NEW FORCES IN THE MANAGEMENT OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

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With approval of the Belgian Common Ethical Health Platform – visa no. 16/V1/7383/078554

Disclosures

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- Cerexa (ceftaroline)

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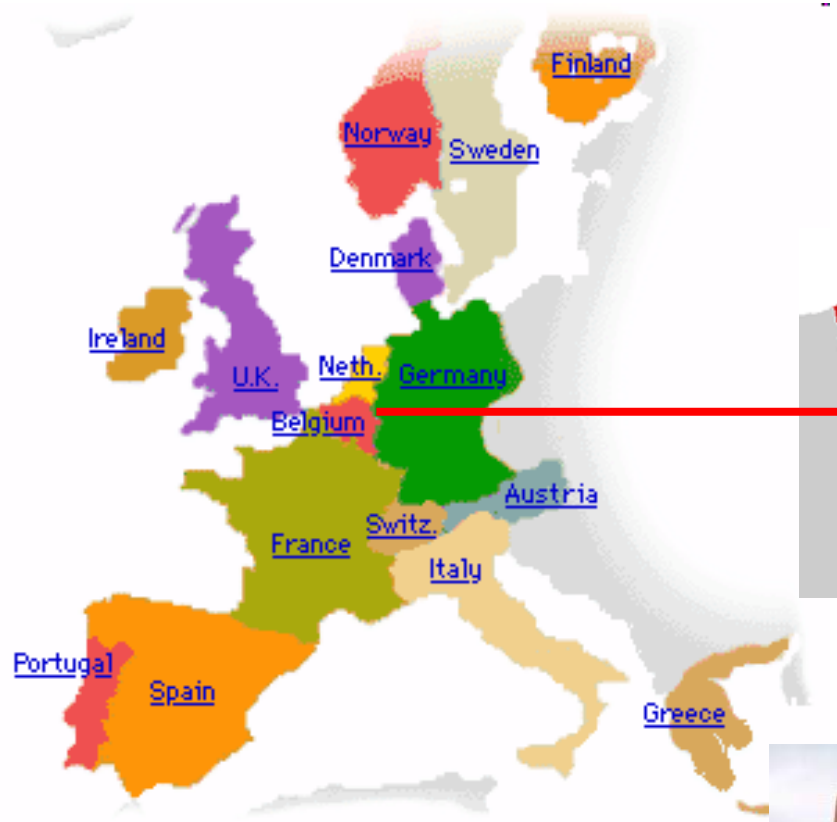
US National Institutes of Health (grant reviewing); General Assembly and Steering committee of EUCAST; European Medicines Agency (EMA); Belgian Drug Reimbursement Committee (CRM / CTG); Belgian Antibiotic Policy Coordination Committee (BAPCOC); EU program "DRIVE AB" (new economical framework for antibiotics)

Belgium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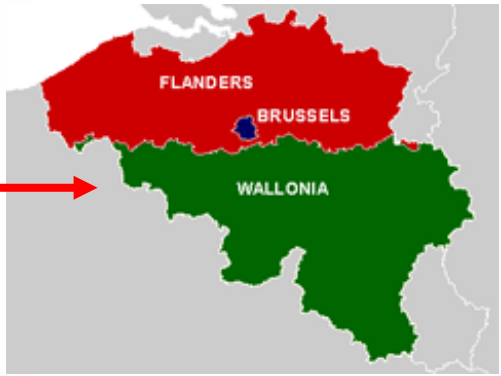
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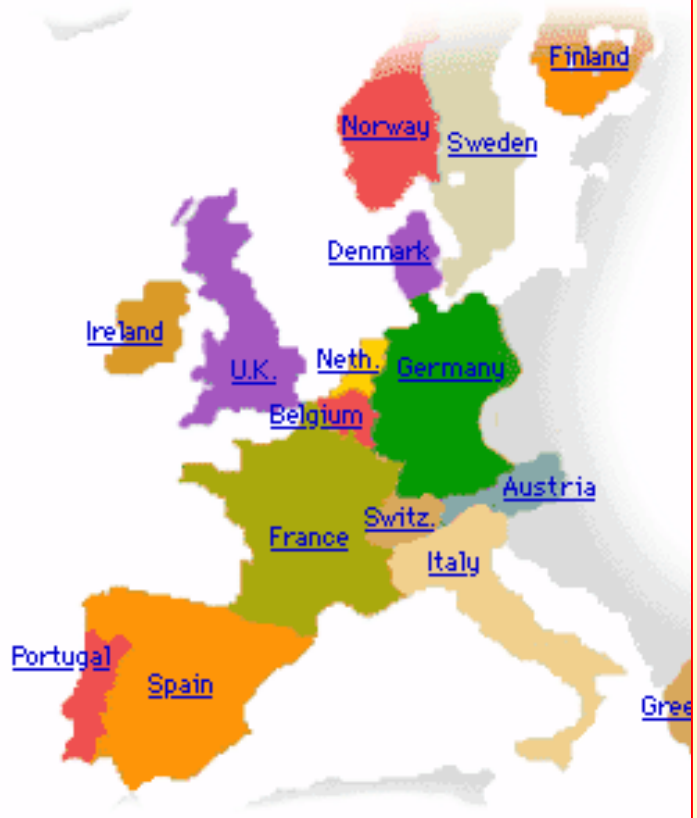


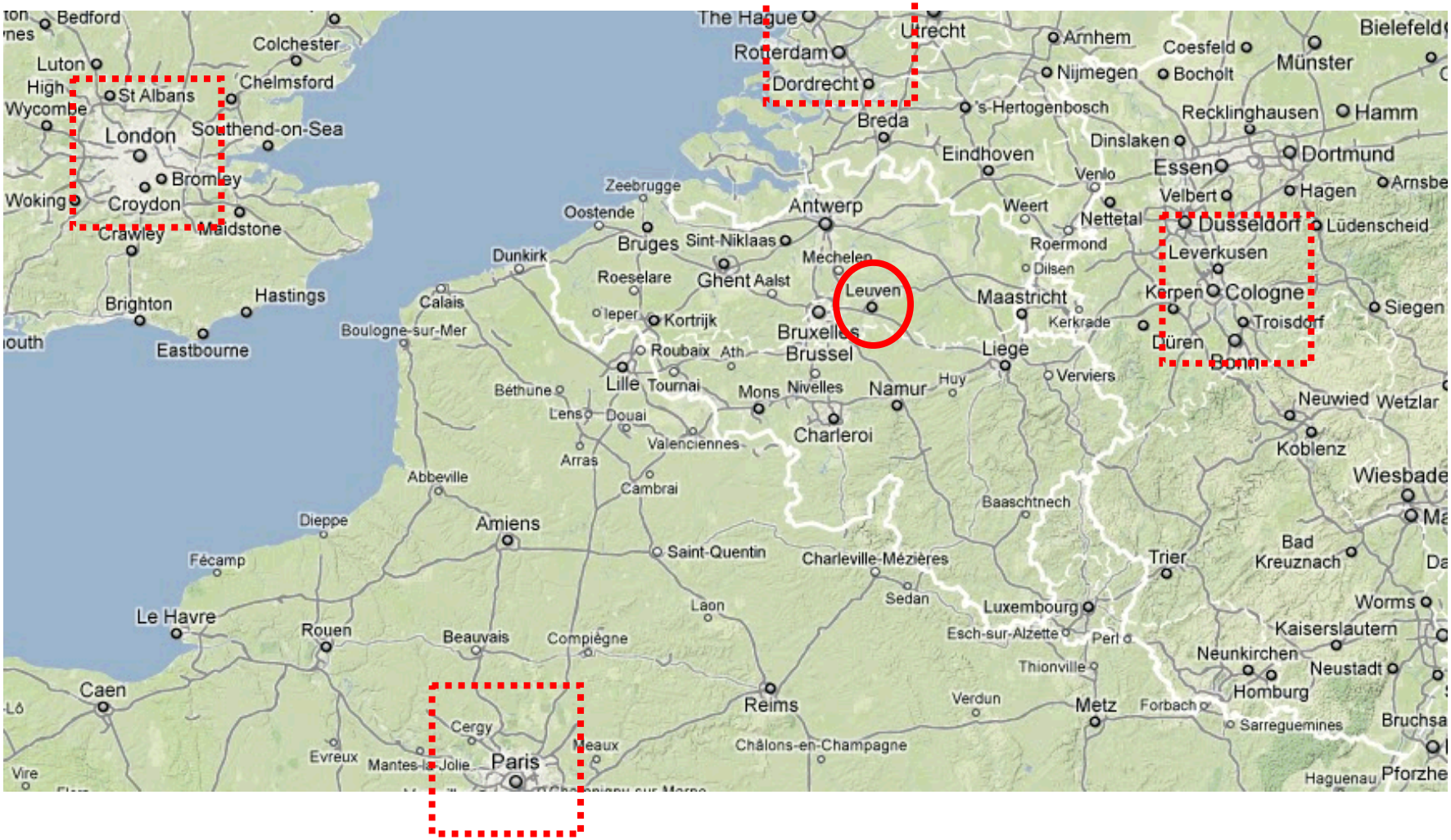
10 millions inhabitants …

10 Nobel prizes (10/850)

- **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 Prigogyne, Brussels (1977)
- **Physics**
  - François Englert, Brussels (2013)

The *Catholic University of Louvain* in brief (1 of 4)

- originally founded in **1425** in the city of **Louvain** (in French and English; known as **Leuven** in Flemish)

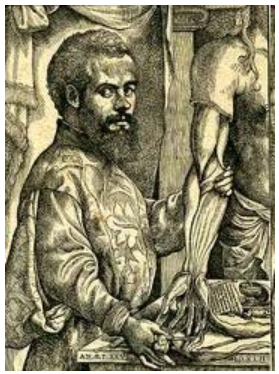


The *Catholic University of Louvain* in brief (2 of 4)

- 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

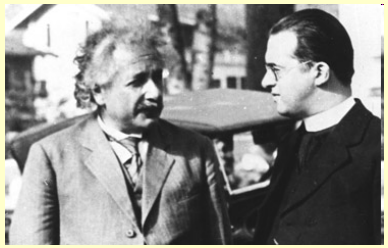
Erasmus



Vesalius

The *Catholic University of Louvain* in brief (3 of 4)

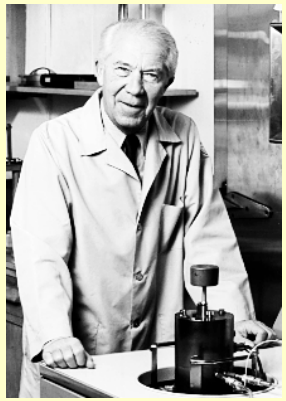
- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…



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 Universiteit 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 (Woluwé)

Université catholique de Louvain
http://www.uclouvain.be

Katholieke Universiteit Leuven
http://www.kuleuven.be

- Together, the two Universities have about **55,000 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 (finafloxacine…)
  - kétolides (solithromycin…)
  - oxazolidinones (tedizolid …)

www.facm.ucl.ac.be

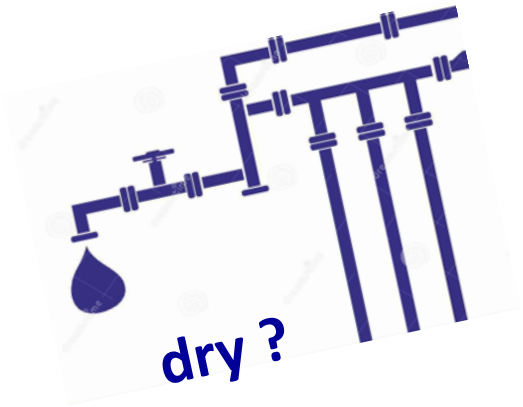
A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium

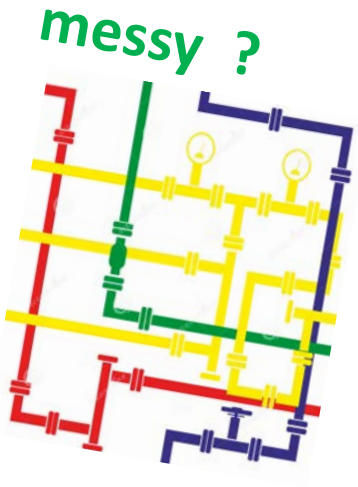
- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

ISAP

www.isap.org

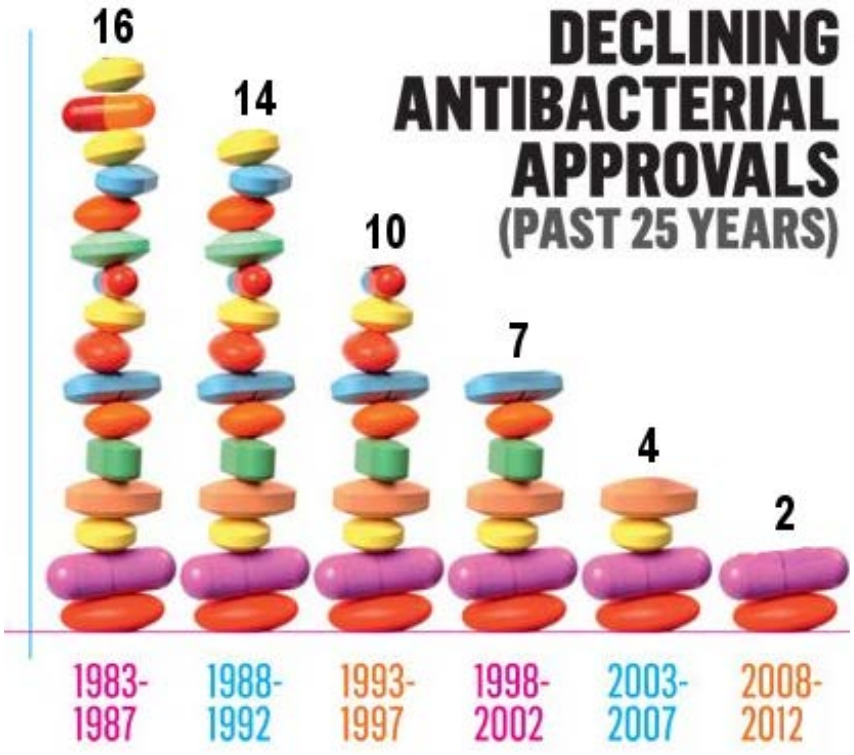
New antibiotics: what is your own view of the pipeline ?





New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics

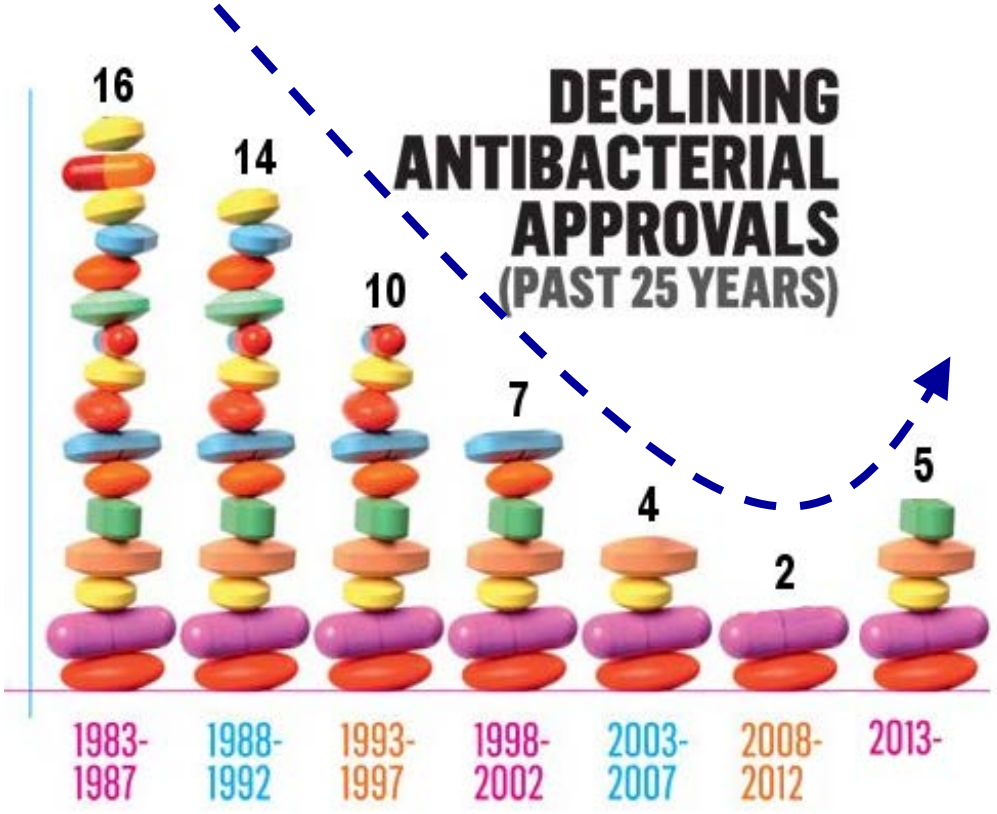


telavancin

ceftaroline

New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics



- dalbavancin
- oritavancin
- **tedizolid**
- ceftazidime/avibactam
- ceftolozane/tazobactam

- telavancin
- **ceftaroline**

Tedizolid

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Bioorganic & Medicinal Chemistry 12 (2004) 5909–5915
Bioorganic & Medicinal Chemistry

Synthesis and antibacterial activity of oxazolidinones containing pyridine substituted with heteroaromatic ring

Yeong Woo Jo,[a,b] Weon Bin Im,[b] Jae Keol Rhee,[b] Mi Ja Shim,[c] Won Bae Kim[b] and Eung Chil Choi[a,*]

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journal homepage: http://www.elsevier.com/locate/ejmech

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Original article

Discovery of torezolid as a novel 5-hydroxymethyl-oxazolidinone antibacterial agent

Weon Bin Im[a,b], Sun Ho Choi[b], Ju-Young Park[a], Sung Hak Choi[b], John Finn[c], Sung-Hwa Yoon[a,*]

[a]Department of Molecular Science and Technology, Ajou University, San 5, Woncheon, Yeongtong, Suwon 443-749, Republic of Korea
[b]Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea
[c]Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

Dong-A pharmaceuticals and tedizolid: step #1

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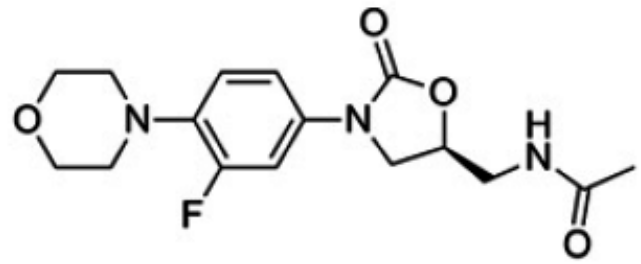
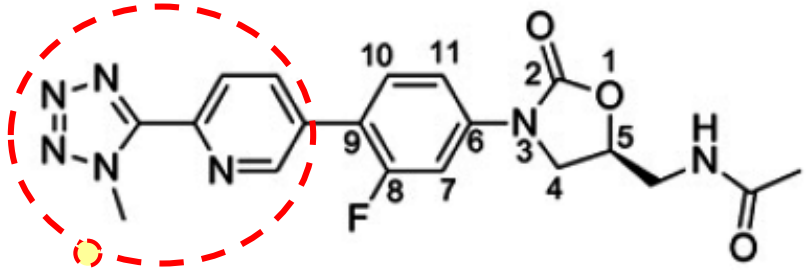


Linezolid



DA-7867

	MIC
MSSA	0.78 ug/ml
MRSA	0.78 ug/ml
VRE	0.125 ug/ml
PRSP	0.39 ug/ml

Replacing the morpholinyl by a **pyridinyl** and adding a **methyl-tetrazolyl** moiety

- **increases activity**
- **prolong half-life**

...ial potency of lead compound (DA-7867).

...a novel 5-hydroxymethyl-oxazolidinone

...agent

Weon Bin Im [a,b], Sun Ho Choi [b], Ju-Young Park [a], Sung Hak Choi [b], John Finn [c], Sung-Hwa Yoon [a,*]

[a] Department of Molecular Science and Technology, Ajou University, San 5, Woncheon, Yeongtong, Suwon 443-749, Republic of Korea
[b] Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea
[c] Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

Tedizolid has more interactions with the ribosome…

W.B. Im et al. / European Journal of Medicinal Chemistry 46 (2011) 1027–1039

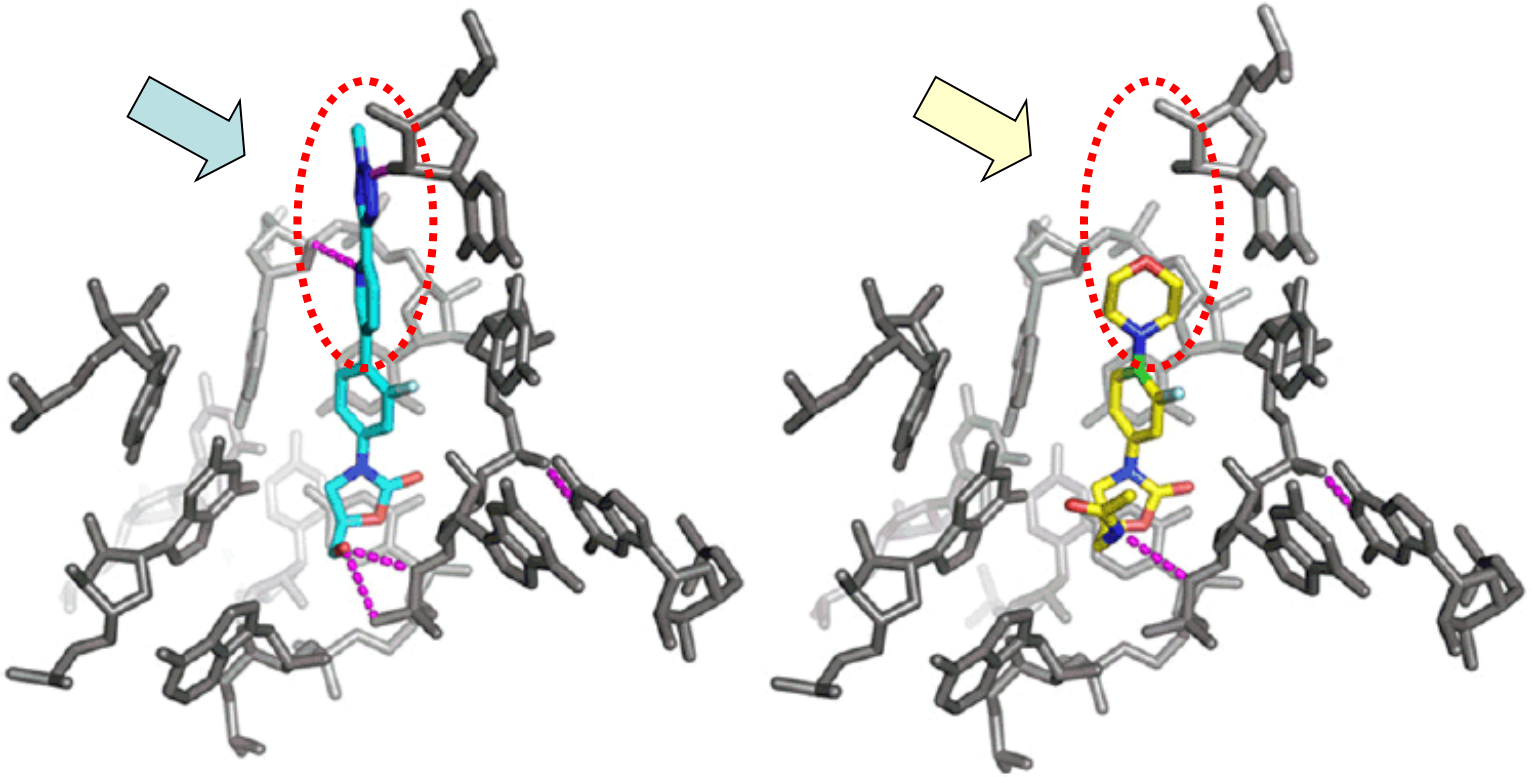
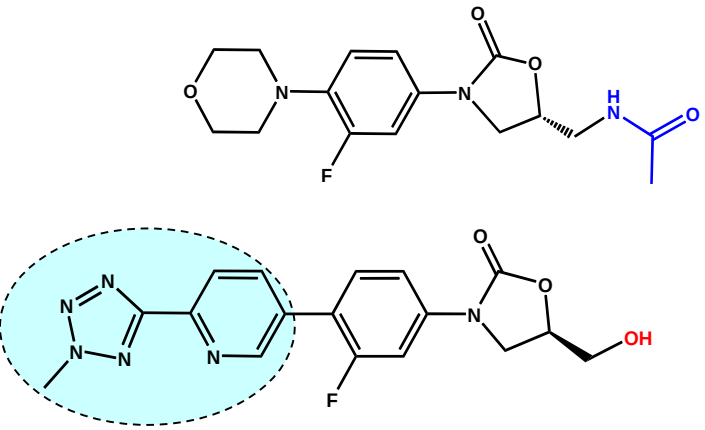


Fig. 2. Models of **11** (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.

tedizolid

Tedizolid is systematically 3-4-x more active than linezolid against LSD^S strains



potential role of the tetrazolyl moiety

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

Species, phenotype and strain no.		MIC (mg/L)[a] linezolid	torezolid
Staphylococcus aureus			
MSSA	ATCC 25923[b]	2	0.25
HA-MRSA	ATCC 33591[b]	1	0.125–0.25
	SA 238[c]	2	0.25–0.5
	CM 05[d]	8	0.25–0.5
CA-MRSA	NRS 192[e]	2	0.125–0.25
	NRS 384 (US300)[e]	2	0.25
VISA	NRS 52[e]	2	0.125
VRSA	VRS 1[e]	1–2	0.125–0.25
	VRS 2[e]	1–2	0.25
animal MRSA	N7112046[f]	2	0.125
Listeria monocytogenes			
	EGD[g]	1–2	0.125
Legionella pneumophila			
	ATCC 33153[b]	4–8	0.25–0.5

LZD^R, resistant to linezolid.
[a]Representative values of at least two determinations.
[b]From the American Tissue Culture Collection (Manassas, VA, USA).
[c]Provided by P. C. Appelbaum.[36]
[d]Provided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.
[e]From the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN272200700055C); details on each strain are available at http://www.narsa.net/content/home.jsp.
[f]Provided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.
[g]Provided by P. Berche, Hôpital Necker, Paris, France.[28]

Lemaire et al. JAC 2009; 64:1035–1043

And even for *S. aureus* of different epidemiological origin…

AAC Journals.ASM.org
Antimicrobial Agents and Chemotherapy 2013 57 p. 2892–2895

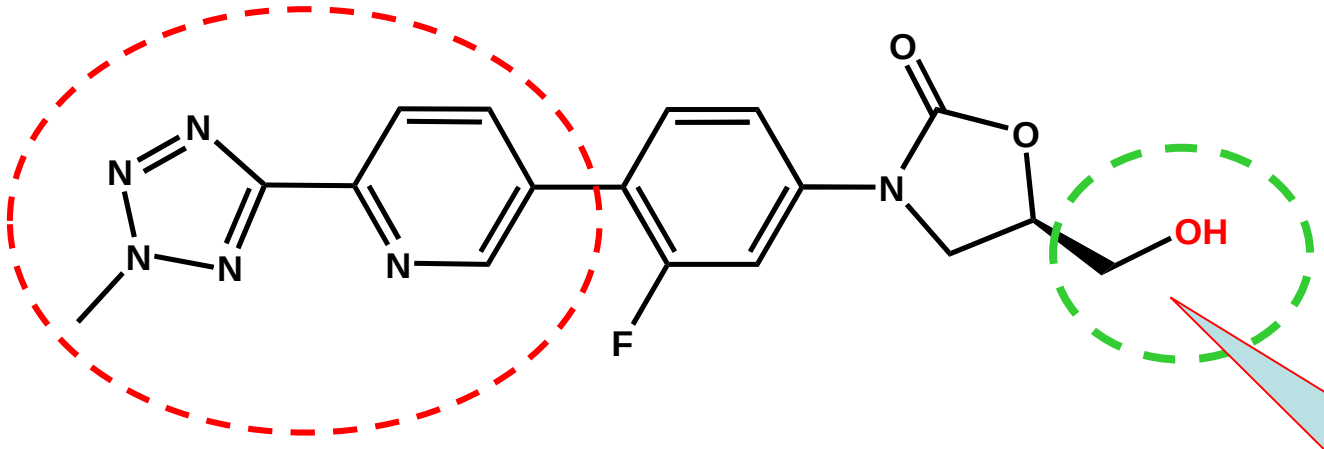
Activity of Tedizolid (TR-700) against Well-Characterized Methicillin-Resistant *Staphylococcus aureus* Strains of Diverse Epidemiological Origins

Kenneth S. Thomson, Richard V. Goering
Creighton University, Omaha, Nebraska, USA

TABLE 1 Drug activity against all MRSA isolates and epidemiological groups[a]

Isolate(s)	Drug(s)	MIC range (μg/ml)	MIC_{90} (μg/ml)
All isolates (n = 111)	Tedizolid	0.12 to 0.5	0.5
	Linezolid	0.5 to 4	2
	Trimethoprim/sulfamethoxazole	≤0.5/9.5 to >2/38	>2/38
	Tigecycline	0.06 to >1	0.5
	Levofloxacin	0.12 to >4	>4
	Clindamycin	0.06 to >16	>16
	Vancomycin	≤0.25 to 4	1
	Daptomycin	≤0.5 to 2	≤0.5
	Oxacillin	0.12 to >4	>4
	Erythromycin	0.12 to >8	>8
	Gentamicin	≤0.06 to >16	>16

Dong-A pharmaceuticals and tedizolid: step #2



#	R	X	MIC (μg/mL)		
			MSSA	MRSA	VRE
Linezolid			2	2	1
11	2-Methyl-2*H*-tetrazol-5-yl	—OH	0.5	0.5	0.125

2. replacing the **acetamido** by an **hydroxyl** maintains the increased activity *vs.* linezolid !

[a] Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea
[b] Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA

Tedizolid and linezolid resistance

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

Activity against Cfr$^+$ resistant strains … (*cfr*$^+$ bacteria)

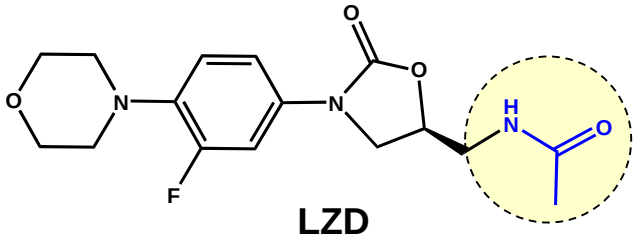
Oxazolidinone MICs for *S. aureus cfr* strains

Strain	Reference	Presence of *cfr*	MIC (μg/ml)[a]	
			LZD	TR-700
RN4220(pLI50)	68	−	2	0.5
RN4220(pLXM1)[b]	68	+	8	0.5
CM05Δ[c]	44	−	2	0.5
CM05[c]	68	+	8	0.5
29213	ATCC	−	2	0.5
29213(p42262)[d]	45	+	16	0.5
42262[e]	51	+	16	0.5

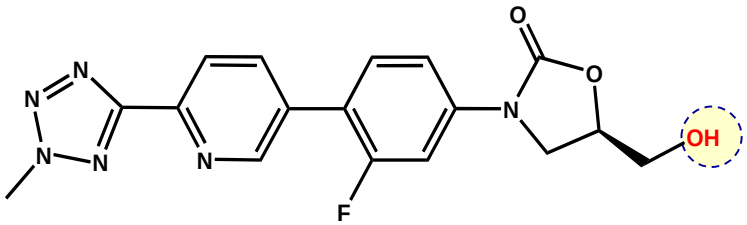
[a] MICs (broth microdilution: CLSI)
[b] The pLXM1 *cfr*-containing plasmid is isogenic to the empty pLI50 vector.
[c] CM05Δ is isogenic to the CM05 clinical *cfr*-positive strain but lacks *cfr* and one copy of *ermB*.
[d] 29213(p42262) was generated through transformation of ATCC 29213
[e] 42262 is a clinical *cfr*-positive isolate from a 2008 hospital outbreak in Madrid, Spain.

Locke et al. AAC 2010;54:5337-5343

Why is tedizolid active against LZD^R strains (*cfr*) ?



LZD



TR700

Locke et al. AAC 2010;54:5337-5343

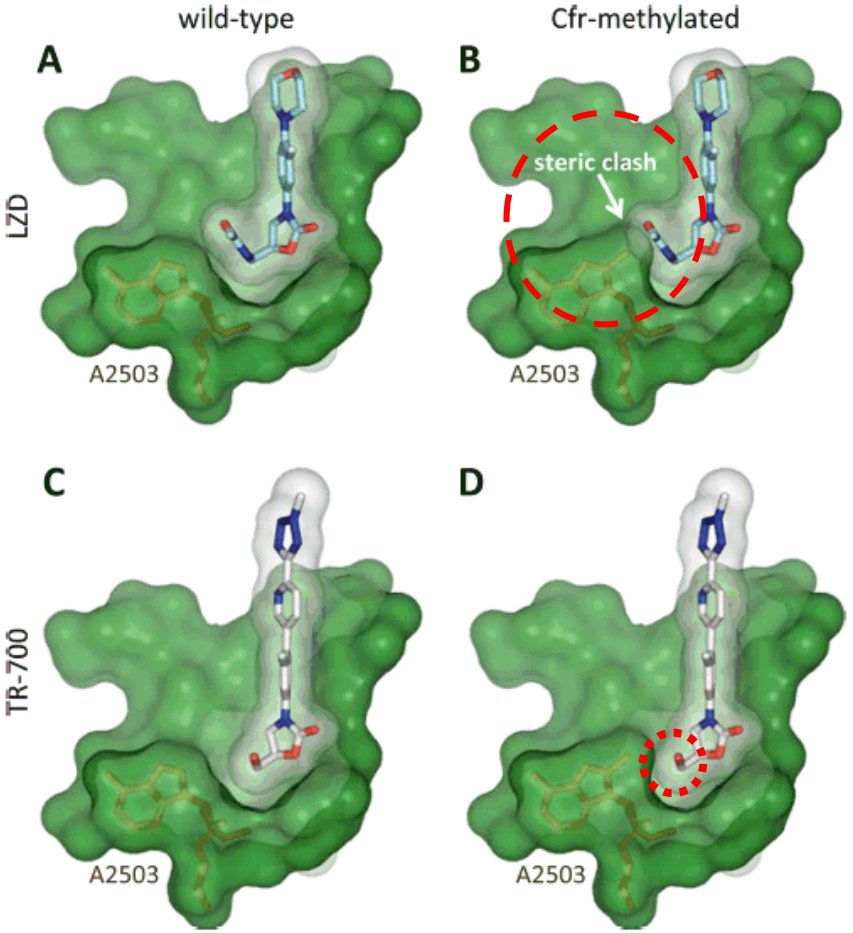
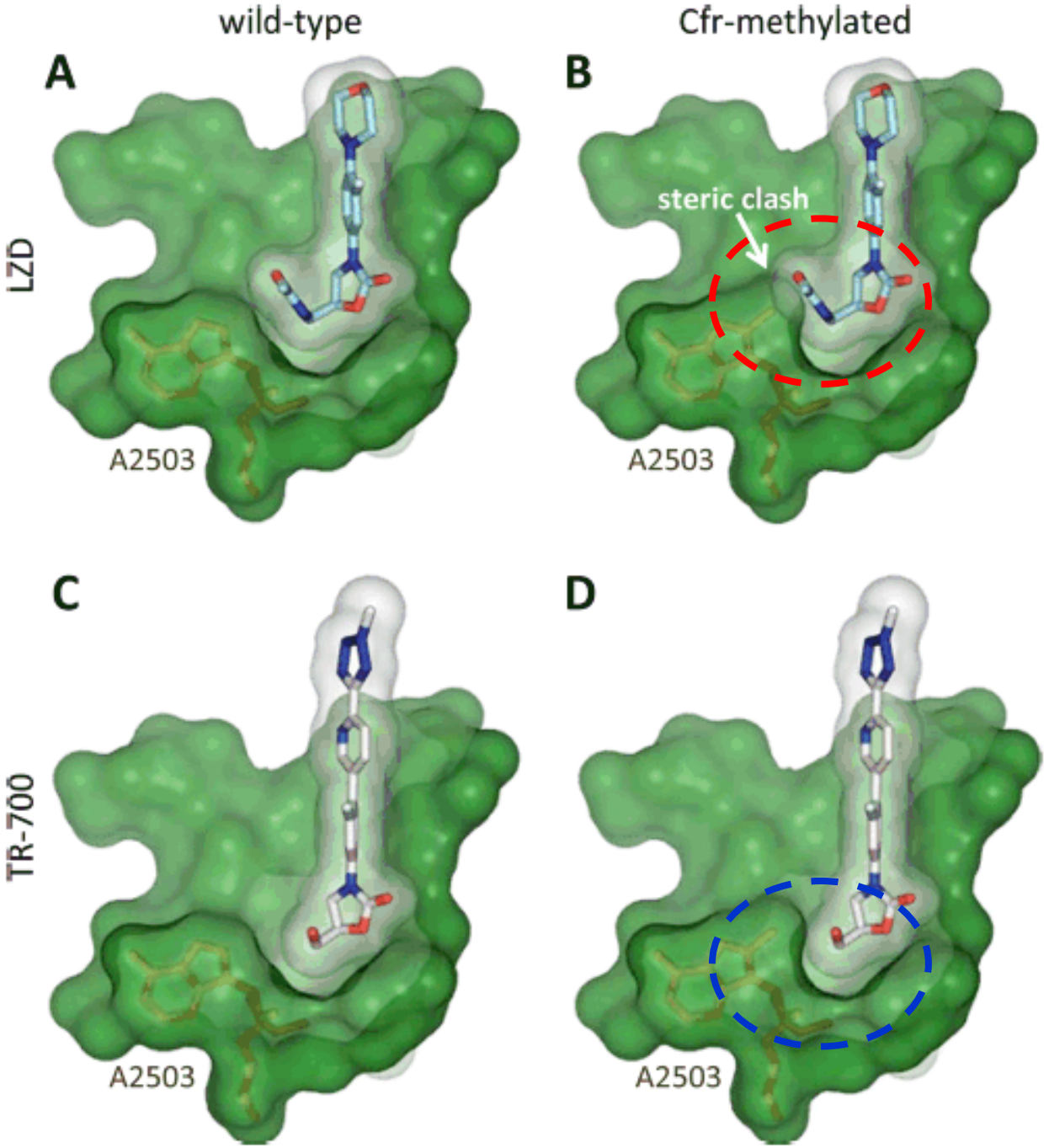


FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome. Substantial steric hindrance between the LZD 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 LZD^R strains (*cfr*) ?

Locke et al. AAC 2010;54:5337-5343



Do we need to be afraid of the *cfr*+ linezolid resistance ?

CARING FOR THE CRITICALLY ILL PATIENT

Clinical Outbreak of Linezolid-Resistant *Staphylococcus aureus* in an Intensive Care Unit

Miguel Sánchez García, MD, PhD
María Ángeles De la Torre, MD
Gracia Morales, PhD
Beatriz Peláez, PhD
María José Tolón, MD
Sara Domingo, MD
Francisco Javier Candel, MD, PhD
Raquel Andrade, PhD
Ana Arribi, MD, PhD
Nicolás García, MD
Fernando Martínez Sagasti, MD, PhD
José Fereres, MD, PhD
Juan Picazo, MD, PhD

Context Linezolid resistance is extremely uncommon in *Staphylococcus aureus*.

Objective To report an outbreak with linezolid and methicillin-resistant *S aureus* (LRSA) in an intensive care department and the effective control measures taken.

Design, Setting, and Patients Outbreak study of consecutive critically ill patients colonized and/or infected with LRSA at an intensive care department of a 1000-bed tertiary care university teaching hospital in Madrid, Spain. Patients were placed under strict contact isolation. Daily updates of outbreak data and recommendations for the use of linezolid were issued. Extensive environmental sampling and screening of the hands of health care workers were performed.

Main Outcome Measures Linezolid use and clinical and epidemiological characteristics and outcomes using minimal inhibitory concentrations, pulsed-field gel electrophoresis, and polymerase chain reaction of LRSA isolates.

Results Between April 13 and June 26, 2008, 12 patients with LRSA were identified. In 6 patients, LRSA caused ventilator-associated pneumonia and in 3 patients it caused bacteremia.

JAMA. 2010 Jun 9;303(22):2260-4.

BRIEF REPORT

Multicity Outbreak of Linezolid-Resistant *Staphylococcus epidermidis* Associated with Clonal Spread of a *cfr*-Containing Strain

Hector Bonilla,[1] Michael D. Huband,[3] Joan Seidel,[2] Helen Schmidt,[2] MaryKay Lescoe,[3] Sandra P. McCurdy,[3] M. Megan Lemmon,[3] Lori A. Brennan,[3] A. Tait-Kamradt,[3] Laura Puzniak,[3] and John P. Quinn[3]

[1]Summa Health System, Akron, and [2]Robinson Memorial Hospital, Ravenna, Ohio; and [3]Pfizer Global Research and Development, Groton, Connecticut

We report a multicity outbreak of *cfr*-containing linezolid-resistant *Staphylococcus epidermidis* in Ohio. Thirty-nine isolates were obtained from 2 hospitals. Two clones with different mechanisms of linezolid resistance were circulating in hospital A. One of these contained the *cfr* gene, and the other a ribosomal mutation. The clone containing *cfr* was identical in both hospitals.

Clin Infect Dis. 2010 Oct 1;51(7):796-800

Do we need to be afraid of the *cfr*+ linezolid resistance ?

CARING FOR THE CRITICALLY ILL PATIENT

Clinica
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Miguel Sánchez
María Ángeles D
Gracia Morales,
Beatriz Peláez,
María José Tolón
Sara Domingo,
Francisco Javier
Raquel Andrade
Ana Arribi, MD,
Nicolás García,
Fernando Martín
José Fereres, MI
Juan Picazo, MI

JAMA. 20

J Antimicrob Chemother 2016; **71**: 587–592
doi:10.1093/jac/dkv391 Advance Access publication 11 December 2015

Journal of Antimicrobial Chemotherapy

Horizontal gene transmission of the *cfr* gene to MRSA and *Enterococcus*: role of *Staphylococcus epidermidis* as a reservoir and alternative pathway for the spread of linezolid resistance

Fabio Cafini[1,2]*, Le Thuy Thi Nguyen[2,3], Masato Higashide[4], Federico Román[5], José Prieto[1] and Kazuya Morikawa[2]

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lates were obtained from 2 hospitals. Two clones with different mechanisms of linezolid resistance were circulating in hospital A. One of these contained the *cfr* gene, and the other a ribosomal mutation. The clone containing *cfr* was identical in both hospitals.

Clin Infect Dis. 2010 Oct 1;51(7):796-800

Oxazolidinones: 2d mechanism of resistance

Chromosomal 23S rRNA mutations

- Low frequency, but local outbreaks have been observed
- First clinical cases of resistant staphylococci and enterococci reported soon after linezolid approval in 2000 (Gonzales 2001; Tsiodras 2001)
- Tedizolid demonstrates 8-fold better potency against these strains (Shaw 2008, Jones 2009, Livermore 2009, Locke 2009)
- Mutations also observed in ribosomal proteins L3 and L4

loses about 2 to 4-fold activity but still

Tedizolid and ribosomal mutations

TABLE 1. Oxazolidinone MICs for *S. aureus* ribosomal mutants

Strain[a]	Source or reference	Resistance mechanism[b]	MIC (μg/ml)[c]	
			LZD	TR-700
29213	ATCC		2	0.5
29213-1	43	23S (G2447T ×3)	32	4
29213-2	43	23S (T2500A ×2)	8	2
29213-3	43	L3 (ΔPhe127-His146)	8	2
33591	ATCC		1	0.25
33591-1	43	23S (G2576T ×3)	16	2
33591-2	43	23S (G2576T/T2571C ×3)	16	2
33591-3	43	L4 (Lys68Gln)	2	0.5
NRS127	NARSA[d]	L3 (ΔSer145)	8	1

[a] ATCC 29213 and ATCC 33591 isogenic mutant panels were generated through selection in the presence of LZD and/or TR-700. NRS127 is an LZD^r clinical isolate.

[b] Mutations in 23S rRNA genes (and mutant allele copy number) or in the ribosomal protein L3 or L4 are shown.

[c] MICs (broth microdilution; CLSI) were determined against the oxazolidinone panel

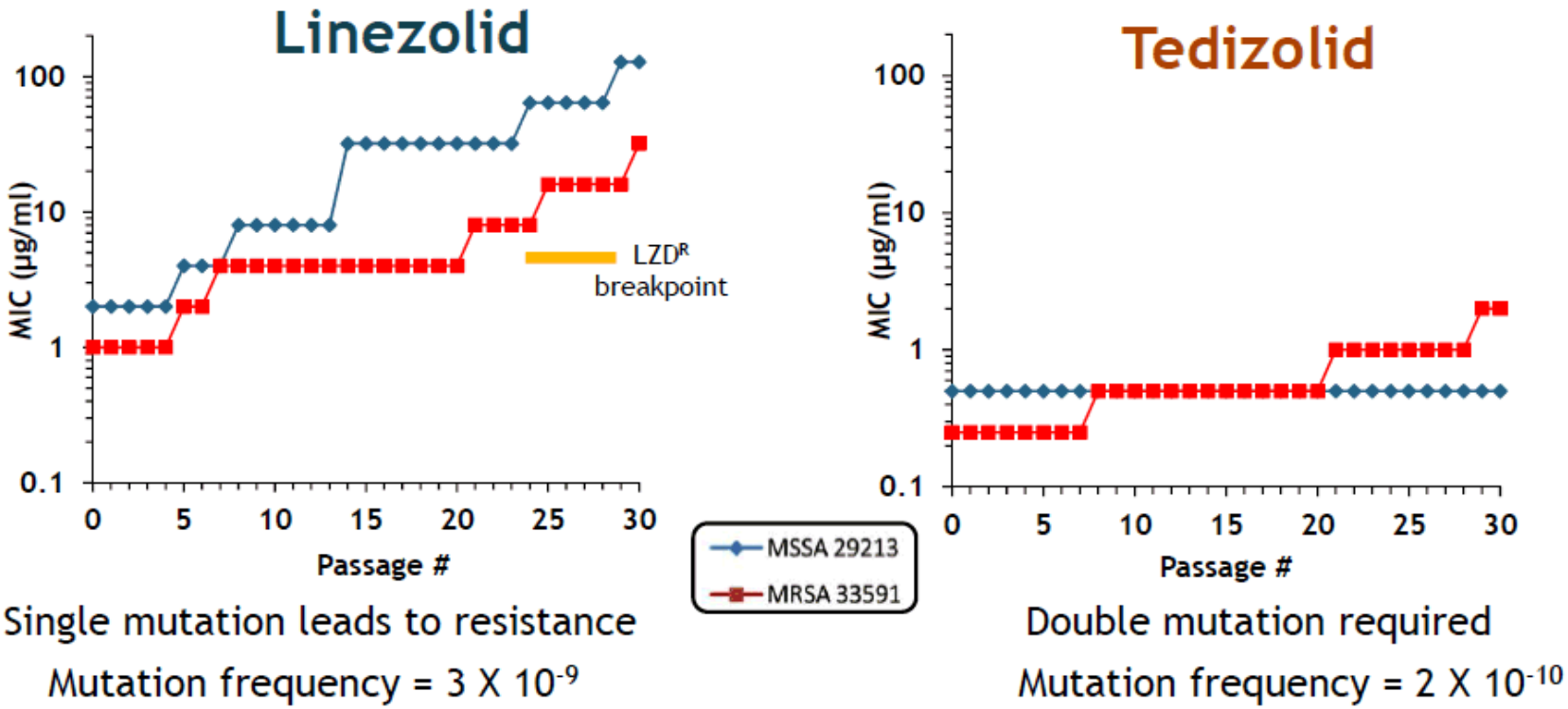
[d] Network of Antimicrobial Resistance in *Staphylococcus aureus*.

TDZ MICs are 8x < than LZD but 2-4x > than for wild type bacteria

Locke et al. AAC 2010;54:5337-5343

Tedizolid has lower propensity to induce resistance

- Spontaneous frequency of resistance is 16-fold lower for tedizolid vs linezolid
- Serial passage experiment (30 cycles of selection)
  - Much more difficult to select resistance to tedizolid vs linezolid



Single mutation leads to resistance

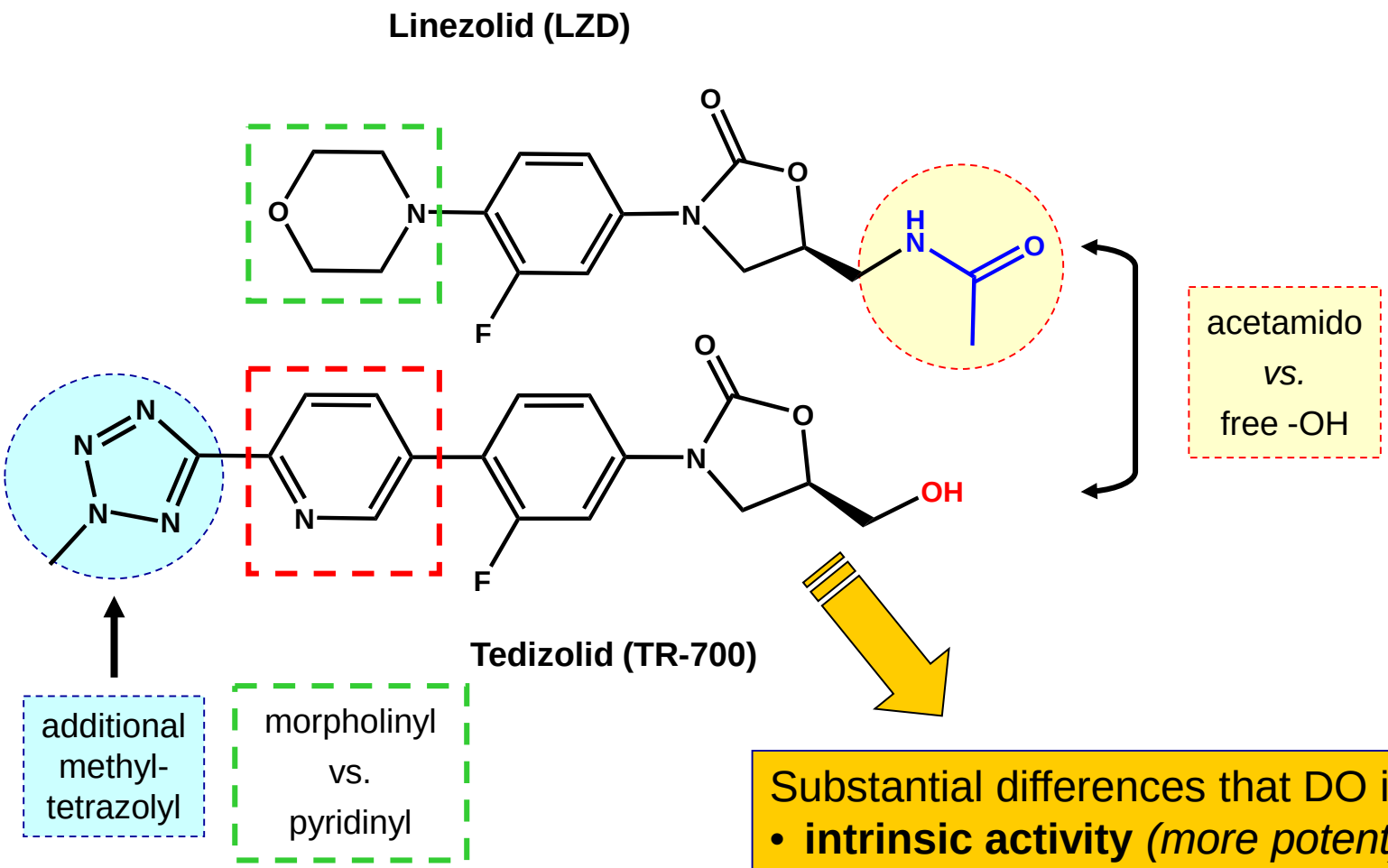
Mutation frequency = 3×10^{-9}

Double mutation required

Mutation frequency = 2×10^{-10}

Locke, et al., 2009. Antimicrob Agents Chemother. 53(12): 5265-5274

To sum up: what are the main differences between linezolid and tedizolid of interest at this point ?

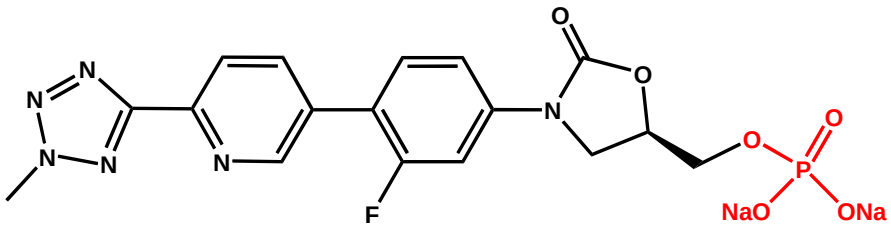


Substantial differences that DO impact on

- **intrinsic activity** *(more potent)*
- **full activity against *cfr*+ resistant strains**
- **MICs < LZD for ribosomal mutants**

Pharmacokinetics / Pharmacodynamics

Tedizolid clinical formulations

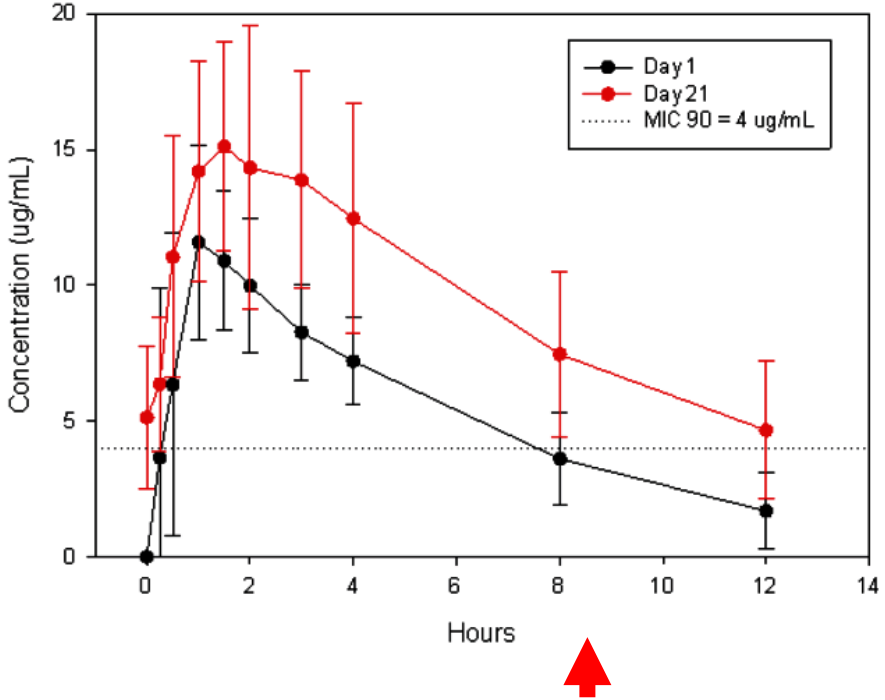


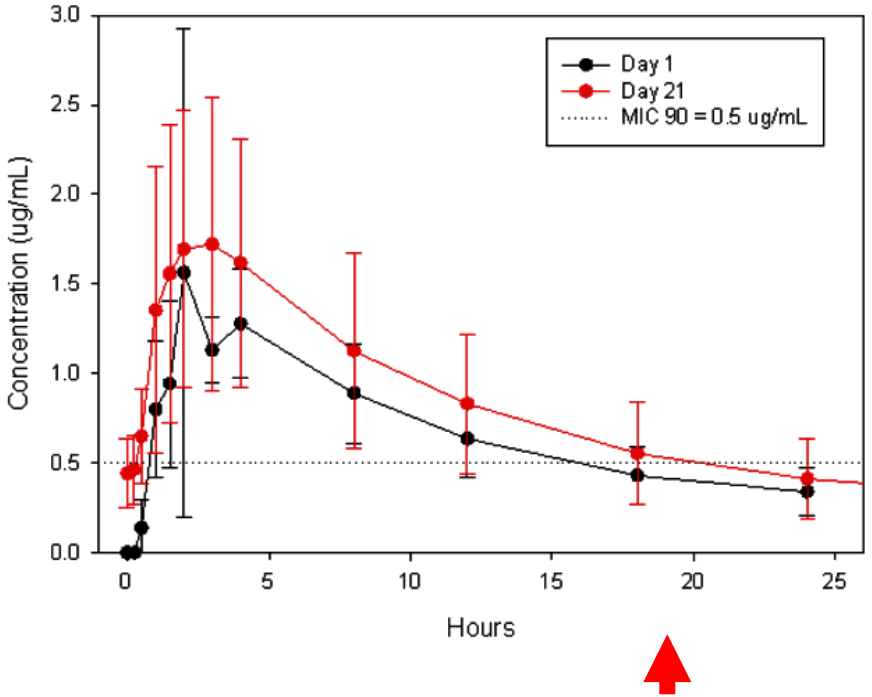
Tedizolid phosphate (pro-drug releasing tedizolid *in vivo*)

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

Tedizolid vs Linezolid human pharmacokinetics:

oral doses (200 mg TR-701* q24h *vs* 600 mg linezolid q12h for 21 days.





Tedizolid :

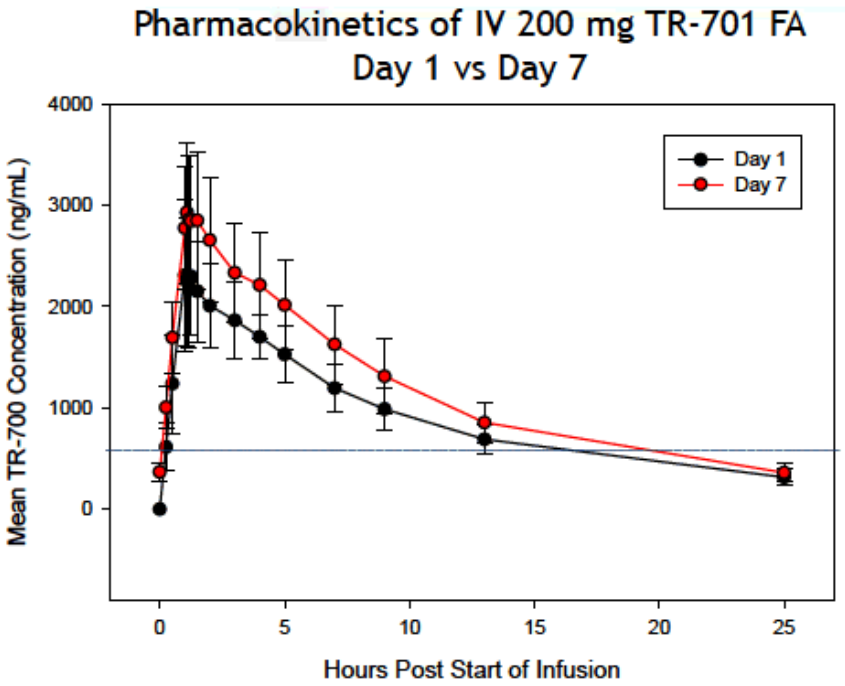
- mean $t_{1/2}$ > 2 x greater than linezolid
- longer initial presence at > 0.5 mg/L (vs. 4 mg/L for linezolid).

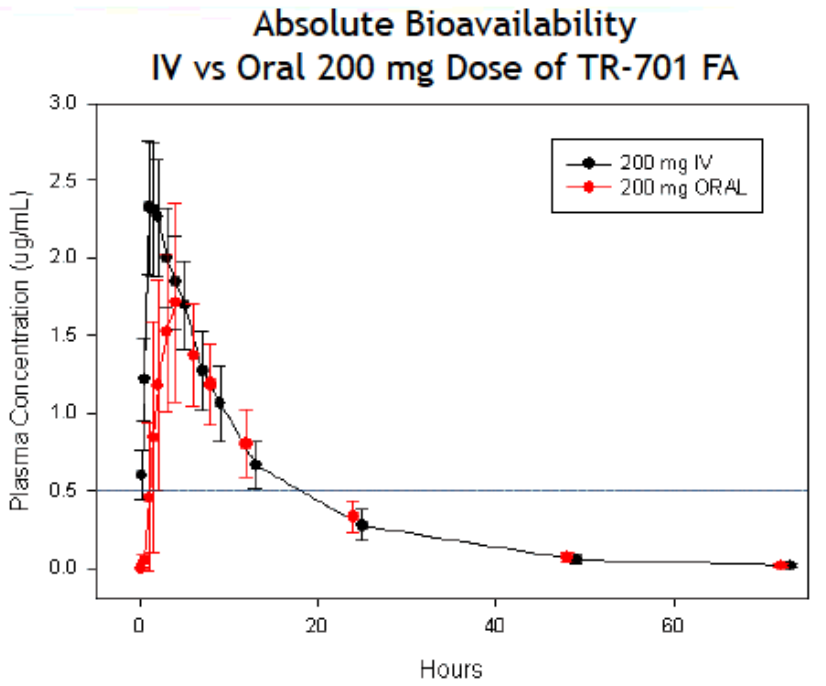
This allows for a once-a-day dosing

* TR-701: tedizolid phosphate

Flanagan SD, *et al*. Pharmacotherapy 2014;34(3):240–250.
Munoz KA, et al. ECCMID 2010. Poster1594.

Human pharmacokinetics: multiple doses and bioavailability





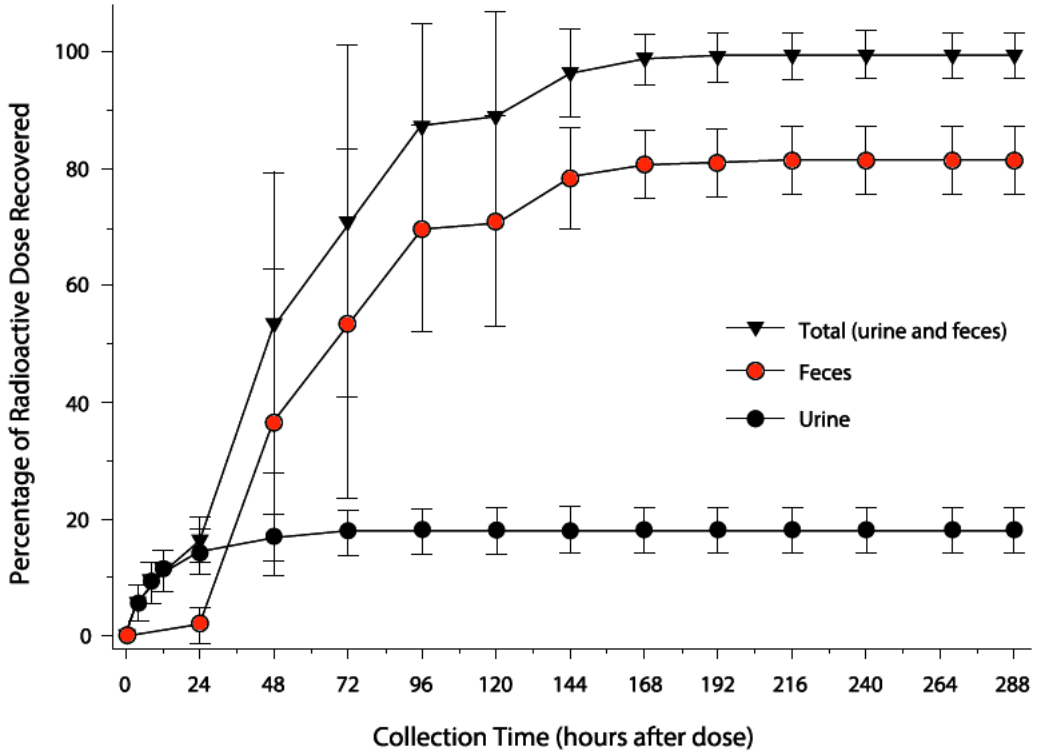
- Single-dose mean C_{max} and $AUC_{0\text{-}inf}$ values of TR-700 increased in a dose proportional manner for TR-701 FA dose levels of 100 to 400 mg (1.16 to 5.13 µg/mL and 17.36 to 58.70 µg•hr/mL, respectively)
- A slight accumulation of ~28% was observed following multiple dosing and was predicted from single dose data
- TR-700 concentrations were generally similar on Day 7 compared to Day 1 at the 200 mg dose level
- The absolute bioavailability of TR-700 from TR-701 FA 200 mg tablets was 91.7%

TR700: tedizolid (active substance)
TR701: tedizolid phosphate (prodrug)

Flanagan S, *et al*. Pharmacotherapy 2014;34:891–900.

Tedizolid elimination …

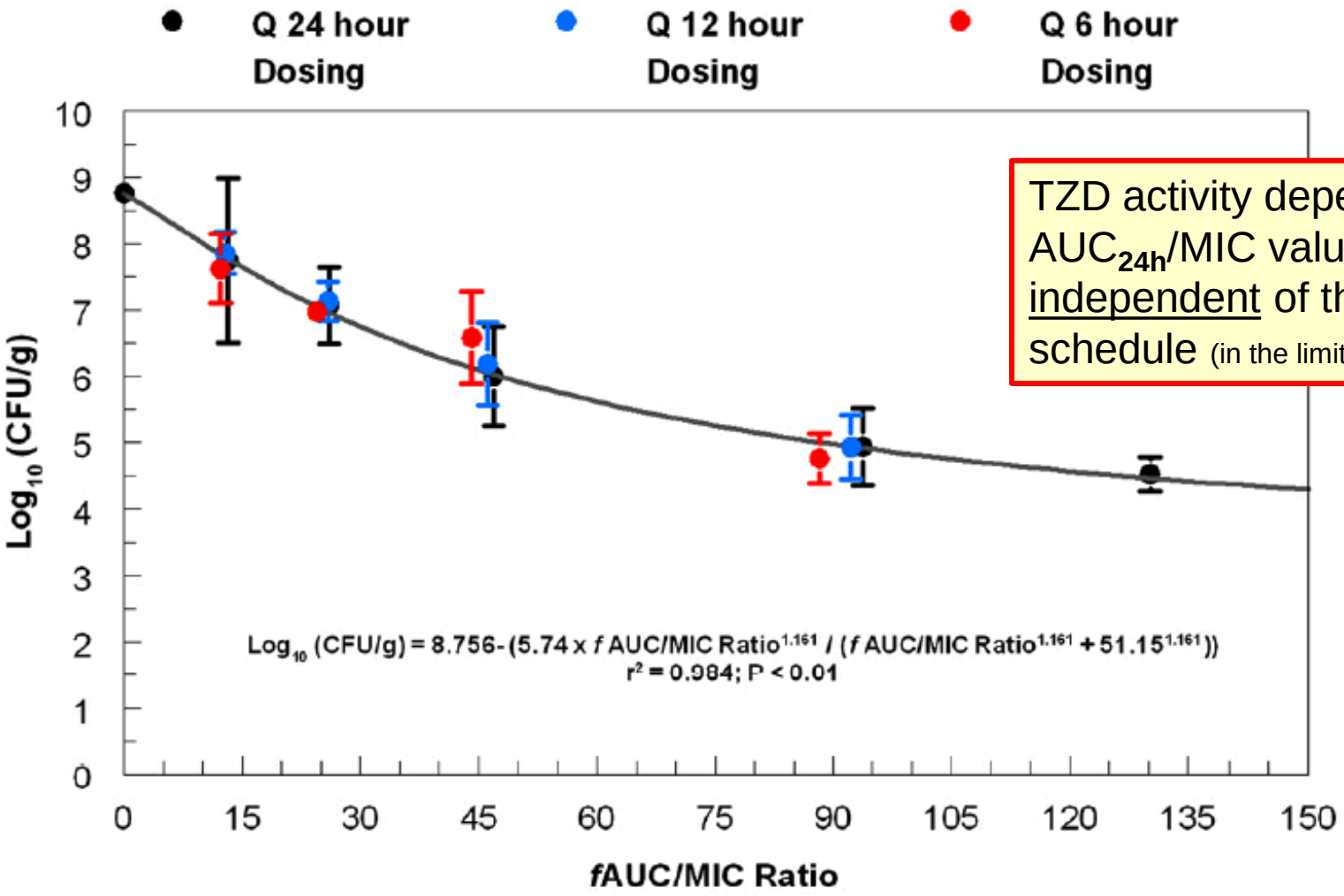
- When using ^{14}C-labelled tedizolid phosphate in humans, most of the radioactivity is excreted in feces



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

Dreskin H. et al, ICAAC 2011; Poster A2-033.
Ong V, et al. Drug Metab Dispos 2014;42:1275-1284.

AUC_{24h} and activity tedizolid



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

Louie et al. AAC 2011; 55:3453-3460

Tedizolid breakpoints… a matter of dispute ?

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Tedizolid

Organism group	Breakpoint (mg/L)	
	S ≤ (mg/L)	R > (mg/L)
Staphylococcus spp.	0.5	0.5
Enterococcus spp.	IE	IE
Streptococcus groups A,B,C,G	0.5	0.5
Viridans group streptococci (*Streptococcus anginosus* group only)	0.25	0.25
PK/PD breakpoints	IE	IE

1 mg/L for *S. aureus* is resistant

1 mg/L for *S. aureus* is intermediate

Table 5 Susceptibility Test Interpretive Criteria for SIVEXTRO

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)		
	S	I	R
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	≤0.5	1	≥2
Streptococcus pyogenes	≤0.5	-	-
Streptococcus agalactiae	≤0.5	-	-
Streptococcus anginosus Group*	≤0.25	-	-
Enterococcus faecalis	≤0.5	-	-

S=susceptible, I=intermediate, R=resistant
* Includes *S. anginosus*, *S. intermedius*, *S. constellatus*

1. EUCAST. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0, 2016. Available at: http://www.eucast.org
2. SIVEXTRO (tedizoid) US prescription information (FDA defined breakpoint). Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205435s000lbl.pdf

Distribution of tedizolid in tissues

Activity of tedizolid towards intracellular bacteria

Journal of Antimicrobial Chemotherapy (2009) **64**, 1035–1043
doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009

JAC

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

Sandrine Lemaire[1], Françoise Van Bambeke[1], Peter C. Appelbaum[2] and Paul M. Tulkens[1]*

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

Accumulation and activity of tedizolid in macrophages

Journal of Antimicrobial Chemotherapy (2009) **64**, 1035–1043
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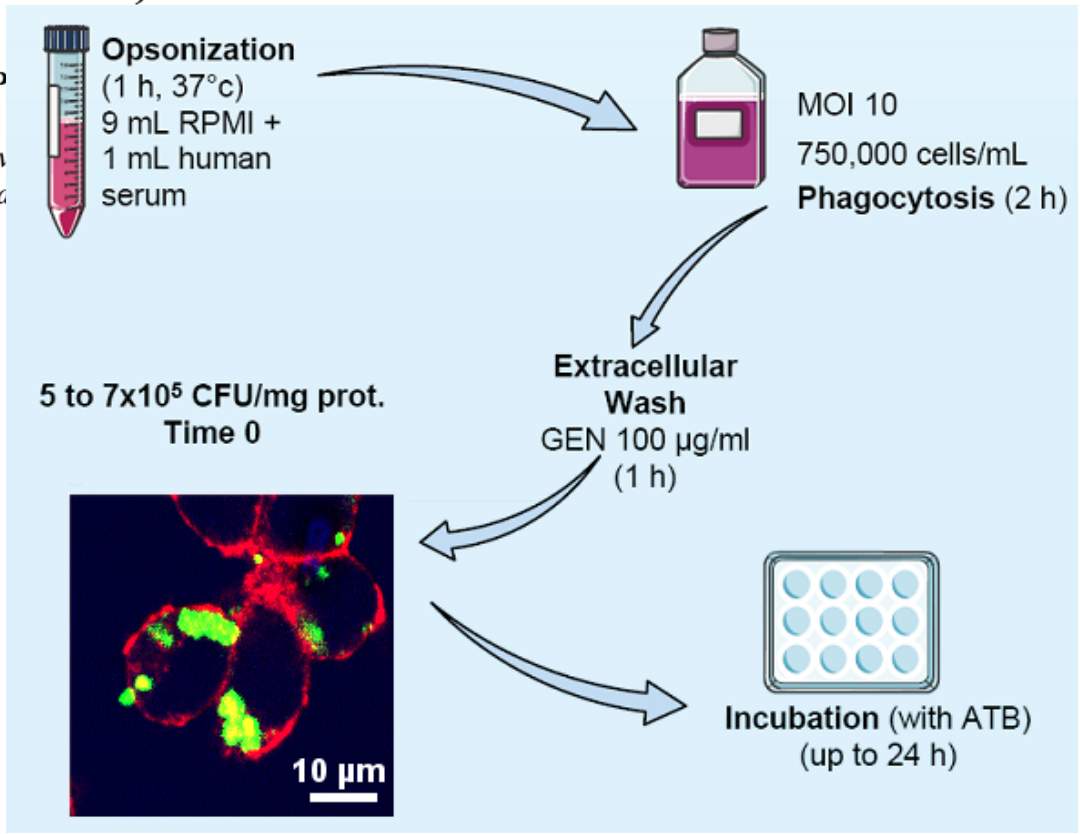
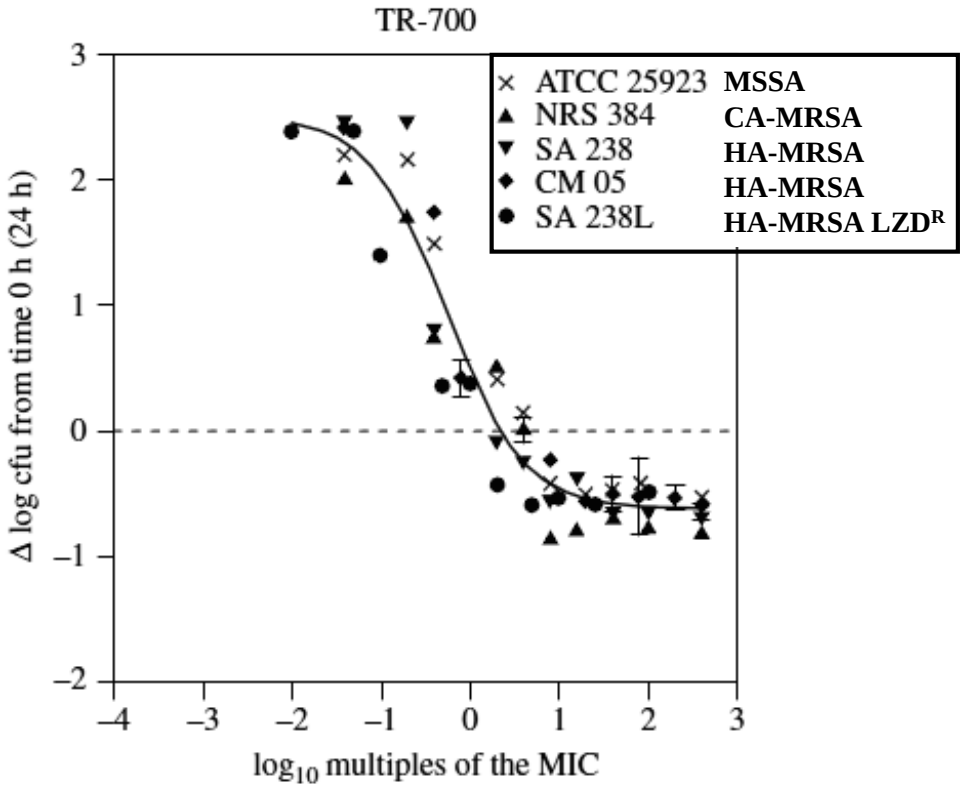


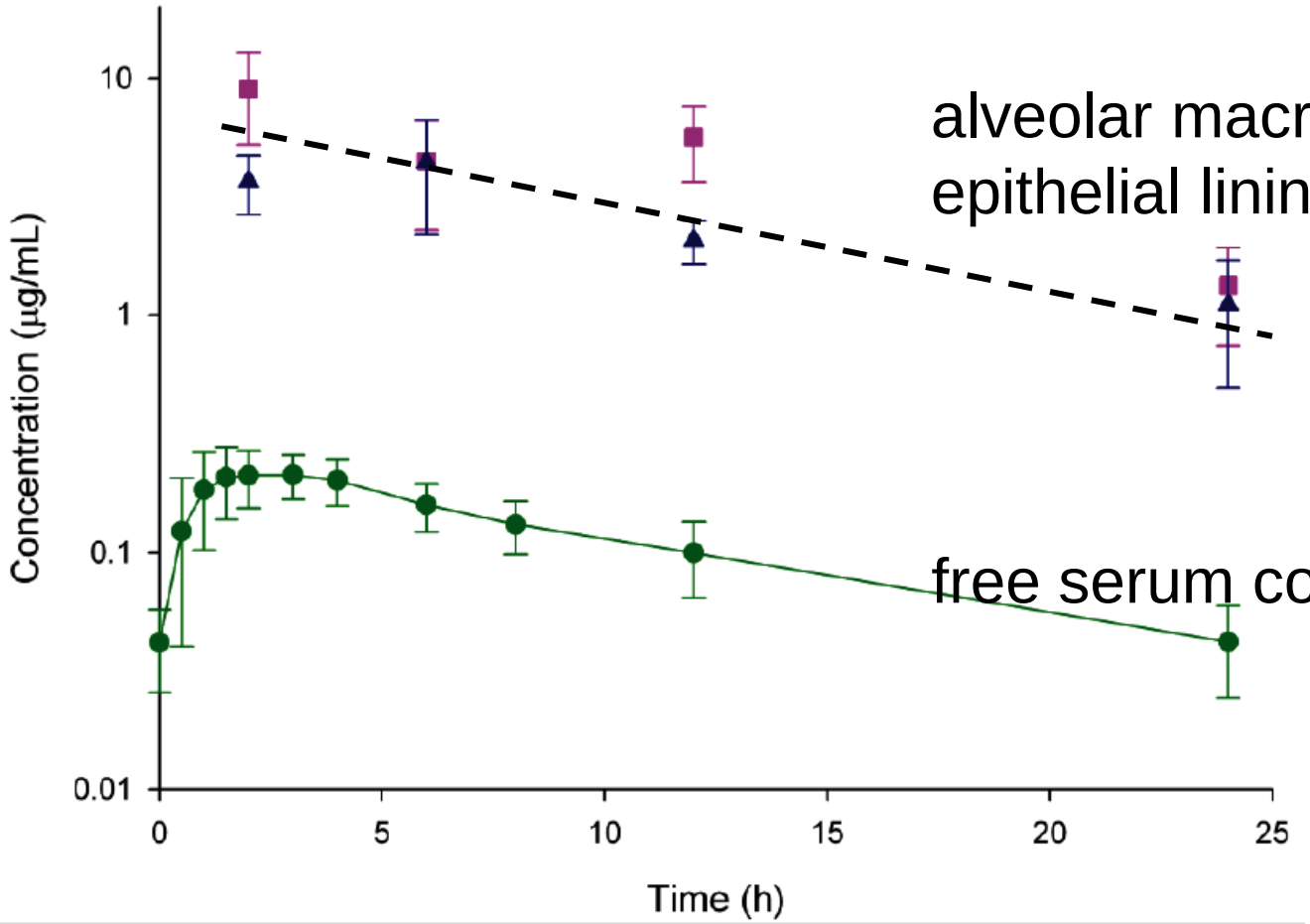
Tedizolid is active intracellularly against MRSA disregarding resistance phenotypes



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

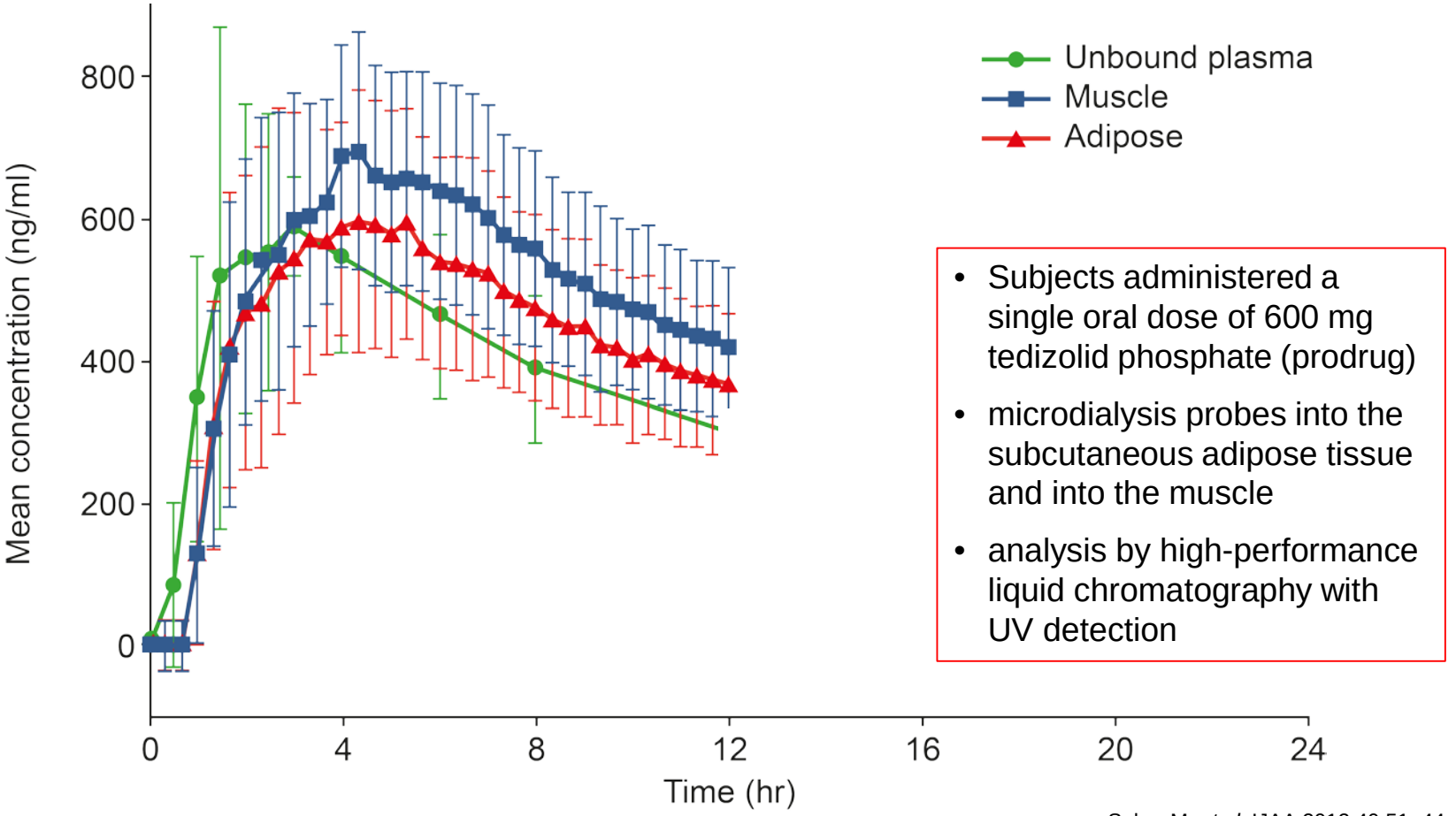
Lemaire et al. JAC 2010; 64:1035–1043

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



Housman et al. ICAAC 2011 – A1-1747
& AAC 2012; 56:2627-34

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

Sahre M, *et al.* IJAA 2012;40:51–44.

The median ratios of *f*AUC$_{0\text{-}12h}$ in tissue / *f*AUC$_{0\text{-}12h}$ in plasma were **1.08 ± 0.22** for adipose and **1.22 ± 0.18** for muscle tissues, respectively

Tedizolid safety
(preclinical and "experimental human")

Linezolid known 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 anemia, leukopenia, pancytopenia, and thrombocytopenia) (WARNING)
- Hypoglycemia
- Lactic acidosis (PRECAUTION – Immediate medical attention)
- Peripheral and Optic Neuropathy (> 28 days)
- Convulsions

* Zyvox (linezolid) US Prescribing Information
Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016,021131s013,021132s014lbl.pdf

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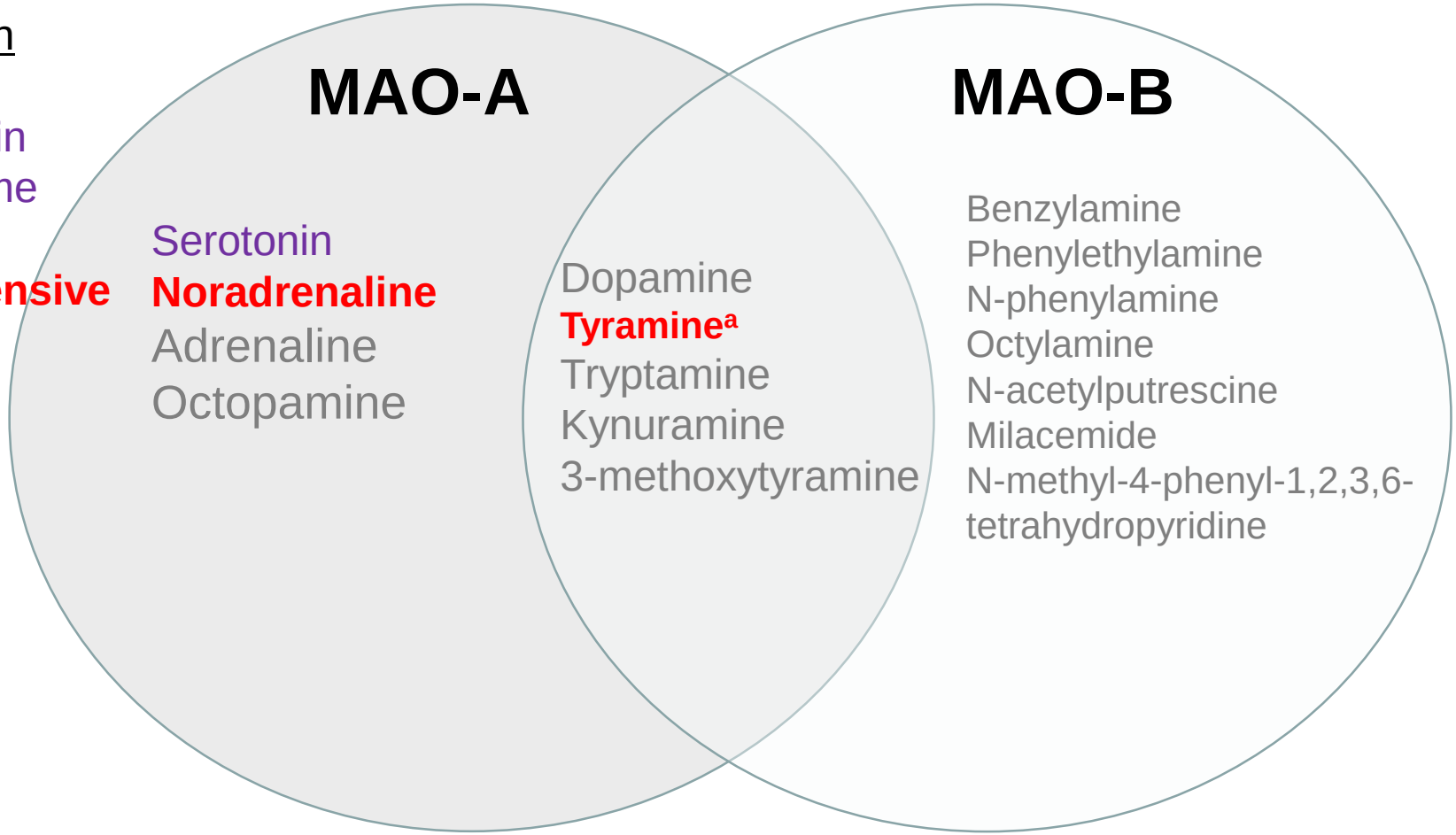
Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016,021131s013,021132s014lbl.pdf

Monoamine Oxidase (MAO) Substrate Specificity

Consequences of MAO-A Inhibition

Serotonin Syndrome

Hypertensive crisis



[a] MAO-A is the predominate form for oxidation of tyramine. Elmer and Bertoni. *Expert Opin Pharmacother*. 2008;9:2759-2772

This is what we tell the pharmacists in Belgium ….

Interactions linezolid - médicaments

Anti-migraineux
triptans
dihydroergotamine

Anti-dépresseurs
tricycliques
IMAO
ISRS

Anti-Parkinsoniens
L-Dopa
bromocryptine
selegiline

Anxiolytiques
buspirone

Sympathomimétiques
bronchodilatateurs
pseudoéphédrine

Vasopresseurs
(nor)adrénaline

Analgésiques
dextropropoxiphène
fentanyl
tramadol

Anti-émétiques
setrons
metoclopramide

Anti-psychotiques
clozapine
olanzapine
risperidone
lithium

Antitussifs
dextromethorphane
codéine

Lawrence et al., CID (2006) 42:1578-83

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

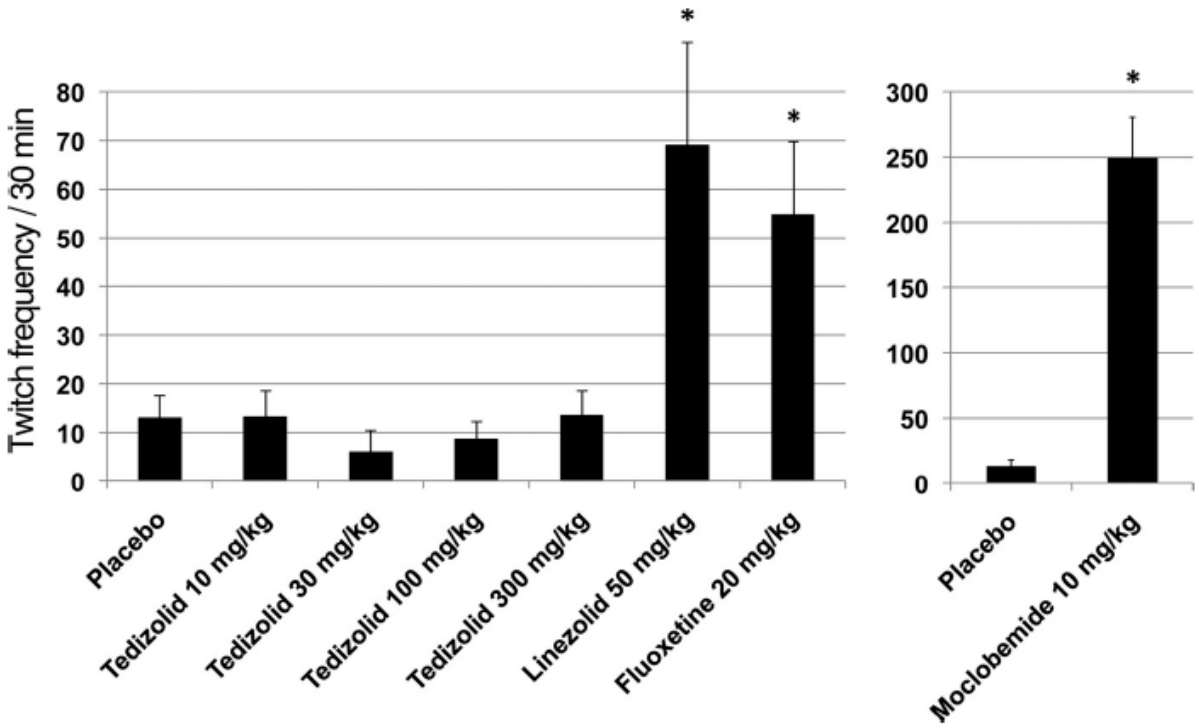


FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD (n = 8 mice/group). Tedizolid refers to tedizolid phosphate. *, $P < 0.05$ versus the control group.

Flanagan S, *et al.* Antimicrob Agents Chemother 2013;57:3060-3066.

Lack of MAO interactions at multiples ~30-fold above therapeutic tedizolid clinical peak exposure

Human data for blood pressure elevation

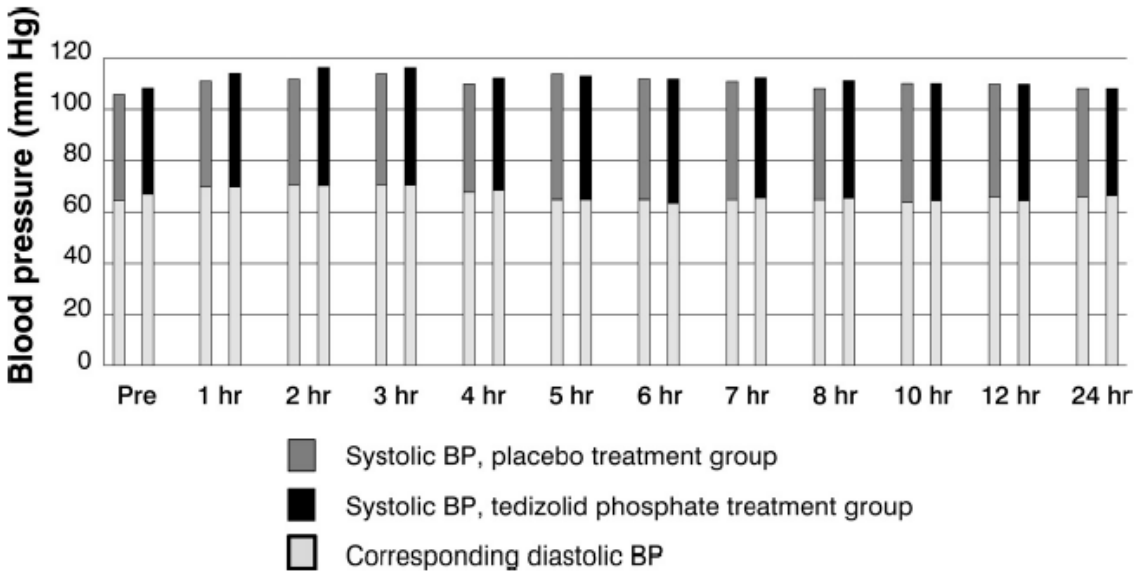


FIG 2 Blood pressure response to 60 mg pseudoephedrine in placebo- and tedizolid phosphate-pretreated study populations. Patients ($n = 18$) were randomized to oral placebo or oral tedizolid phosphate doses of 200 mg per day for 4 days; on the fifth day, 60 mg pseudoephedrine was administered with the 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.

Flanagan S, *et al*. Antimicrob Agents Chemother 2013;57:3060-3066.

Tedizolid has no effect on blood pressure *vs* placebo.

Linezolid known 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)
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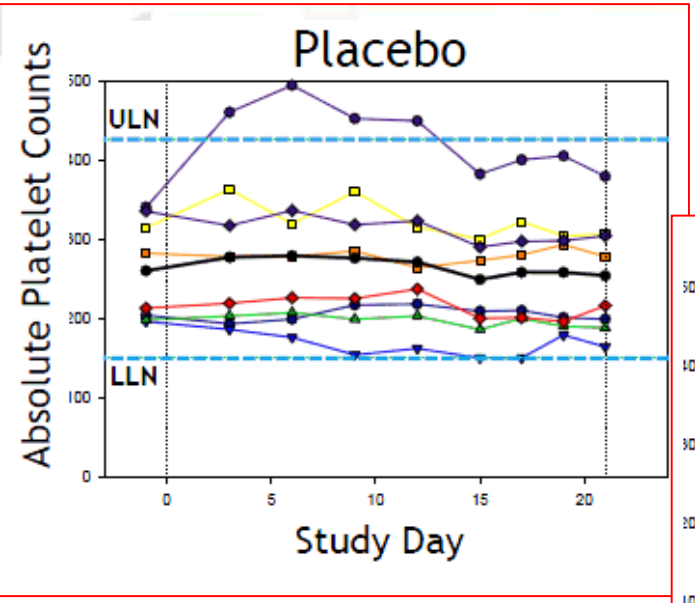
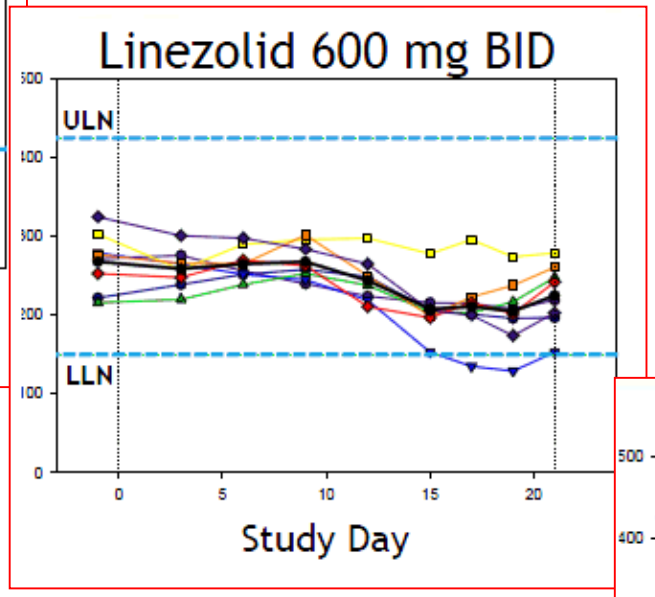
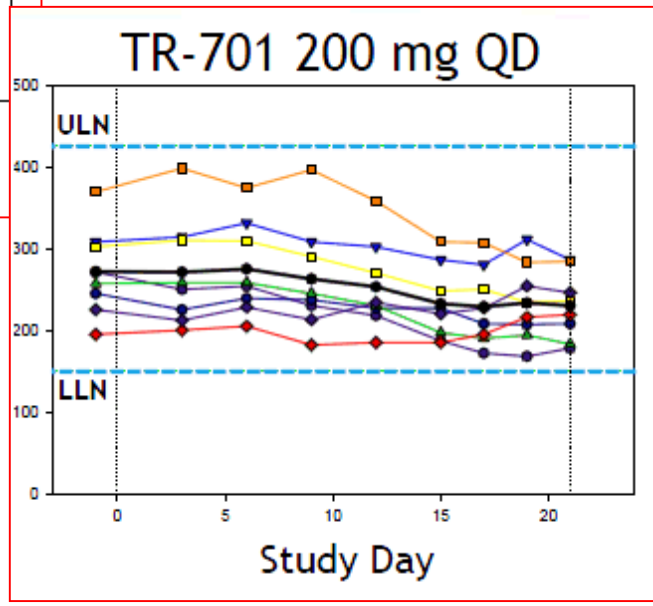
Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016,021131s013,021132s014lbl.pdf

TEDIZOLID Phase I: platelets at 21 days *





TR-701: tedizolid phosphate



* treatment duration in phase III is limited to 6 days

Summary of Tedizolid Non-clinical Safety Attributes

No 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)
- No serotonergic effect in head twitch model

No Safety Pharmacology Issues Identified

- 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

Tedizolid
Clinical development

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

Philippe Prokocimer, MD
Carisa De Anda, PharmD
Edward Fang, MD
Purvi Mehra, 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.

Prokocimer *et al*. JAMA. 2013; 309:559-69 -PMID: 23403680.

Articles

Lancet Infect Dis 2014; 14: 696–705
Published Online June 6, 2014
http://dx.doi.org/10.1016/

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.

Moran *et al*. Lancet Infect Dis. 2014; 14:696-705 - PMID: 24909499.

FDA new clinical guidance

Indication	Prior Guidance (1998)	New Guidance* (2013)
	cSSSI	ABSSSI
Infection Type	Large Abscess, Wound, Cellulitis, DFI, Chronic Ulcer	Large Abscess, Wound, Cellulitis – min. 75 cm^2
Infection Severity	Intermediate/Severe	Severe
Primary Endpoints	**Subjective** Clinicians Assessment at 7-14 Days After EOT	**Objective** ≥20% reduction in lesion size at 48–72 hours
Secondary Endpoints	Varied **Low Potential for Differentiation**	• Primary Endpoint Sustained to EOT • Clinician's Assessment at EOT **Higher Potential for differentiation**

- **ABSSI = 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

* Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (FDA - CDER -- October 2013 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185 (last accessed: 8 March 2016)

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	cSSSI	ABSSSI
Infection Type	Large Abscess, Wound, Cellulitis, DFI, Chronic Ulce	**Large Abscess, Wound, Cellulitis – min. 75 cm^2**
Infection Severity	Intermediate/Severe	Severe
		ctive lesion size at 48–72 urs
		Sustained to EOT ment at EOT **Potential entiation**

Cellulitis/erysipelas	• Diffuse skin infection characterized by spreading of edema, redness, and heat [1,2] • May accompany 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 edema, 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
[2] Stevens *et al.* Clin Infect Dis. 2005;41:1373–1406 – PMID 16231249

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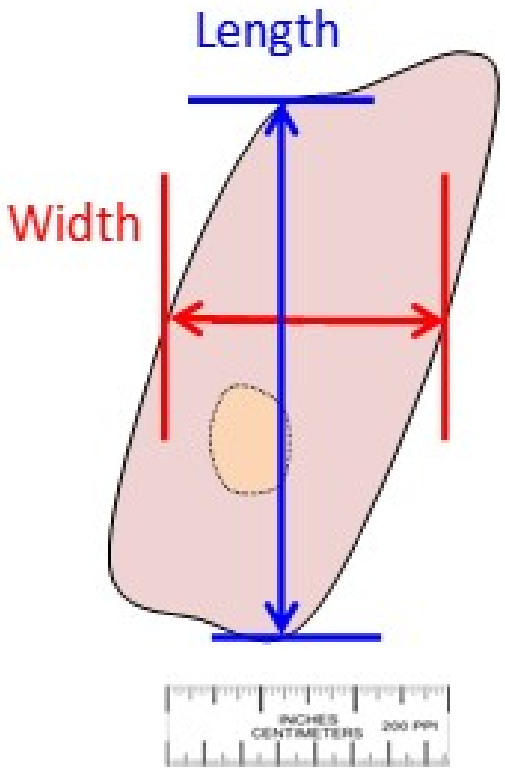
Measurement of Lesions

Measurement for All Lesions

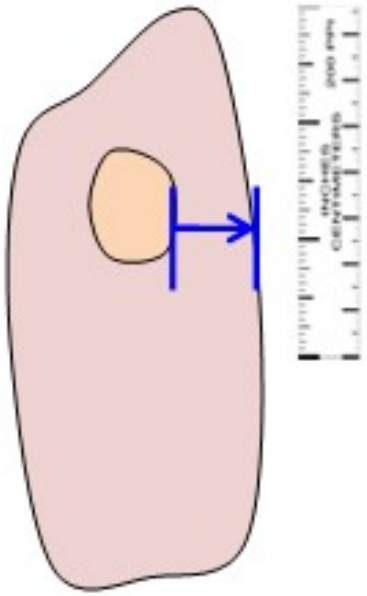
Head-to-toe vs
largest perpendicular width



Additional Measurement for Abscesses and Wounds*

(at screening only)

Abscess/wound margin to perimeter of erythema, oedema, and/or induration/cellulitis

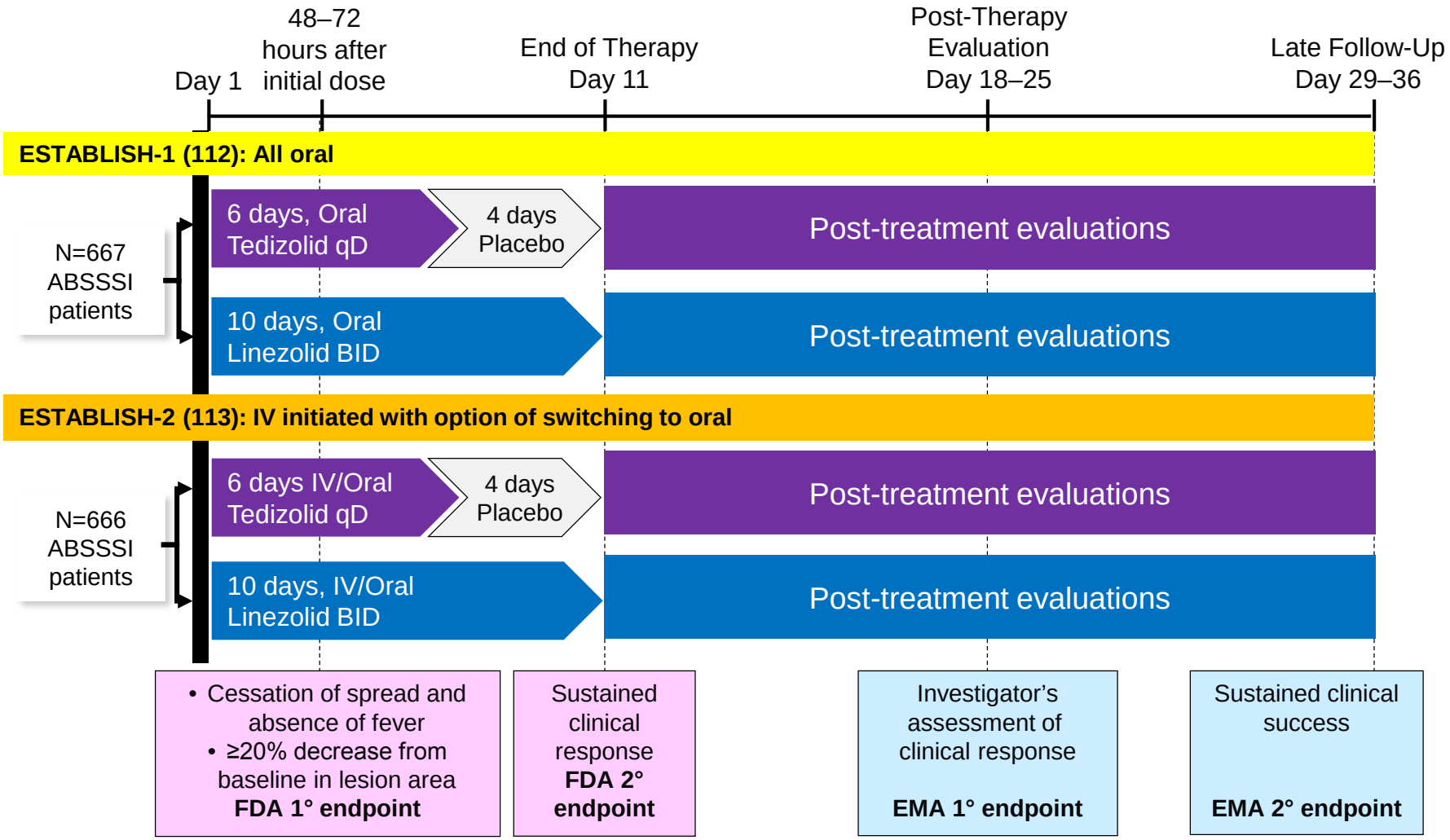


*Erythema extending at least 5cm in the shortest distance from the peripheral margin of the abscess or wound

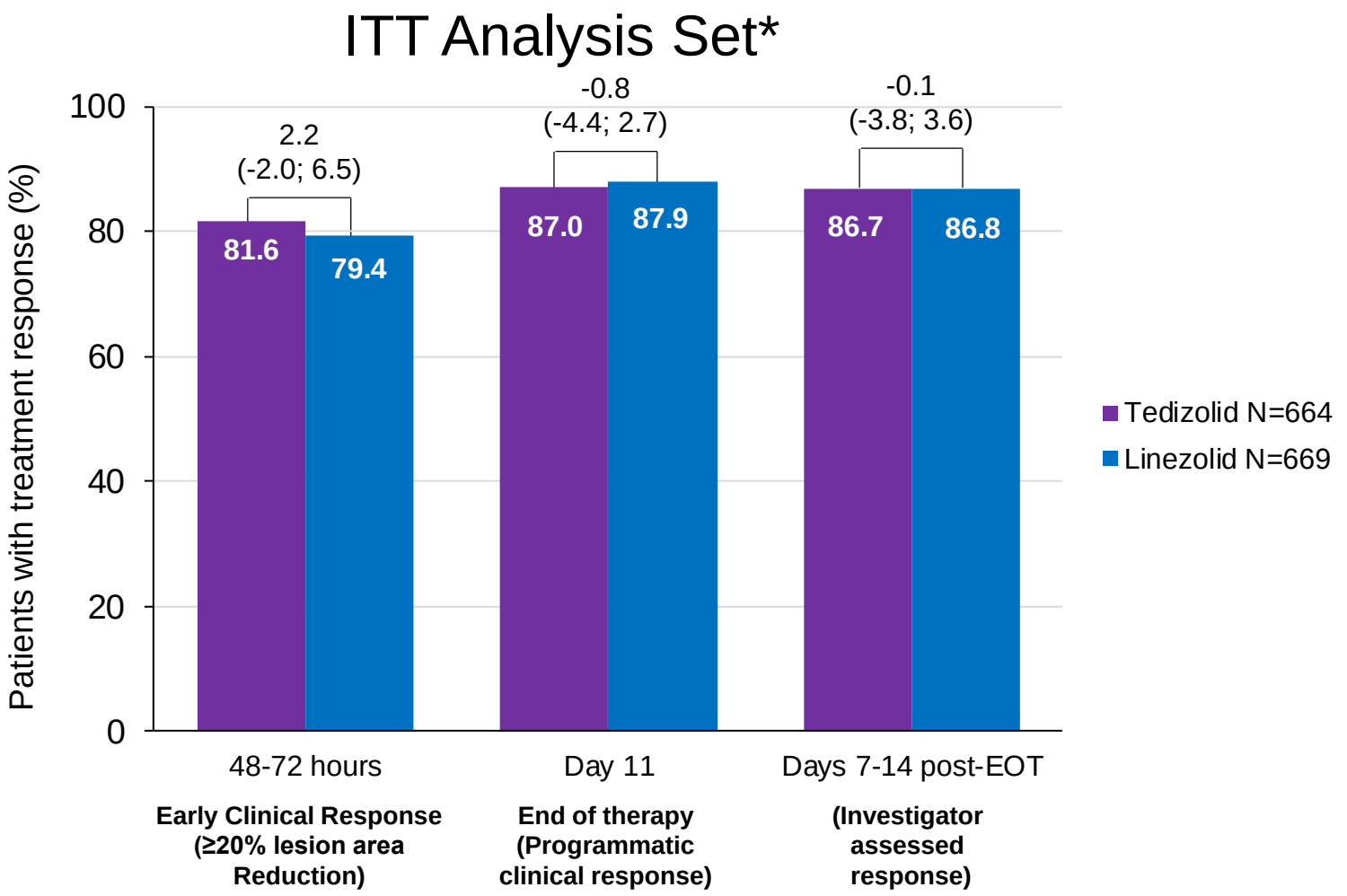
Bien *et al.* Surg Infect 2014;15(2):105–110.

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

(double-blind, double-dummy)



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

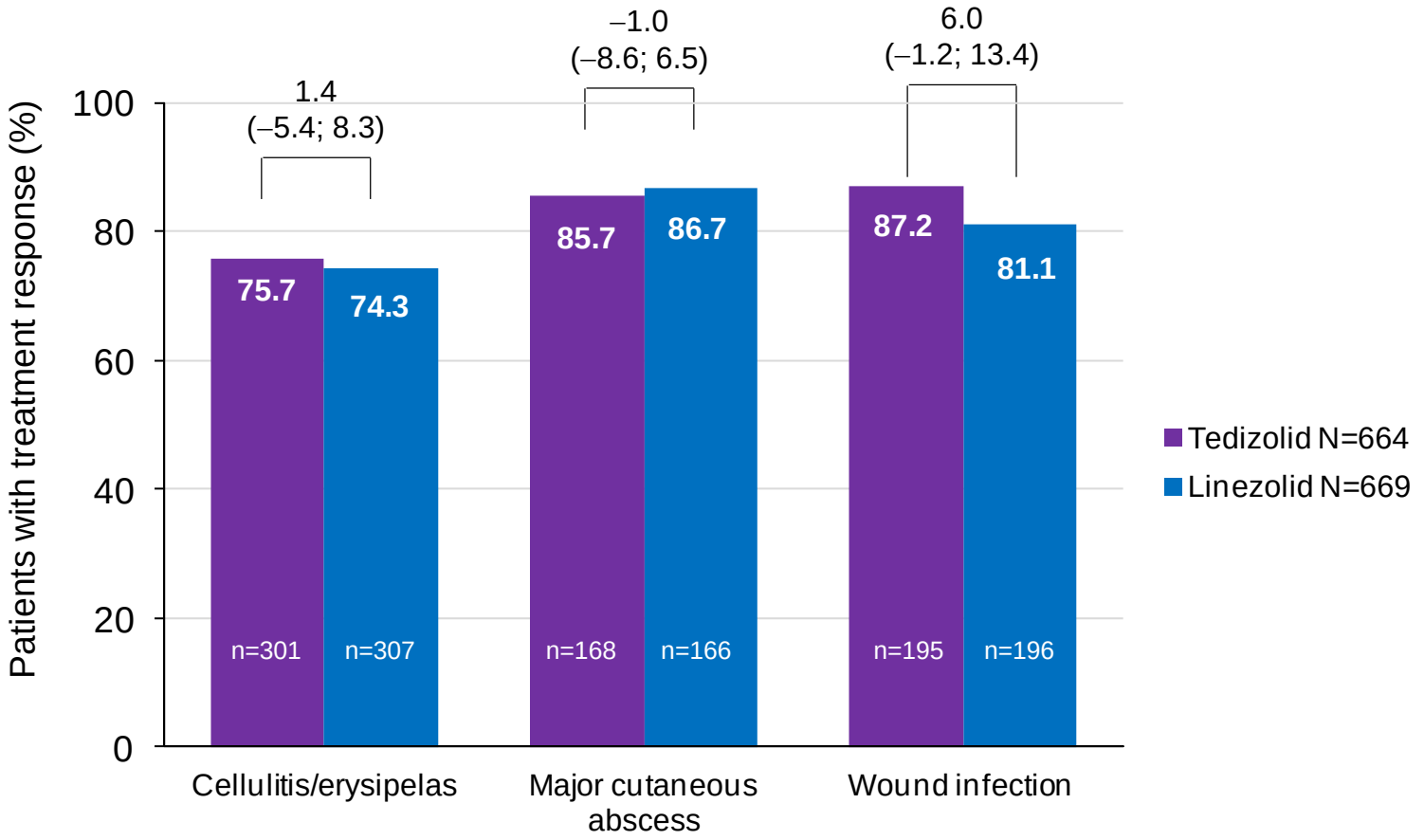


* Pooled data

Prokocimer *et al*. JAMA 2013;309(6):559–569.
Shorr *et al.* AAC 2015;59(2):864–871.
Moran *et al.* LID 2014;14(8):696–705.

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

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



* Pooled data

Prokocimer *et al*. JAMA 2013;309(6):559–569.
Shorr *et al*. AAC 2015;59(2):864–871.
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

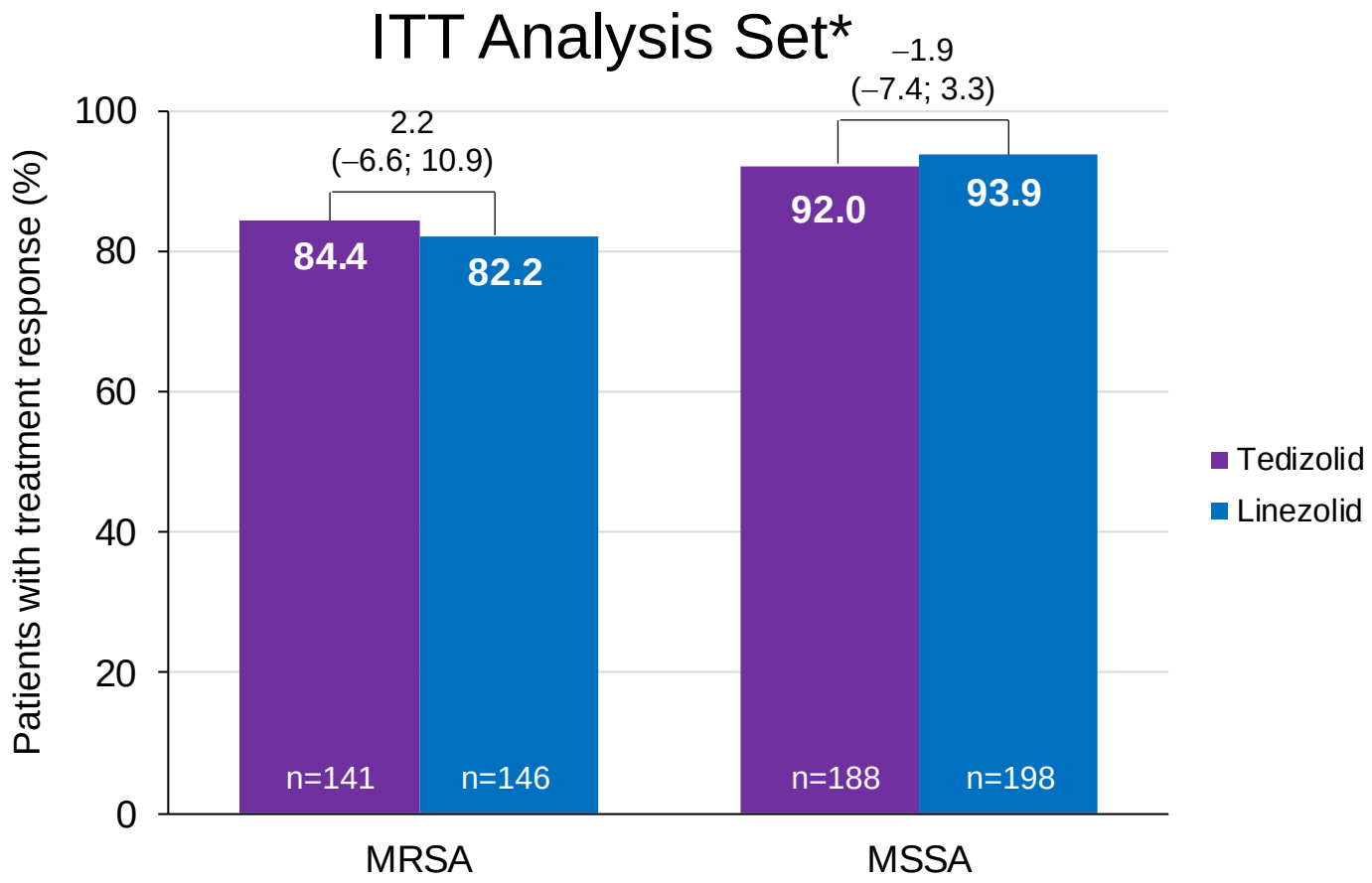
ITT analysis set	Tedizolid, % (n/N)	Linezolid, % (n/N)	Treatment difference (95% CI)
Age			
<65 years	82.6 (489/592)	79.5 (485/610)	**3.1 (-1.3; 7.6)**
≥65 years	73.6 (53/72)	78.0 (46/59)	**-4.9 (-19.4; 10.1)**
Sex			
Male	83.0 (356/429)	80.1 (330/412)	**2.8 (-2.4; 8.1)**
Female	79.1 (186/235)	78.2 (201/257)	**1.0 (-6.4; 8.2)**
BMI			
<30 kg/m^2	83.8 (389/464)	79.4 (347/437)	**4.4 (-0.6; 9.5)**
≥30 kg/m^2	76.5 (153/200)	79.3 (184/232)	**-2.8 (-10.8; 5.0)**
IV drug use	82.5 (151/183)	79.6 (164/206)	**2.9 (-5.0; 10.7)**
Diabetes	70.7 (41/58)	82.1 (55/67)	**-10.9 (-26.1; 4.0)**
Bacteraemia at baseline	100 (11/11)[a]	69 (11/16)	**ND**

[a]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.

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

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



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

* Pooled data

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

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

	ESTABLISH-1 & ESTABLISH-2		
MITT Analysis Set	Tedizolid **200mg qD for 6 days** % (n)	Linezolid **600mg BID for 10 days** % (n)	**95% CI**
Staphylococcus aureus	**88.8 (292/329)**	**88.9 (304/342)**	**-0.1 (-5.0; 4.7)**
MRSA	**84.4 (119/141)**	**82.2 (120/146)**	**2.2 (-6.6; 10.9)**
MSSA	**92.0 (173/188)**	**93.9 (186/198)**	**-1.9 (-7.4; 3.3)**
Streptococcus pyogenes	**90.9 (30/33)**	**95.0 (19/20)**	**-4.1 (-19.8; 16.1)**
S. anginosus-milleri group	**73.3 (22/30)**	**89.3 (25/28)**	**-15.7 (-35.4; 5.7)**

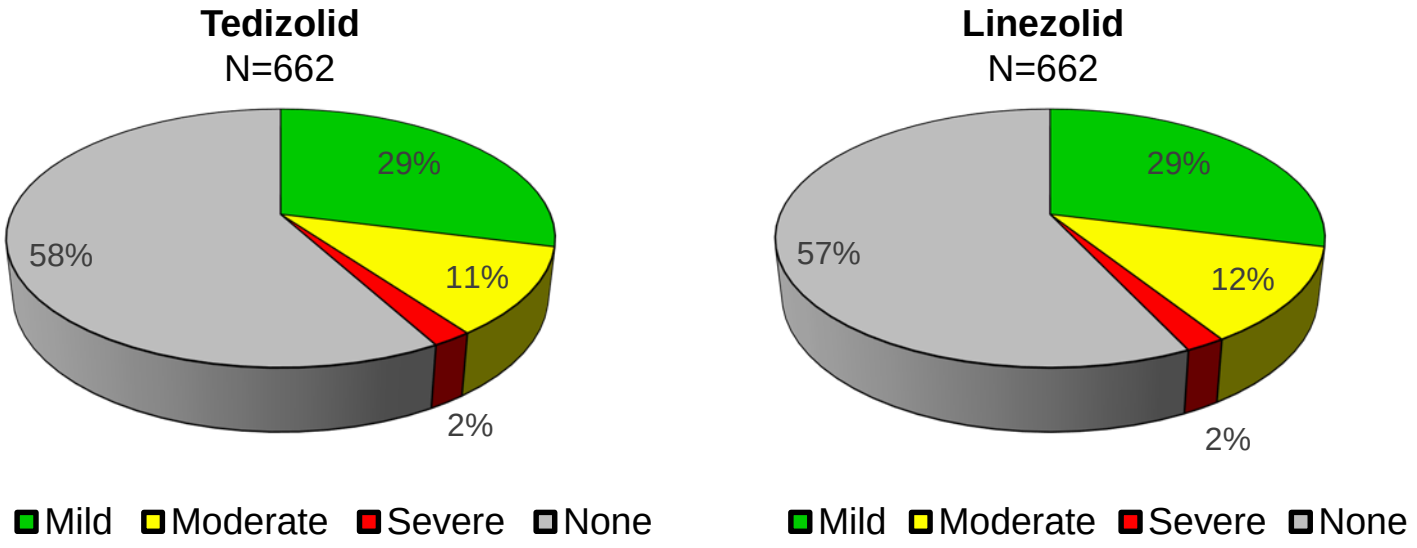
High potency against Gram + pathogens

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

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

Treatment-Emergent Adverse Event (TEAE)	Tedizolid % (n=662)	Linezolid % (n=662)
Any TEAE	**283 (42.7)**	**286 (43.2)**

Most Adverse Events Reported were Mild or Moderate in Severity



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

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

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

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

* Not related to study drug

Prokocimer *et al*. JAMA 2013;309(6):559–569.
Shorr *et al.* AAC 2015;59(2):864–871.
Moran *et al*. LID 2014;14(8):696–705.
Fang *et al*. Respirology 2013;18(Suppl4):165. Poster295.

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

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

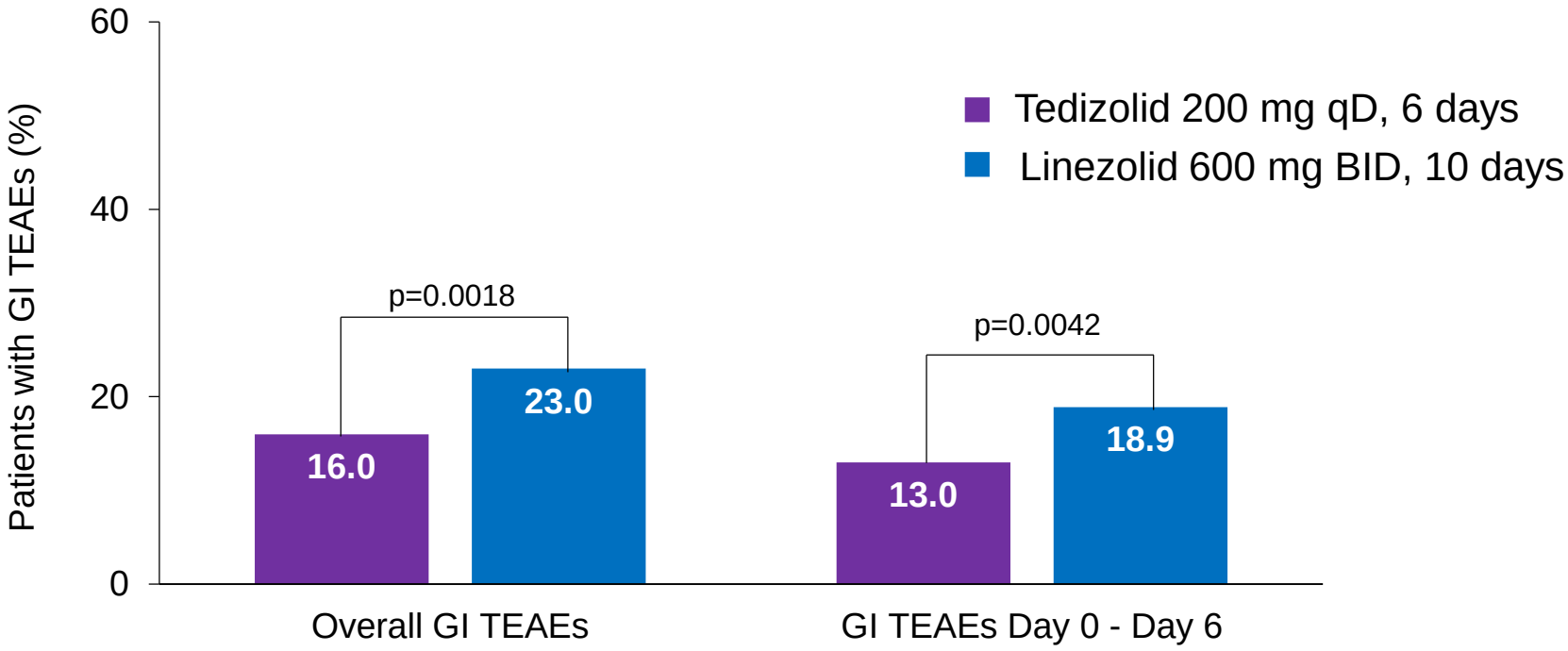
*P<0.05

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

Prokocimer *et al*. JAMA 2013;309(6):559–569.
Shorr *et al*. AAC 2015;59(2):864–871.
Moran et al. LID 2014;14(8):696–705.

ESTABLISH-1 and -2 Integrated Safety

Tedizolid treatment was associated with a lower incidence of GI Adverse Events



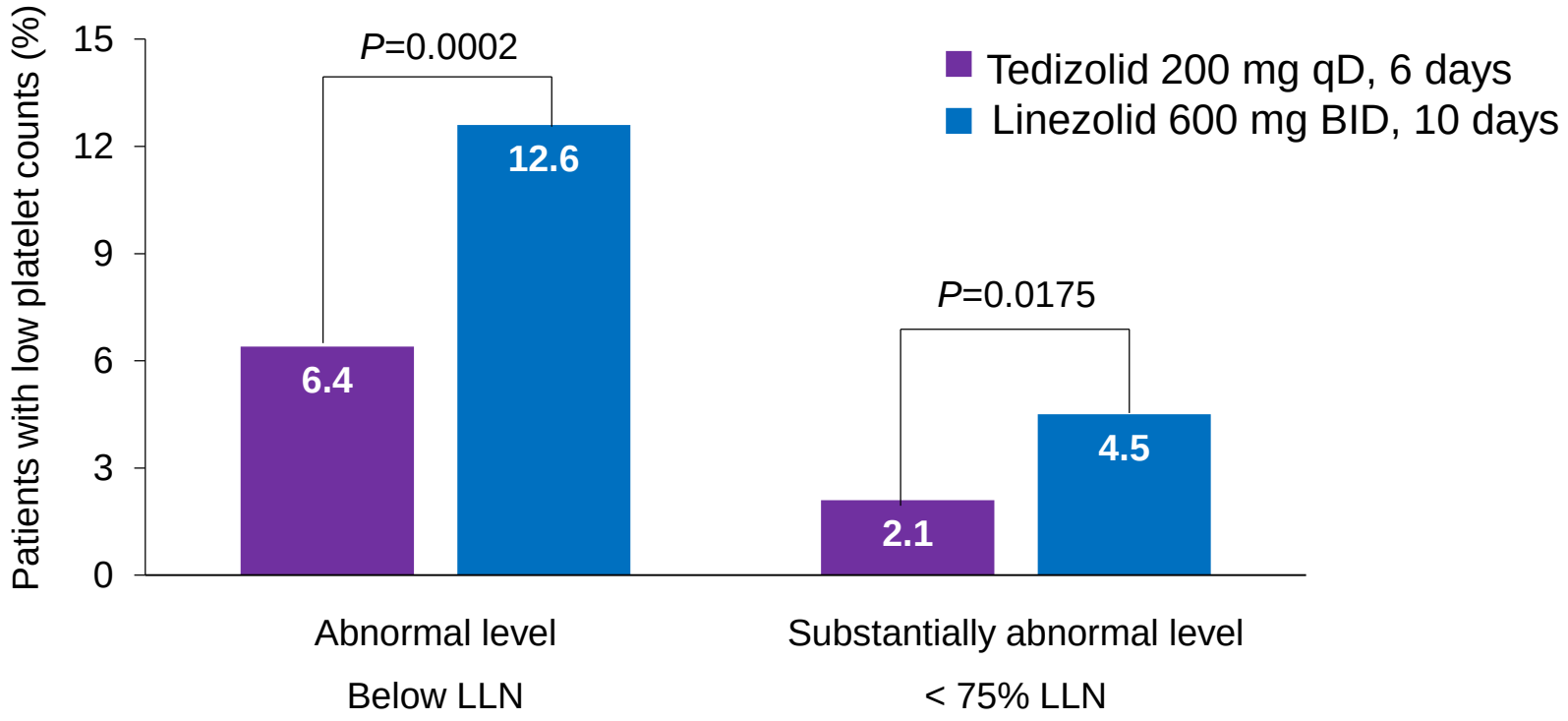
Tedizolid was associated with a significantly lower incidence of GI adverse events irrespective of duration of therapy

TEAE = treatment-emergent adverse events; GI = gastrointestinal.

Prokocimer *et al*. JAMA 2013;309(6):559–569.
Shorr *et al*. AAC 2015;59(2):864–871.
Moran et al. LID 2014;14(8):696–705.

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 anemia, leukopenia, or pancytopenia

LLN = lower limit of normal.

Prokocimer *et al*. JAMA 2013;309(6):559–569.
Shorr *et al*. AAC 2015;59(2):864–871.
Moran et al. LID 2014;14(8):696–705.

Summary – Clinical

- Non-inferior to linezolid overall and in all infection types
  - **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

Can we make a comparison list for ABSSI ?

drug	availability	points to consider *
vancomycin	all generics	• **IV only** • > 7 days • BID or continuous infusion • nephrotoxicity • **failures if MIC >2** (MIC creep)
daptomycin	generics coming	• **IV only** • ≥ 7 days • **beware of VISA** (↘ susceptibility) • **beware of rabdomyolysis** (check CPK)
ceftaroline	branded	• **IV only** • ≥ 7 day • tested only against vancomycin
tedizolid	branded	• **IV and oral** • 6 days (against linezolid 10 days) • **active against *cfr*+ linezolid^{R} strains**

* based on analysis of the prescription information and literature data

What about the future ?