 29–36

ESTABLISH-1 (112): All oral

N=667 ABSSSI patients

6 days, Oral Tedizolid QD
4 days Placebo

10 days, Oral Linezolid BID

Post-treatment evaluations

ESTABLISH-2 (113): IV initiated with option of switching to oral

N=666 ABSSSI patients

6 days IV/Oral Tedizolid QD
4 days Placebo

10 days, IV/Oral Linezolid BID

Post-treatment evaluations

• Cessation of spread and absence of fever
• ≥20% decrease from baseline in lesion area
FDA 1° endpoint

Sustained clinical response
FDA 2° endpoint

Investigator’s assessment of clinical response
EMA 1° endpoint

Sustained clinical success
EMA 2° endpoint

4-29 Nov 2017
mRSA Management - Singapore - Kuala-Lumpur
Establish-1 and Establish-2
Integrated Efficacy Data

with 200 mg/daily and 6 days only!

Can we do it?

### Baseline Key Demographics and Infection Types

<table>
<thead>
<tr>
<th>All randomised patients *</th>
<th>ESTABLISH-1 &amp; ESTABLISH-2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Tedizolid 200mg QD for 6 days</td>
</tr>
<tr>
<td></td>
<td>%, ITT (n=664)</td>
</tr>
<tr>
<td>Age (yrs), mean</td>
<td>44.6</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>89.2</td>
</tr>
<tr>
<td>≥65 years</td>
<td>10.8</td>
</tr>
<tr>
<td>Male, %</td>
<td>64.6</td>
</tr>
<tr>
<td>IV drug use</td>
<td>27.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.7</td>
</tr>
<tr>
<td>BMI (Range), kg/m²</td>
<td>14.2–69.9</td>
</tr>
<tr>
<td>Types of infection:</td>
<td></td>
</tr>
<tr>
<td>Cellulitis/erysipelas</td>
<td>45.3</td>
</tr>
<tr>
<td>Major abscess</td>
<td>25.3</td>
</tr>
<tr>
<td>Wound infection</td>
<td>29.4</td>
</tr>
<tr>
<td>Med. Lesion Surface Area (cm²)</td>
<td>197.1</td>
</tr>
</tbody>
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* Integrated data

Geographical distribution of patients similar between the two treatment arms from US, Canada, Europe, South Africa and Pacific Rim

Prokocimer et al. JAMA 2013;309(6):559–569
Moran et al. LID 2014;14(8):696–705
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<tr>
<td>BMI (Range), kg/m²</td>
<td>14.2–69.9</td>
</tr>
<tr>
<td>Types of infection:</td>
<td></td>
</tr>
<tr>
<td>Cellulitis/erysipelas</td>
<td>45.3</td>
</tr>
<tr>
<td>Major abscess</td>
<td>25.3</td>
</tr>
<tr>
<td>Wound infection</td>
<td>29.4</td>
</tr>
<tr>
<td>Med. Lesion Surface Area (cm²)</td>
<td>197.1</td>
</tr>
</tbody>
</table>

* Integrated data

Geographical distribution of patients similar between the two treatment arms from US, Canada, Europe, South Africa and Pacific Rim

Prokocimer et al. JAMA 2013;309(6):559–569
Moran et al. LID 2014;14(8):696–705
## Baseline Pathogen Distribution

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>ESTABLISH-1 &amp; ESTABLISH-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tedizolid 200mg QD for 6 days %, ITT (n=664)</td>
<td>Linezolid 600mg BID for 10 days %, ITT (n=669)</td>
</tr>
<tr>
<td><strong>All randomised patients</strong> *</td>
<td></td>
</tr>
<tr>
<td>No pathogen identified</td>
<td>38.9</td>
</tr>
<tr>
<td>Any Gram-positive pathogen</td>
<td>61.1</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>49.5</td>
</tr>
<tr>
<td><strong>MRSA</strong></td>
<td>21.2</td>
</tr>
<tr>
<td>MSSA</td>
<td>28.3</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>5.0</td>
</tr>
<tr>
<td><em>S. anginosus-milleri</em> group</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*Integrated data

Prokocimer et al. JAMA 2013;309(6):559–569
Moran et al. LID 2014;14(8):696–705
ESTABLISH-1 and -2 Integrated Efficacy
Non-inferiority was Achieved at 48-72 hours in All Subgroups

<table>
<thead>
<tr>
<th>ITT analysis set</th>
<th>Tedizolid, % (n/N)</th>
<th>Linezolid, % (n/N)</th>
<th>Treatment difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>82.6 (489/592)</td>
<td>79.5 (485/610)</td>
<td>3.1 (-1.3; 7.6)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>73.6 (53/72)</td>
<td>78.0 (46/59)</td>
<td>-4.9 (-19.4; 10.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83.0 (356/429)</td>
<td>80.1 (330/412)</td>
<td>2.8 (-2.4; 8.1)</td>
</tr>
<tr>
<td>Female</td>
<td>79.1 (186/235)</td>
<td>78.2 (201/257)</td>
<td>1.0 (-6.4; 8.2)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 kg/m²</td>
<td>83.8 (389/464)</td>
<td>79.4 (347/437)</td>
<td>4.4 (-0.6; 9.5)</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>76.5 (153/200)</td>
<td>79.3 (184/232)</td>
<td>-2.8 (-10.8; 5.0)</td>
</tr>
<tr>
<td>IV drug use</td>
<td>82.5 (151/183)</td>
<td>79.6 (164/206)</td>
<td>2.9 (-5.0; 10.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>70.7 (41/58)</td>
<td>82.1 (55/67)</td>
<td>-10.9 (-26.1; 4.0)</td>
</tr>
<tr>
<td>Bacteraemia at baseline</td>
<td>100 (11/11)a</td>
<td>69 (11/16)</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Pathogens isolated included: Staphylococcus aureus (methicillin-resistant S. aureus, 2 patients; methicillin-sensitive S. aureus, 4 patients; eradication confirmed for all), Streptococcus pyogenes (2 patients), Streptococcus constellatus (1 patient), Staphylococcus hominis (1 patient), Streptococcus agalactiae (1 patient).

BMI = body mass index; CI = confidence interval; ND = not done; ITT = intent to treat; IV = intravenous.

What about lesion localizations?
What about lesion localizations?

Tedizolid and Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections of the Lower Extremity versus Non-Lower Extremity: Pooled Analysis of Two Phase 3 Trials

What about lesion localizations?

Conclusions: Post-therapy evaluations showed that the clinical response of lower-extremity ABSSSI to tedizolid and linezolid was comparable to that of ABSSSI in other locations. A short 6-day course of once-daily tedizolid was as effective as a 10-day course of twice-daily linezolid in treating patients with lower-extremity ABSSSI.
Are these approaches in line with other clinical symptoms?

Clinician-reported lesion measurements in skin infection trials: Definitions, reliability, and association with patient-reported pain

John H. Powers III MD, Anita F. Das PhD, Carisa De Anda PharmD, Philippe Prokocimer MD

* George Washington University School of Medicine, Washington, DC, USA
b InClin, San Mateo, CA, USA
c Merck & Co, Inc., Kenilworth, NJ, USA

Are these approaches in line with other clinical symptoms?

Association of patient-reported pain with median ABSSSI lesion area in the Phase 3 trials, illustrating that pain decreases along with a reduction in lesion size, regardless of whether pain is measured by (A) the Visual Analog Scale or (B) Faces Rating Scale.

ESTABLISH-1 and -2 Integrated Per-pathogen Microbiological Response at PTE

<table>
<thead>
<tr>
<th>MITT Analysis Set</th>
<th>Tedizolid 200mg QD for 6 days % (n)</th>
<th>Linezolid 600mg BID for 10 days % (n)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>88.8 (292/329)</td>
<td>88.9 (304/342)</td>
<td>-0.1 (-5.0; 4.7)</td>
</tr>
<tr>
<td>MRSA</td>
<td>84.4 (119/141)</td>
<td>82.2 (120/146)</td>
<td>2.2 (-6.6; 10.9)</td>
</tr>
<tr>
<td>MSSA</td>
<td>92.0 (173/188)</td>
<td>93.9 (186/198)</td>
<td>-1.9 (-7.4; 3.3)</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>90.9 (30/33)</td>
<td>95.0 (19/20)</td>
<td>-4.1 (-19.8; 16.1)</td>
</tr>
<tr>
<td>S. anginosus-milleri group</td>
<td>73.3 (22/30)</td>
<td>89.3 (25/28)</td>
<td>-15.7 (-35.4; 5.7)</td>
</tr>
</tbody>
</table>

High potency across all Gram + isolates!

Establish-1 and Establish-2
Integrated Safety Data

are we safe with our patients?

### ESTABLISH-1 and -2 Integrated Safety: Overall Adverse Events

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event (TEAE)</th>
<th>Tedizolid % (n=662)</th>
<th>Linezolid % (n=662)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>283 (42.7)</td>
<td>286 (43.2)</td>
</tr>
</tbody>
</table>

Most Adverse Events Reported were Mild or Moderate in Severity

#### Tedizolid
- Mild: 58%
- Moderate: 29%
- Severe: 11%
- None: 2%

#### Linezolid
- Mild: 57%
- Moderate: 29%
- Severe: 12%
- None: 2%

### ESTABLISH-1 and -2 Integrated Safety: Overall Adverse Events

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event (TEAE)</th>
<th>Tedizolid % (n=662)</th>
<th>Linezolid % (n=662)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related TEAE</td>
<td>148 (22.4)</td>
<td>185 (27.9)</td>
</tr>
<tr>
<td>TEAE leading to discontinuation of study drug</td>
<td>3 (0.5)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>12 (1.8)</td>
<td>13 (2.0)</td>
</tr>
<tr>
<td>Drug-related serious TEAE</td>
<td>0 (0.0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Any TEAE leading to death*</td>
<td>2 (0.3)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Overall TEAE rates were similar between tedizolid- and linezolid-treated patients

* Not related to study drug

---

### ESTABLISH-1 and -2 Integrated Safety: TEAEs ≥ 1% in "Preferred Terms"

<table>
<thead>
<tr>
<th>System Organ Class &quot;Preferred Term&quot;</th>
<th>Tedizolid % (n=662)</th>
<th>Linezolid % (n=662)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>106 (16.0)*</td>
<td>152 (23.0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>54 (8.2)*</td>
<td>81 (12.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 (3.9)</td>
<td>35 (5.3)</td>
</tr>
<tr>
<td></td>
<td>19 (2.9)*</td>
<td>37 (5.6)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(IV site reactions &lt;2% both groups)</td>
<td>36 (5.4)</td>
<td>39 (5.9)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>91 (13.7)</td>
<td>78 (11.8)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>35 (5.3)</td>
<td>26 (3.9)</td>
</tr>
<tr>
<td></td>
<td>17 (2.6)</td>
<td>14 (2.1)</td>
</tr>
</tbody>
</table>

*P<0.05

**Lower incidence of gastrointestinal TEAEs in tedizolid- vs linezolid-treated patients**

Tedizolid- and linezolid-associated GI Adverse Events: time of occurrence

Tedizolid was associated with a significantly lower incidence of GI adverse events irrespective of duration of therapy

GI = gastrointestinal.

Shorr et al. AAC 2015;59(2):864-871.