New antimicrobial agents for the management of MRSA acute bacterial skin and skin structure infections (ABSSSI)

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Cellular and Molecular Pharmacology & Centre for Clinical Pharmacy
Louvain Drug Research Institute
Catholic University of Louvain, Brussels, Belgium

- 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)

Presentation: slides 1 to 87 – Back-up: slides 88 to 189

With approval of the Belgian Common Ethical Health Platform – visa no. 17/V1/8979/093661
Disclosures

Financial support from

• Non-profit Institutions:
  – 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

• Industry:
  – 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…
- Do we have an antibiotic crisis? What is available?
- Tedizolid: discovery and main properties
- ABSSSI: what are those?
- Tedizolid: an analysis of the clinical data
- Questions, objections, suggestions …

Ask questions … Stop me!
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…

Prof. G. Lemaitre, professor of Physics and Mathematics at the University who, in the 1930's, made the first suggestion of the continuous expansion of the Universe ("big bang")
(here in conversation with A. Einstein)

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)

• in 1968, the University was divided into
  – a French-speaking Université catholique de Louvain
  – a Flemish-speaking Katholieke Universiteit Leuven…
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 *…)
  - ketolides (solithromycin *…)
  - oxazolidinones (tedizolid …)
  * 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 to the Gulf States to speak about tedizolid?

to leave this?
to find the sun?
Why should a Belgian come to the Gulf States to speak about tedizolid?

or to see the Kuwait Skyline?

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

called "torezolid"
or TR-700at 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…

- **Do we have an antibiotic crisis?** What is available?
  
  - Tedizolid: discovery and main properties
  
  - **ABSSSI: what are those?**
  
  - Tedizolid: an analysis of the clinical data
  
  - Questions, objections, suggestions …
New antibiotics: what is your own view of the pipeline?
New antibiotics: where are we?

Approvals by FDA/EMA – systemic antibiotics

![Graph showing declining antibacterial approvals from 1983-1987 to 2008-2012 with labels for telavancin and ceftarolone]

New antibiotics: where are we?

Approvals by FDA/EMA – systemic antibiotics

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


Shall we succeed?
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 $^b,f$
  - 1 oxazolidinone: tedizolid $^c$

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

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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$g$ 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>
<tbody>
<tr>
<td>vancomycin</td>
<td>15 mg/kg every 12 h or continuous infusion</td>
<td>• long first choice for IV treatment of MRSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IV only and requires drug monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• may cause nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• beware of MICs ≥ 1 mg/L</td>
</tr>
<tr>
<td>linezolid</td>
<td>600 mg every 12 h IV or PO</td>
<td>• allows for efficient IV → oral switch</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• toxicities (↑ if renal insufficiency)</td>
</tr>
<tr>
<td>daptomycin</td>
<td>4 – 6 mg/kg Q24h IV</td>
<td>• bactericidal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• doses uncertain (myopathies if ↑)</td>
</tr>
<tr>
<td>ceftaroline</td>
<td>600 mg every 12 h IV</td>
<td>• bactericidal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IV only and requires compliance</td>
</tr>
<tr>
<td>oritavancin *</td>
<td>1200 mg once + 1000 mg + 500 mg at day 7</td>
<td>• bactericidal (VISA and VRSA not susceptible !)</td>
</tr>
<tr>
<td>dalbavancin *</td>
<td></td>
<td>• convenient use but long infusion time (3h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• prolonged tissue accumulation (risk ?)</td>
</tr>
<tr>
<td>delafloxacin *</td>
<td>300 mg every 12h IV 450 mg every 12h PO</td>
<td>• bactericidal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• efficient IV → oral switch</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• many severe toxicities in label (black box)</td>
</tr>
</tbody>
</table>


* 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 >1 µg/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>
<th>Odds ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events</td>
<td>163</td>
<td>188</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>424</td>
<td>1015</td>
<td>100%</td>
<td>2.69 (1.60, 4.51)</td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.38; c² = 22.59, df 10 (P = 0.01); I² = 56%. Test for overall effect: Z = 3.75 (P = 0.0002)</td>
<td></td>
<td></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

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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bae et al.</td>
<td>14</td>
<td>37</td>
<td>12</td>
</tr>
<tr>
<td>Choi et al.</td>
<td>12</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>Ferry et al.</td>
<td>9</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Hidayat et al.</td>
<td>20</td>
<td>51</td>
<td>7</td>
</tr>
<tr>
<td>Hsu et al.</td>
<td>17</td>
<td>45</td>
<td>4</td>
</tr>
<tr>
<td>Laloueza et al.</td>
<td>3</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Lodise et al.</td>
<td>6</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td>Moise et al.</td>
<td>11</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Moise-Brodet et al.</td>
<td>23</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Takesue et al.</td>
<td>34</td>
<td>97</td>
<td>85</td>
</tr>
<tr>
<td>Yoon et al.</td>
<td>14</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>163</td>
<td>424</td>
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Heterogeneity: Tau² = 0.38; c² = 22.59, df 10 (P = 0.01); I² = 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

The programme…

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

• Do we have an antibiotic crisis? What is available?

• **Tedizolid: discovery and main properties**

  • ABSSSI: what are those?

  • Tedizolid help: an analysis of the clinical data

• Questions, objections, suggestions …
But where does tedizolid come from?

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

Linezolid (LZD) vs. Tedizolid (TR-700)

- Additional methyl-tetrazolyl
- Pyridinyl replacing the morpholinyl
- Acetamido vs. free -OH

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

![Chemical structures](image)

Potential role of the tetrazolyl moiety

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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>MIC (mg/L)⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>linezolid</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td>MSSA ATCC 25923</td>
<td>2</td>
</tr>
<tr>
<td>HA-MRSA ATCC 33591</td>
<td>1</td>
</tr>
<tr>
<td>SA 238</td>
<td>2</td>
</tr>
<tr>
<td>CM 05</td>
<td>8</td>
</tr>
<tr>
<td>CA-MRSA NRS 192</td>
<td>2</td>
</tr>
<tr>
<td>NRS 384 (US300)</td>
<td>2</td>
</tr>
<tr>
<td>VISA NRS 52</td>
<td>2</td>
</tr>
<tr>
<td>VRSA VRS 1</td>
<td>1–2</td>
</tr>
<tr>
<td>VRSA VRS 2</td>
<td>1–2</td>
</tr>
<tr>
<td>animal MRSA N7112046</td>
<td>2</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td></td>
</tr>
<tr>
<td>EGD</td>
<td>1–2</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td></td>
</tr>
<tr>
<td>ATCC 33153</td>
<td>4–8</td>
</tr>
</tbody>
</table>

LZD⁸, resistant to linezolid.

⁴Representative values of at least two determinations.

⁵From the American Tissue Culture Collection (Manassas, VA, USA).

⁶Provided by P. C. Appelbaum.³⁶

⁷Provided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.

⁸From the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARS) 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.

⁹Provided by Y. Głupszynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.

³⁸Provided by P. Berche, Hôpital Necker, Paris, France.²⁸

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

- **S. aureus** (n=4499)

- **Coagulase (-) staphylococci** (n=537)

- **Enterococci** (n=873)

- **β-haemolytic streptococci** (n=975)

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, Robert K. Flamm, Ronald N. Jones, David J. Farrell, Rodrigo E. Mendes

JMI Laboratories, North Liberty, Iowa, USA; University of Iowa College of Medicine, Iowa City, Iowa, USA

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. Pfaffer, Robert K. Flamm
JMI Laboratories, North Liberty, Iowa, USA; University of Basel, Switzerland

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

![Graph showing the cumulative percentage of E. faecalis isolates with different mG/L concentrations for tedizolid and linezolid.](image)

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)
Tedizolid is also active against linezolid-resistant isolates (*cfr*⁺)

![Chemical structure of Tedizolid](image)

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<td>2</td>
<td>0.25–0.5</td>
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Activity against $cfr^+$ resistant strains …

### Oxazolidinone MICs for *S. aureus* $cfr$ strains

<table>
<thead>
<tr>
<th>Strain</th>
<th>Reference</th>
<th>Presence of $cfr$</th>
<th>MIC (μg/ml)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LZD</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>CM05Δ$^c$</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.

$^c$ CM05Δ 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.

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How to report tedizolid susceptibility?

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

Mark H Wilcox¹, Natalia Dmitrieva³, Ana Cristina Gales³, Irina Petukhova³, Suleiman Al-Obeid⁴, Flavia Rossi³ & Joseph M Blondeau⁵,⁶

How to report tedizolid susceptibility?

Susceptibility testing of new antibiotics with a new international workshop

Mark H Wilcox¹, Natalia Dmitrieva², Ana Cristina Suleiman Al-Obeid³, Flavia Rossi³ & Joseph H Brown II


Figure 1. Recommended approach for routine reporting of susceptibility of new antibiotics, for example, tedizolid. *Use of broth microdilution is also applicable.

As recommended by published evidence/according to susceptibility testing guidance [43, 47].

N5: Nonsusceptible; S: Susceptible.
Tedizolid clinical presentations

- 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

Tedizolid phosphate

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: $S \leq 0.5$ mg/L – $R > 0.5$ (EUCAST) or $\geq 2$ (FDA)

- elimination mainly by the faeces

  ✓ no need of dose adjustment in patients with renal impairment or in hemodialysis
Impact of variations in excretory functions on tedizolid pharmacokinetics

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

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

Flanagan et al Pharmacotherapy 2014;34:240–50 – PMID 23926058

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 is active in neutropenic mice

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

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

Pharmacokinetics, breakpoints, tissue distribution…

• longer half-life than linezolid $\rightarrow$ 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 macrophages (not shown)
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but what about safety?

Linezolid adverse effects

- Drug interactions:
  - cytochrome P450: no special effect
  - antibiotics: rifampin causes a 21% drop 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

**Monoamine Oxidase (MAO) Substrate Specificity**

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

**MAO-A**
- Serotonin
- Tyramine
- Dopamine
- Tryptamine
- Kynuramine
- 3-methoxytyramine

**MAO-B**
- Benzylamine
- Phenylethylamine
- N-phenylamine
- Octylamine
- N-acetylputrescine
- Milacemide
- N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

*a 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. Bartzal,* 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.

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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
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A long-term (9 months) animal study showed no evidence of neurotoxic effects of tedizolid


Nonclinical and Pharmacokinetic Assessments To Evaluate the Potential of Tedizolid and Linezolid To Affect Mitochondrial Function


Cubist Pharmaceuticals, San Diego, California, USA; College of Medicine, Central Michigan University, Mount Pleasant, Michigan, USA; Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium; WIL Research, Ashland, Ohio, USA; Cognigen Corporation, Buffalo, New York, USA
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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Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents


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

QTcF: QT interval corrected with Fridericia's formula

Tedizolid and cardiac safety

PQTCf placebo-corrected change from baseline versus tedizolid plasma concentration. ΔΔQTcF, QTcF at each post-administration time point to baseline using the delta delta approach; QTcF, QT interval corrected with Fridericia’s formula.

ΔΔQTcF = 2.9141741 + (0.3164) × (tedizolid plasma concentration).

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…

• Do we have an antibiotic crisis? What is available?

• Tedizolid: discovery and main properties

• **ABSSSI**: what are those?

• Tedizolid: an analysis of the clinical data

• Questions, objections, suggestions …
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

Clinical presentations of skin infections

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Tedizolid phase III studies

**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
Parvi 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 surgery and hospitalization. Increasingly, ABSSSIs are associated with drug-resistant pathogens, and many antimicrobial agents 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: 200 mg once daily for 6 days
- Linezolid: 600 mg twice daily for 10 days (as per label)
### 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)

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

Oct 2017
New antimicrobial agents for the management of MRSA ABSSSI
## Baseline Key Demographics and Infection Types

<table>
<thead>
<tr>
<th>All randomised patients *</th>
<th>ESTABLISH-1 &amp; ESTABLISH-2</th>
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<tr>
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<td>Tedizolid 200mg QD for 6 days</td>
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<tr>
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<td>%, ITT (n=664)</td>
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<td>Age (yrs), mean %</td>
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<tr>
<td>Male, %</td>
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<tr>
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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

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# Baseline Pathogen Distribution

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</thead>
<tbody>
<tr>
<td></td>
<td>Tedizolid 200mg QD for 6 days %, ITT (n=664)</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>MRSA</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>S. anginosus-milleri group</td>
<td>4.5</td>
</tr>
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Moran *et al.* LID 2014;14(8):696–705
Establish-1 and Establish-2
Integrated Efficacy Data

Can we do it?

with 200 mg/daily and 6 days only!

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

**ITT Analysis Set***

<table>
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<th>Time</th>
<th>Tedizolid N=664</th>
<th>Linezolid N=669</th>
</tr>
</thead>
<tbody>
<tr>
<td>48-72 hours</td>
<td>81.6</td>
<td>79.4</td>
</tr>
<tr>
<td>Early Clinical Response (≥20% lesion area Reduction)</td>
<td>2.2 (-2.0; 6.5)</td>
<td>(-4.4; 2.7)</td>
</tr>
<tr>
<td>Day 11</td>
<td>87.0</td>
<td>87.9</td>
</tr>
<tr>
<td>End of therapy (Programmatic clinical response)</td>
<td>-0.8</td>
<td>-0.1 (-3.8; 3.6)</td>
</tr>
<tr>
<td>Days 7-14 post-EOT</td>
<td>86.7</td>
<td>86.8</td>
</tr>
<tr>
<td>(Investigator assessed response)</td>
<td></td>
<td></td>
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* 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*

- **Cellulitis/erysipelas**: Tedizolid 75.7% (n=301), Linezolid 74.3% (n=307)
- **Major cutaneous abscess**: Tedizolid 85.7% (n=168), Linezolid 86.7% (n=166)
- **Wound infection**: Tedizolid 87.2% (n=195), Linezolid 81.1% (n=196)

* Pooled data

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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

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

<table>
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<th>MITT Analysis Set</th>
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<tr>
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<td>Tedizolid 200mg QD for 6 days % (n)</td>
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<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>88.8 (292/329)</td>
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<tr>
<td><strong>MRSA</strong></td>
<td>84.4 (119/141)</td>
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<tr>
<td><strong>MSSA</strong></td>
<td>92.0 (173/188)</td>
</tr>
<tr>
<td><strong>Streptococcus pyogenes</strong></td>
<td>90.9 (30/33)</td>
</tr>
<tr>
<td><strong>S. anginosus-milleri group</strong></td>
<td>73.3 (22/30)</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>
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</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 N=662

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

Linezolid N=662

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

---

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

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</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>Gastrointestinal disorders</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>General disorders and administration site conditions (IV site reactions &lt;2% both groups)</td>
<td>36 (5.4)</td>
<td>39 (5.9)</td>
</tr>
<tr>
<td>Infections and infestations</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.

Tedizolid Use was Associated with Overall Reduced Risk of Myelosuppression

Patients with reduced platelet counts during the entire study period

**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.

Tedizolid was associated with a significantly lower risk of developing thrombocytopenia.

Tedizolid is not known to increase the risk of anaemia, leukopenia, or pancytopenia.
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 McCool, Ian M. Gould, Jacqui Eales, Teresa Barata, Mick Arber, Kelly Fleetwood, Julie Glanville, and Teresa L. Kauf

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

BMC Infectious Diseases

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

Rachael McColl and Teresa L. Marsh

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?

### Table: Clinical Response

<table>
<thead>
<tr>
<th>Study</th>
<th>Train Events</th>
<th>Train Total</th>
<th>Test Events</th>
<th>Test Total</th>
<th>Odds ratio (95% CI/95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moran 2014</td>
<td>304</td>
<td>332</td>
<td>301</td>
<td>334</td>
<td>1.2 [0.7, 2.0]</td>
</tr>
<tr>
<td>ProkoTraining 2013</td>
<td>230</td>
<td>332</td>
<td>241</td>
<td>335</td>
<td>0.9 [0.6, 1.2]</td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td>[0.7, 1.3]</td>
</tr>
</tbody>
</table>

#### Figure 3: Clinical response at the end of treatment: all trials. Odds ratios (fixed-effects model)

- **Tedizolid v Linezolid**
  - Odds ratio (95% CI/95%): 0.7 [0.0, 30.6]
- **Tedizolid v Ceftaroline**
  - Odds ratio (95% CI/95%): 2.2 [0.6, 9.0]
- **Tedizolid v Teicoplanin**
  - Odds ratio (95% CI/95%): 1.7 [1.0, 3.0]
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>Study</th>
<th>Tedizolid</th>
<th>Linezolid</th>
<th>Odds ratio (95% CI/Crl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moran 2014</td>
<td>1</td>
<td>334</td>
<td>0.2 [0.0, 2.2]</td>
</tr>
<tr>
<td>Prokocevic 2013</td>
<td>2</td>
<td>331</td>
<td>1.0 [0.1, 7.2]</td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td>332</td>
<td>335</td>
<td>0.5 [0.1, 1.9]</td>
</tr>
<tr>
<td>Tedizolid v Ceftaroline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tedizolid v Daptomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tedizolid v Telavancin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tedizolid v Vancomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed Effect ITC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

risk of discontinuation
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
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

Compare also with the other available antibiotics that you have used so far …

* as shown in this presentation
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.
Please, ask questions …

Vesalius - anatomy

be critical, ask for facts!

All slide are available on [http://www.facm.ucl.ac.be](http://www.facm.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, Ghent (1904)
  - Auguste Beernaert (1909)
  - Henri Lafontaine (1913)
  - Father Dominique Pire (1958)

• Literature
  - Maurice Maeterlinck, Ghent (1911)

• Medicine
  - Jules Bordet, Brussels (1919)
  - Corneille Heymans, Ghent (1938)
  - Christian de Duve, Louvain (1974)
  - Albert Claude, Brussels (1974)

• Chemistry
  - Ilya Prigogine, Brussels (1977)

• Physics
  - François Englert, Brussels (2013)

source: http://www.nobelprize.org/
Last accessed: 10 May 2016
Discovery and Microbiology
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

Fig. 2. Models of 11 (blue) and linezolid (yellow) binding to the Escherichia coli ribosome.

tedizolid
Oxazolidinones: 1st mechanism of resistance

Chloramphenicol-florfenicol resistance (Cfr)

- First identified in several staphylococcal species (cattle, swine) (Schwarz 2000; Kehrenberg 2006)
- CM05 (Colombia) - first clinical isolate documented to carry the cfr gene (Toh 2007)
- C-8 methylation of ribosome target at A2503 (Kehrenberg 2005; Giessing 2009)
- PhLOPS_A phenotype leads to cross resistance to 6 drug classes!
  - Phenicols, Lincosamides, Oxazolidinones, Pleuromutilins, Streptogramin A and 16 membered macrolides (Long, 2006; Smith & Mankin 2008)
- Tedizolid retains potency against cfr strains and demonstrates 8 fold better activity than linezolid (Shaw 2008, Jones 2009, Livermore 2009, Locke 2009)

full
to 16
Why is tedizolid active against LZD$_R$ strains (cfr)?

LZD

TR700

Fig. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 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 C5 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 LZD strains (cfr)?

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>MIC₅₀</th>
<th>MIC₉₀</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 another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

Activities of Tedizole in Broth Microdilution against Isolates Collected in 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*</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>

* 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, Kerry E. Greenwood Quaintance, Melissa J. Karau, Robin Patel

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

Table 1. Tedizolid MIC distribution and MIC\textsubscript{90} values for tested isolates

<table>
<thead>
<tr>
<th>Strain</th>
<th>TZD—number (cumulative percentage) inhibited at MIC (mg/L)</th>
<th>TZD MIC\textsubscript{90} (mg/L)</th>
<th>TZD MIC range (mg/L)</th>
<th>LZD MIC\textsubscript{90} (mg/L)</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></td>
<td></td>
<td></td>
<td></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) 2\textsuperscript{a} (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 LR\textsuperscript{b} (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><em>E. faecium</em> (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><em>E. faecalis</em> (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 <em>E. faecium</em> (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 <em>E. faecium</em> (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.

\textsuperscript{a}These two hVISA isolates were LR, with linezolid MIC values of 8 mg/L.

\textsuperscript{b}The three isolates with tedizolid MICs of 1 mg/L did not possess the *cfr* gene.

1. hetero-vancomycin intermediate (MIC\textsubscript{90}=2 mg/L) \rightarrow associated with an increased risk of clinical failures
2. vancomycin-intermediate (MIC\textsubscript{90}=8) \rightarrow categorized as resistant by EUCAST
3. daptomycin-resistant (MIC\textsubscript{90}=8 mg/L)
4. Ilmezolid-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, South Korea, and Trius Therapeutics, Inc., San Diego, California, USA

### TABLE 1 MICs for tedizolid and linezolid against PRSP

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (µg/ml)</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>
</tr>
<tr>
<td>Linezolid</td>
<td>0.125–1</td>
<td>0.5</td>
<td>1</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 nonmeningitis pneumococcal isolates (≥2 µg/ml). For penicillin G tested against these isolates, the MIC range was 2 to 4 µg/ml, the MIC$_{50}$ was 2 µg/ml, and the MIC$_{90}$ 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.
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*

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

¹Unité de Pharmacologie cellulaire et moléculaire & Louvain, Brussels, Belgium; ²Hershey Medical Center

doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009
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
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 risk of failures!

3. Linezolid is fraught with toxicities
   – drug interactions (MAO inhibition)
   – myelosuppression, lactic acidosis…
      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

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Vancomycin Penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternal bone¹</td>
<td>57%</td>
</tr>
<tr>
<td>Heart valve⁴</td>
<td>12%</td>
</tr>
<tr>
<td>CNS</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Epithelial lining fluid³</td>
<td>18%</td>
</tr>
<tr>
<td>Lung tissue²</td>
<td>17%–24%</td>
</tr>
<tr>
<td>Bone⁵</td>
<td>7%–13%</td>
</tr>
<tr>
<td>Fat⁴</td>
<td>14%</td>
</tr>
<tr>
<td>Muscle⁴</td>
<td>9%</td>
</tr>
</tbody>
</table>

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

*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

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 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).

Muñoz et al. ECCMID 2010 P1594

This allows for a once-a-day dosing.
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 elimination is largely not through the kidney …

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

Mean cumulative percentage of radioactive dose was recovered in urine and faeces after single 204-mg (100-mCi) oral $^{14}$C-tedizolid phosphate to healthy male subjects (+/- SD)

No need of adjustment for decreased renal function

Tedizolid: Impact of renal and hepatic dysfunction

FIG 1 Plasma tedizolid concentrations over time in subjects with severe renal impairment and matched controls, shown on a semi-logarithmic scale (B).

FIG 2 Plasma tedizolid concentrations over time in subjects with impaired hepatic function and matched controls, shown on a semilogarithmic scale (B).

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

1. renal dysfunction

<table>
<thead>
<tr>
<th>Study group</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$\text{AUC}_{0-\infty}$ (µg · h/ml)</th>
<th>$\text{AUC}_{0-t}$ (µg · 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>Postdialysis 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>

$^a$ AUC$_{0-t}$, 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>
<thead>
<tr>
<th>Study group</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$\text{AUC}_{0-t}$ (µg · h/ml)</th>
<th>$\text{AUC}_{0-\infty}$ (µg · 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>

$^a$ AUC$_{0-t}$, 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 (mg/L)</td>
<td>adults *</td>
</tr>
<tr>
<td>IV</td>
<td>$C_{\text{max}}$</td>
<td>3.66 (10)</td>
<td>2.55 (34)</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-\infty}$ (µg x h/mL)</td>
<td>26.95 (10)</td>
<td>29.11 (33)</td>
</tr>
<tr>
<td>oral</td>
<td>$C_{\text{max}}$</td>
<td>2.17 (10)</td>
<td>2.23 (37)</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-\infty}$ (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

- $C_{\text{max}}$
- $fT > \text{MIC}$
- $AUC_{24h} / \text{MIC}$

Graph showing concentration over time with key PK parameters highlighted.
How to determine which PK parameter is critical?

- If you fractionate the daily dose, you change $C_{\text{max}}$ without changing $\text{AUC}_{24\text{h}}$.

![Graph](Image)

$C_{\text{max}}$ is independent of the schedule.

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

$\text{AUC}_{24\text{h}}$ is independent of the schedule.
How to determine which PK parameter is critical?

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

$$\text{AUC}_{24\text{h}} = \text{Dose}_{24\text{h}} / \text{Clearance}$$

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

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

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

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

TABLE 2. Calculated pharmacodynamic variables for 4 total daily dosages of TR-701 administered as one, two, or four equally divided doses over 24 h

<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}}/\text{MIC ratio}&lt;sup&gt;b&lt;/sup&gt;)</th>
<th>(f\text{AUC}/\text{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> \(fC_{\text{max}}/\text{MIC ratio}\), 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> \(f\text{AUC}/\text{MIC ratio}\), 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).
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*

**Graphs:**
- **Granulocytopenic Mice**
  - 24 Hour Results
  - 48 Hour Results
  - 72 Hour Results

- **Normal Mice**
  - 24 Hour Results
  - 48 Hour Results
  - 72 Hour Results

**Legend:**
- Stasis Line

**Text:**
Tedizolid becomes cidal at low doses (equivalent to human 200 mg dose) in the presence of PMN

Drusano et al. AAC 2011; 55-5300-5305
Tedizolid is cidal \textit{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$_{24h}$ = 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 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

Figure 2-1: Probability of PK/PD target attainment for tedizolid at the target AUC\(_{0-24}/\text{MIC}\) Ratio of 15

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
http://www.fda.gov/downloads/advisorycommittees/committ
esmeetingmaterials/drugs/anti-
infectivedrugsadvisorycommittee/uem390789.pdf
Last accessed: May 17, 2015
Tedizolid breakpoints (200 mg/once daily)...

<table>
<thead>
<tr>
<th>Organism group</th>
<th>S ≤ (mg/L)</th>
<th>R &gt; (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus spp.</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>IE</td>
<td>IE</td>
</tr>
<tr>
<td>Streptococcus groups A, B, C, G</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Viridans group streptococci (Streptococcus anginosus group only)</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>PK/PD breakpoints</td>
<td>IE</td>
<td>IE</td>
</tr>
</tbody>
</table>

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>Enterococcus faecalis</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)

<table>
<thead>
<tr>
<th></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

Prokocimer et al. ICAAC 2011 P1090
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>-</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>-</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

- 200 Mg TR-701
- 300 Mg TR-701
- 400 Mg TR-701
- PLACEBO

- Upper Normals
- Lower Normals
- Upper Normals
- 6 Days Dosing

Study Day

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

<table>
<thead>
<tr>
<th></th>
<th>Linezolid(^1)</th>
<th>Tedizolid(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) Tyr(_{30}) 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 = \(\frac{\text{Tyr}_{30} \text{ following Placebo or pretreatment}}{\text{Tyr}_{30} \text{ following TZD or LZD}}\). 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>Mean (SD) Maximum SBP and SBP Changes (mm Hg)</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>
<td>Mean Maximum SBP Change</td>
</tr>
<tr>
<td>Pseudoephedrine alone/+ placebo</td>
<td>18 (9)</td>
<td>133 (17)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Pseudoephedrine + drug</td>
<td>32 (10)</td>
<td>151 (15)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Difference</td>
<td>14</td>
<td>18</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


Acute Bacterial Skin and Skin Structures Infections: The new paradigms and the current situation
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


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

New antimicrobial agents for the management of MRSA ABSSSI
Inappropriate antibiotic treatment in patients with surgical site infections resulted in worse clinical outcomes

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

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

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"…

The New England Journal of Medicine

Clinical Decisions
Interactive at NEJM.org

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

Incision and Drainage Alone

Robert S. Daum, M.D.

Treatment Option 2

Incision and Drainage Followed by Trimethoprim–Sulfamethoxazole Therapy

Howard S. Gold, M.D.
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.)


we do need antibiotics…
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

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.

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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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- What is the useful dose?
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- What are the efficacy and safety profiles against "standard of care" in a large meaningful population?
  → Phase III studies
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

P. Prokocimer,1* P. Bien,1 J. Surber,2 P. Mehra,3 C. DeAnda,1 J. B. Bulitta,4 and G. R. Corey5

Trius Therapeutics, Inc., 6310 Nancy Ridge Road, Suite 105, San Diego, California 921211; SERRG, Inc., 5210 Armour Road Suite 400, Columbus, Georgia 319042; eStudy Site, 752 Medical Center Court, Suite 105, Chula Vista, California 919153; Ordway Research Institute, 150 New Scotland Avenue, Albany, New York 122084; and Duke Clinical Research Institute, 2400 Pratt Street, Durham, North Carolina 277055
Tedizolid phase II study

Phase 2, Randomized, Double-blind, Placebo-controlled Study:
the Safety, Tolerability, and Efficacy of Oral Torenzolid Phosphate for the Treatment of Skin and Skin Structure Infections

P. Prokocimer,1* P. Bien,1 J. Surber,2 P. Kolb,1 S. Jovanovic,1 J. Kipnis,1 and K. Becskei1

1Trius Therapeutics, Inc., 6310 Nancy Ridge Drive Suite 400, San Diego, CA 92121; 2Dermatologische Klinik und Poliklinik, Charité-Universitätsmedizin Berlin, Germany; 3Ordway Research Institute, Farmington, NY; 4Department of Dermatology, Duke University Medical Center, Durham, NC

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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></td>
<td>300 mg</td>
</tr>
<tr>
<td>Abscess</td>
<td>36/38 (94.7)</td>
</tr>
<tr>
<td>Wound</td>
<td>3/4 (75)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>12/12 (100)</td>
</tr>
<tr>
<td></td>
<td>400 mg</td>
</tr>
<tr>
<td>Abscess</td>
<td>39/42 (92.9)</td>
</tr>
<tr>
<td>Wound</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>7/7 (100)</td>
</tr>
<tr>
<td></td>
<td></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>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14/15 (93.3)</td>
</tr>
<tr>
<td></td>
<td>26/28 (92.9)</td>
</tr>
<tr>
<td></td>
<td>11/11 (100)</td>
</tr>
<tr>
<td></td>
<td>15/17 (88.2)</td>
</tr>
<tr>
<td></td>
<td>28/28 (100)</td>
</tr>
<tr>
<td></td>
<td>8/9 (88.9)</td>
</tr>
</tbody>
</table>


Tedizolid phase II study

<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>300 mg</td>
</tr>
<tr>
<td></td>
<td>400 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>
</tr>
</tbody>
</table>

200 mg

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)
Tedizolid phase III studies: why two non-inferiority trials?

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)

- 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)
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?

Journal of the American Podiatric Medical Association

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

Warren S. Joseph, DPM,1,2, Darrell Prokocimer, MD

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?
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.

New data on tedizolid
Post-marketing experience: a survey of selected published data

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.

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

These 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.
2. New applications

Tedizolid alone or tedizolid combined with rifampin was active in a rat model of MRSA 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.