New agents for MRSA: recently released or in the pipeline

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Disclosures

Research grants for work on investigational compounds discussed in this presentation from

• Cempra Pharmaceuticals ¹
• Cerexa
• GSK
• Melinta Therapeutics
• The Medicine Company
• MerLion Pharmaceuticals
• Theravance
• Trius Therapeutics ²

Influenced by my participation to the

• Belgian Drug Reimbursement Committee (CRM/CTG; up to 2006)
• EUCAST steering committee (2008-2010) and General Assembly (current)
• the Governance Body of DRIVE-AB (2014-2017)
    (an EU programme aiming at (re)designing the economic framework of the discovery, development and commercialization processes for new antibiotics)

¹ now merged with and renamed as Melinta Therapeutics
² acquired by Cubist, which was then acquired by Merck
New antibiotics: what is your own view of the pipeline?
Here are the questions …

The pipeline is

1. empty
2. has only mee-too's (no interest for the clinician)
3. contains compounds with useful properties compared to old friends…
4. contains truly novel compounds

Please, think about what YOU would choose!
Newly registered anti-Gram(+) antibiotics in 2008-2012

Approvals by FDA/EMA – systemic antibiotics

DECLINING ANTIBACTERIAL APPROVALS (PAST 25 YEARS)

16 14 10 7 4 2


telavancin ceftaroline
Newly registered anti-Gram (+) antibiotics since 2013

Approvals by FDA/EMA – systemic antibiotics

Telavancin
Ceftaroline

Oritavancin
Dalbavancin
Tedizolid
Dalafloxacine
Ceftobiprole

Telavancin
Ceftaroline

Shall we succeed?
<table>
<thead>
<tr>
<th>company</th>
<th>drug</th>
<th>class</th>
<th>approved indications</th>
<th>useful activity against</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Theravance</td>
<td>Telavancin</td>
<td>lipoglycopeptides</td>
<td>cSSSI / HABP/VABP</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>VRE: VanB only</td>
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<tr>
<td>Durata Ther.</td>
<td>Dalbavancin</td>
<td></td>
<td>ABSSSI</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<td>VRE: VanB only</td>
</tr>
<tr>
<td>The MedCo</td>
<td>Oritavancin</td>
<td></td>
<td>ABSSSI</td>
<td>✓</td>
<td>✓</td>
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<td>MSD / Bayer</td>
<td>Tedizolid</td>
<td>oxazolidinone</td>
<td>ABSSSI</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Forrest Astra-Zeneca</td>
<td>Ceftaroline</td>
<td>β-lactams</td>
<td>ABSSSI / CABP</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Basilea</td>
<td>Ceftobiprole</td>
<td></td>
<td>CAP / HAP</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Melinta</td>
<td>Delafloxacin</td>
<td>fluoroquinolone</td>
<td>ABSSSI</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

1. FDA (US Food and Drug Administration) and/or EMA (European Medicines Agency) unless indicated otherwise
2. approved in 13 EU countries: AT, BE, CH, DE, DK, ES, FI, FR, IT, LU, NO, SE, UK;
3. approved by FDA only at this stage
4. activity also demonstrated against several Gram-negative organisms

MRSA: Methicillin-resistant *Staphylococcus aureus*
MSRSP: multidrug resistant *Streptococcus pneumoniae*
VRE: vancomycin resistant *Enterococci*
Lipoglycopeptides

- prolonged half-life
- membrane anchoring
- dimerization

- decreased half-life

Lipoglycopeptides: dual mode of action

Oritavancin (lipoglycopeptide)

- highly bactericidal
- activity on VR strains

### Lipoglycopeptides: pharmacokinetics

<table>
<thead>
<tr>
<th>parameter</th>
<th>VAN</th>
<th>ORI</th>
<th>TLV</th>
<th>TEC</th>
<th>DAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>15 mg/kg</td>
<td>1200 mg</td>
<td>10 mg/kg</td>
<td>6 mg/kg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>20-50</td>
<td>138</td>
<td>93</td>
<td>43</td>
<td>287</td>
</tr>
<tr>
<td>AUC (mg.h/L)</td>
<td>260</td>
<td>1110 (24h)</td>
<td>668</td>
<td>600</td>
<td>3185 (24h)</td>
</tr>
<tr>
<td>(% prot. binding)</td>
<td>55</td>
<td>85</td>
<td>95</td>
<td>88-94</td>
<td>99</td>
</tr>
<tr>
<td>T ½ (h)</td>
<td>1 (β) 3-9 (γ)</td>
<td>14 (β) 245 (γ)</td>
<td>8</td>
<td>10 (β) 168 (γ)</td>
<td>346 (γ)</td>
</tr>
</tbody>
</table>

- single dose treatment !
- once-a-week dose treatment (2 doses)
Participants underwent randomization in a 1:1 ratio to receive either
• a **single** intravenous dose of 1200 mg of oritavancin followed by intravenously administered placebo, or
• an intravenous dose of vancomycin (1 g, or 15 mg per kilogram of body weight) **every 12 hours** for 7 to 10 days
## Oritavancin: a unusual development …

### Table: Primary and Secondary Efficacy End Points According to Analysis Population and MRSA Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Oritavancin</th>
<th>Vancomycin</th>
<th>Percentage-Point Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modified intention-to-treat population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary efficacy outcome at ECE</td>
<td>391/475 (82.3)</td>
<td>378/479 (78.9)</td>
<td>3.4 (−1.6 to 8.4)</td>
</tr>
<tr>
<td>Investigator-assessed clinical cure at PTE</td>
<td>378/475 (79.6)</td>
<td>383/479 (80.0)</td>
<td>−0.4 (−5.5 to 4.7)</td>
</tr>
<tr>
<td>Lesion size reduction ≥20% at ECE</td>
<td>413/475 (86.9)</td>
<td>397/479 (82.9)</td>
<td>4.1 (−0.5 to 8.6)</td>
</tr>
<tr>
<td><strong>CE population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary efficacy outcome at ECE</td>
<td>344/394 (87.3)</td>
<td>342/397 (86.1)</td>
<td>1.2 (−3.6 to 5.9)</td>
</tr>
<tr>
<td>Investigator-assessed clinical cure at PTE</td>
<td>357/394 (90.6)</td>
<td>352/397 (88.7)</td>
<td>1.9 (−2.3 to 6.2)</td>
</tr>
<tr>
<td>Lesion size reduction ≥20% at ECE</td>
<td>362/394 (91.9)</td>
<td>370/397 (93.2)</td>
<td>−1.3 (−5.0 to 2.3)</td>
</tr>
<tr>
<td><strong>Patients infected with MRSA in intention-to-treat population with microbiologic evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary efficacy outcome at ECE</td>
<td>84/104 (80.8)</td>
<td>80/100 (80.0)</td>
<td>0.8 (−10.1 to 11.7)</td>
</tr>
<tr>
<td>Investigator-assessed clinical cure at PTE</td>
<td>86/104 (82.7)</td>
<td>83/100 (83.0)</td>
<td>−0.3 (−10.7 to 10.0)</td>
</tr>
<tr>
<td>Lesion size reduction ≥20% at ECE</td>
<td>94/104 (90.4)</td>
<td>84/100 (84.0)</td>
<td>6.4 (−2.8 to 15.5)</td>
</tr>
<tr>
<td><strong>Patients infected with MSSA in intention-to-treat population with microbiologic evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary efficacy outcome at ECE</td>
<td>96/116 (82.8)</td>
<td>92/110 (83.6)</td>
<td>−0.9 (−10.6 to 8.9)</td>
</tr>
<tr>
<td>Investigator-assessed clinical cure at PTE</td>
<td>89/116 (76.7)</td>
<td>88/110 (80.0)</td>
<td>−3.3 (−14.0 to 7.4)</td>
</tr>
<tr>
<td>Lesion size reduction ≥20% at ECE</td>
<td>98/116 (84.5)</td>
<td>94/110 (85.5)</td>
<td>−1.0 (−10.3 to 8.3)</td>
</tr>
</tbody>
</table>

**Figure 2. Primary and Secondary Efficacy End Points According to Analysis Population and MRSA Subgroup.** CE denotes clinical evaluation, ECE early clinical evaluation, MRSA methicillin-resistant *Staphylococcus aureus*, MSSA methicillin-susceptible *S. aureus*, and PTE post-therapy evaluation.

Tedizolid

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 Cho a, *

a College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 151-742, Korea
b Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin, Kyunggi 449-905, Korea
c Department of Life Science, The University of Seoul, Seoul 130-743, Korea

Received 29 July 2004; revised 18 August 2004; accepted 18 August 2004
Available online 11 September 2004

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 Titas Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA
Dong-A pharmaceuticals and tedizolid: step #1

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

- increases activity
- prolongs half-life

**Linezolid**

**DA-7867**

<table>
<thead>
<tr>
<th>Agent</th>
<th>MSSA</th>
<th>MRSA</th>
<th>VRE</th>
<th>PRSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC</td>
<td>0.78 ug/ml</td>
<td>0.78 ug/ml</td>
<td>0.125 ug/ml</td>
<td>0.39 ug/ml</td>
</tr>
</tbody>
</table>

**bacterial potency of lead compound (DA-7867).**

as a novel 5-hydroxymethyl-oxazolidinone

**Weon Bin Im**<sup>a,b</sup>, **Sun Ho Choi**<sup>b</sup>, **Ju-Young Park**<sup>a</sup>, **Sung Hak Choi**<sup>b</sup>, **John Finn**<sup>c</sup>, **Sung-Hwa Yoon**<sup>a,**+**</sup>

<sup>a</sup>Department of Molecular Science and Technology, Ajou University, San 5, Woncheon, Yeongtong, Suwon 443-749, Republic of Korea

<sup>b</sup>Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea

<sup>c</sup>Triba Therapeutics, 5310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA
Tedizolid has more interactions with the ribosome...

Fig. 2. Models of 11 (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.
Dong-A pharmaceuticals and tedizolid: step #2

2. replacing the acetamido by an hydroxyl maintains the increased activity vs. linezolid!
Oxazolidinones: the cfr+ mechanism of resistance

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

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

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

FIG. 1. Binding of the phenicol, lincosamide, pleuromutilin, and streptogramin A classes of antimicrobials to overlapping sites at the ribosomal peptidyl transferase center. (A) The structure of the bacterial 50S ribosomal subunit showing the slice plane used in panel B. (B) An expanded view showing the structures of four drugs bound at the peptidyl transferase center. The structural data can be found in reference 22 and references therein. The names and chemical structures of the four antimicrobial agents are shown at the bottom on background colors that correspond to the bound structures (depicted in stick representation). The target of the Cfr methyltransferase, nucleotide A2503, is shown in red. The surrounding RNA is shown in light gray. (C) The Cfr-mediated resistance patterns with S. aureus for chloramphenicol, clindamycin, tiamulin, and virginiamycin M₄. The data are from Table 1. The MICs are depicted on a logarithmic scale with strains lacking Cfr shown in the left column of each pair of bars (marked −), whereas those of strains containing Cfr are shown in the right column of each pair of bars (marked +). The numbers above the +Cfr columns are the n-fold differences in MICs between −Cfr and +Cfr strains. Details on the visualization of the 50S ribosomal subunit and antibiotic-50S subunit complexes are provided in Materials and Methods.
Oxazolidinones: the *cfr*+ mechanism of resistance

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

1. Toh et al. Mol Microbiol 2007;64:1506-14 - PMID 17555436
5. Giessing et al. RNA 2009;15:327-36 - PMID 19144912

**Tedizolid retains full potency against cfr+ strains and we know why... (see next slides)**

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

<table>
<thead>
<tr>
<th>Strain</th>
<th>Reference</th>
<th>Presence of cfr</th>
<th>MIC ((\mu g/ml))(^a)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RN4220(pLI50)</td>
<td>68</td>
<td>−</td>
<td>2</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>RN4220(pLXM1)(^b)</td>
<td>68</td>
<td>+</td>
<td>8</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>CM05(^c)</td>
<td>44</td>
<td>−</td>
<td>2</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>CM05(^c)</td>
<td>68</td>
<td>+</td>
<td>8</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>29213</td>
<td>ATCC</td>
<td>−</td>
<td>2</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>29213(p42262)(^d)</td>
<td>45</td>
<td>+</td>
<td>16</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>42262(^e)</td>
<td>51</td>
<td>+</td>
<td>16</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) MICs (broth microdilution: CLSI)
\(^b\) The pLXM1 cfr-containing plasmid is isogenic to the empty pLI50 vector.
\(^c\) CM05\(^\Delta\) is isogenic to the CM05 clinical cfr-positive strain but lacks cfr and one copy of ermB.
\(^d\) 29213(p42262) was generated through transformation of ATCC 29213
\(^e\) 42262 is a clinical cfr-positive isolate from a 2008 hospital outbreak in Madrid, Spain.
Why is tedizolid active against LZD$^R$ strains (cfr) ?

LZD

\[
\text{\textbf{LZD}}
\]

TR700

\[
\text{\textbf{TR700}}
\]

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 C-5 acamidine 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 docs 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).

Locke et al. AAC 2010;54:5337-5343
Why is tedizolid active against LZDR \textsuperscript{R} strains (cfr)?

Locke et al. AAC 2010;54:5337-5343
Tedizolid: key PK/PD parameters and breakpoints

- excellent oral bioavailability (IV ~ oral)
- long half-life (~12 h) (with concentrations > 0.5 mg/L for ~18 h)
- activity dependent from the AUC$_{24h}$ (total daily dose/clearance) irrespective of the dosing scheme (Q8, Q12, Q24)

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

- elimination mainly by the faeces

✓ no need of dose adjustment in patients with renal impairment or in hemodialysis
Tedizolid phase III studies

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 (ABSSIs), including cellulitis or erysipelas, major cutaneous abscesses, and wound infections, can be life-threatening and may require surgery and hospitalization. Increasingly, ABSSIs 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 ABSSIs.


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

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

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

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

Ceftobiprole and ceftaroline

Fig. 130.4 Structural modifications of β-lactam antibiotics in order to overcome methicillin resistance, as applied to cephalosporins (with ceftobiprole and ceftaroline as examples). The bulky hydrophobic moieties (dotted-lined ellipse) added to the molecules forces a conformational change in PBP2a resulting in the opening of the active site and allowing acylation (inactivation) by the antibiotic. Although activity is largely restored towards methicillin-resistant organisms, MICs remain still typically one to four dilutions higher than for susceptible ones. The increase in lipophilicity also makes it necessary to administer the molecules as prodrugs – medocaril for ceftobiprole and fosamyl for ceftaroline (not shown).

Van Bambeke, Glupczynski, Mingeot-Leclercq & Tulkens
Infectious Diseases, 3d Edition
Chap. 130: Mechanisms of action
Elsevier/Mosby, 2010
Available on line at http://www.expertconsultbook.com/
The ceftobiprole PBP2a "opening" hypothesis

Figure 5. Loss of secondary structure accompanies acylation.

Lovering et al. ECCMID 2006, Abstract P1586.
Why does ceftaroline act on PBP2a: the new (and probably correct) mechanism


Fig. 1. Domains of PBP2a and key ligands. (A) The chemical structures of a synthetic NAG-NAM(pentapeptide) (1) and ceftaroline (2). The R1 and R2 groups of 2 are labeled. (B) Ribbon representation of PBP2a acylated by ceftaroline. The N-terminal extension is colored in green, the remaining allosteric domain is colored in gold, and the transpeptidase (TP) domain is colored in blue. These domain colors are retained in all other figures. Two molecules of ceftaroline (capped sticks in red) are found in complex with protein: one covalently bound as an acyl-enzyme in the TP domain (CFT1) and one intact at the allosteric domain (CFT2). A muramic acid saccharide (capped sticks in magenta) is found at the center of the allosteric domain. The arrow indicates the point of attachment of the membrane anchor. (C) The solvent-accessible surface representation for PBP2a is shown. The distance between the two ceftaroline molecules is 60 Å. (D) Ribbon representation of PBP2a in complex with 1 (black sticks). This view is rotated ~45° on the y axis compared with the view of C.
Ceftaroline vs MSSA and MRSA *

MSSA / MRSA (n = 83 / 157)

** The S-breakpoint is based on standard dosage (0.6 g x 2 iv over 1 hour); a I breakpoint (2 mg/L) implies a high dosage (0.6 g x 3 over 2 hours). In pneumonia, there is no clinical data on the treatment of S. aureus with MICs above 1 mg/L.

* isolates collected between 2011 and 2012 from patients suffering of wound infections in 3 hospitals (1 in South-East of Brussels; 1 in North of Brussels; 1 in Hainaut)

Tuikens et al. 26th ICC, 2013 and unpublished
Ceftaroline vs MSSA and MRSA (EUCAST) *

**The S-breakpoint is based on standard dosage (0.6 g x 2 iv over 1 hour); a l breakpoint (2 mg/L) implies a high dosage (0.6 g x 3 over 2 hours). In pneumonia, there is no clinical data on the treatment of S. aureus with MICs above 1 mg/L.**

Delafloxacin, a non-zwitterionic fluoroquinolone in Phase III of clinical development: evaluation of its pharmacology, pharmacokinetics, pharmacodynamics and clinical efficacy

Françoise Van Bambeke*

**ABSTRACT** Delafloxacin is a fluoroquinolone lacking a basic substituent in position 7. It shows MICs remarkably low against Gram-positive organisms and anaerobes and similar to those of ciprofloxacin against Gram-negative bacteria. It remains active against most fluoroquinolone-resistant strains, except enterococci. Its potency is further increased in acidic environments (found in many infection sites). Delafloxacin is active on staphylococci growing intracellularly or in biofilms. It is currently evaluated as an intravenous and intravenous/oral stepdown therapy in Phase III trials for the treatment of complicated skin/skin structure infections. It was also granted as Qualified Infectious Disease Product for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia, due to its high activity on pneumococci and atypical pathogens.

Delafloxacin, the first “non-zwitterionic” quinolone
Delafloxacin, the first “non-zwitterionic” quinolone

Increased
- uptake by bacteria
- activity at acidic pH

1 INDICATIONS AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections

BAXDELA is indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following:

Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus, Staphylococcus lugdunensis, Streptococcusagalactiae, Streptococcus anginosus Group* (including *Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus*), *Streptococcus pyogenes*, and *Enterococcus faecalis*.

Gram-negative organisms: *Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.
1 INDICATIONS AND USAGE
1.1 Acute Bacterial Skin and Skin Structure Infections

BAXDELA is indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following:

Gram-positive organisms: Staphylococcus aureus (including susceptible [MSSA] isolates), Staphylococcus haemolyticus, Streptococcus agalactiae, Streptococcus anginosus Group (including Streptococcus constellatus), Streptococcus pyogenes.

Gram-negative organisms: Escherichia coli, Enterobacter aerogenosa.

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS, and EXACERBATION OF MYASTHENIA GRAVIS

See full prescribing information for complete boxed warning.

Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:

- Tendinitis and tendon rupture (5.2)
- Peripheral neuropathy (5.3)
- Central nervous system effects (5.4)

Discontinue BAXDELA immediately and avoid the use of fluoroquinolones, including BAXDELA, in patients who experience any of these serious adverse reactions. (5.1)

- Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. Avoid BAXDELA in patients with known history of myasthenia gravis. (5.5)
How to choose?

A short personal view...

- simple dosing
- short treatment with oral relay
- toxicity
- failure due to insusceptibility
How to choose?

- Simple dosing
- Avoid vancomycin
- Failure due to insusceptibility
- Toxicity
- Short treatment with oral relay

A short personal view…
How to choose?

Avoid vancomycin

Failure due to insusceptibility

Simple dosing

Toxicity

- Delafloxacin "quinolones" effects
- Lipoglycopeptides: long tissue residence

Short treatment with oral relay

Avoid vancomycin

A short personal view...
How to choose?

- Simple dosing
- Failure due to insusceptibility
- Toxicity
- Short treatment with oral relay

Avoid vancomycin
- Delafloxacin "quinolones" effects
- Lipoglycopeptides: long tissue residence
- A short personal view...
How to choose?

- simple dosing
  - oritavancin "once" dosing
  - tedizolid 6 days treatment?

- short treatment with oral relay
  - failure due insusceptibility
    - avoid vancomycin
    - toxicity
      - delafloxacin "quinolones" effects
    - avoid vancomycin
      - lipoglycopeptides: long tissue residence

A short personal view...
Short effective treatments may be the way to go…

Am I OK to go home?
We have criteria since long!

BMC Infectious Diseases

Research article

A new approach to treatment of resistant gram-positive infections: potential impact of targeted IV to oral switch on length of stay
Mohammed Desai2, Bryony Dean Franklin2,5, Alison H Holmes1,4, Sarah Trust2, Mike Richards4, Ann Jacklin2 and Kathleen B Bamford*1,3

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

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

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

Here are useful (early) criteria...

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

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

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

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

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

| 2. Oral route compromised | - Vomiting or severe diarrhoea
|                          | - Other ongoing or potential absorption problem
But what about the pre-registration pipeline…
### Anti Gram-positive antibiotics in the pipeline (phases II/III) – 1/2

<table>
<thead>
<tr>
<th>company</th>
<th>drug</th>
<th>class</th>
<th>status</th>
<th>MRSA</th>
<th>MDRSP</th>
<th>VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cempra *</td>
<td>solithromycin</td>
<td>ketolide</td>
<td>Phase III CAPB</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>TaiGen</td>
<td>nemonoxacin</td>
<td>fluoroquinolone</td>
<td>Phase III CAPB / ABSSSI</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Dong</td>
<td>zabofloxacin</td>
<td></td>
<td>Phase III CAPB</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Activis</td>
<td>avarofloxacin</td>
<td></td>
<td>Phase II completed CAPB / ABSSSI</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>MerLion</td>
<td>finafloxacin</td>
<td></td>
<td>Phase II ABSSSI</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>GSK *</td>
<td>geoptidacin</td>
<td>topoisomerase inhibitor</td>
<td>Phase II respiratory / ABSSSI</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Motif</td>
<td>iclaprim</td>
<td>dihydrofolate reductase inhibitor</td>
<td>Phase III completed ABSSI</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

*Constructed based on [www.pewtrusts.org](http://www.pewtrusts.org) (not exhaustive)*
## Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

<table>
<thead>
<tr>
<th>company</th>
<th>drug</th>
<th>class</th>
<th>status</th>
<th>MRSA</th>
<th>MDRSP</th>
<th>VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melinta</td>
<td>radezolid</td>
<td>oxazolidinone</td>
<td>Phase II CAPB / ABSSSI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Paratek</td>
<td>omadacycline</td>
<td>aminomethyl cyclines</td>
<td>Phase III CAPB / ABSSSI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cempra</td>
<td>fusidic acid</td>
<td>fusidane</td>
<td>Phase III ABSSSI</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debiopharm*</td>
<td>Debio1452</td>
<td>FabI inhibitor</td>
<td>Phase II S. aureus ABSSSI</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystal-</td>
<td>CG-400549</td>
<td></td>
<td>Phase II ABSSSI / osteomyelitis</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>genomics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theravance</td>
<td>TD-1792</td>
<td>glycopeptide + cephalosporine</td>
<td>Phase II completed cSSSI</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Nabriva</td>
<td>lefamulin</td>
<td>pleuromutilin</td>
<td>Phase II completed ABSSSI/CABP/HA-VABP</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cellceutix *</td>
<td>brilacidin</td>
<td>defensin-mimetic</td>
<td>Phase II completed ABSSSI</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

*Constructed based on [www.pewtrusts.org](http://www.pewtrusts.org) (not exhaustive)
From telithromycin to solithromycin ...

- binding to ribosomal domain II
- poor recognition by pneumococci efflux pumps

**Absence of inducibility of MLS_{B} resistance**

- increased activity

**lower interaction with nicotinic receptor**

- further increased activity

---

*Adapted from Van Bambeke, Ann. Med (2014) 46:512-29*
The FDA stated in its CRL that the risk of hepatotoxicity had not been adequately characterized, noting that the size of the safety database is limited to 920 patients who received solithromycin at the proposed dose and duration—a group too small to adequately characterize the nature and frequency of serious hepatic adverse effects, in the agency’s view.

GSK2140944 (gepotidacin) – topoisomerase inhibitor

No cross-resistance with fluoroquinolones

GSK2140944 (gepotidacin) – *In vitro* activity

Isolates Associated with Lower Respiratory Tract and Skin Infections

<table>
<thead>
<tr>
<th>Organism (N)</th>
<th>MIC Range</th>
<th>MIC$_{50}$</th>
<th>MIC$_{90}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA (1,008)</td>
<td>≤0.06 - 2</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Methicillin-resistant SA (490)</td>
<td>≤0.06-1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Levofloxacin-resistant MRSA (375)</td>
<td>≤0.06-1</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Spy (201)</td>
<td>0.03-0.5</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Spn (549)</td>
<td>0.03-1</td>
<td>0.12</td>
<td>0.25</td>
</tr>
<tr>
<td>Levofloxacin-resistant Spn (22)</td>
<td>0.06-0.5</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>HI (n=981)</td>
<td>≤0.015-8</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>MC (n=158)</td>
<td>≤0.06 - 0.12</td>
<td>≤0.06</td>
<td>≤0.06</td>
</tr>
</tbody>
</table>

*ICAAC (2013) F1216*
Efficacy, Safety, and Tolerability of Gepotidacin (GSK2140944) in the Treatment of Patients with Suspected or Confirmed Gram-Positive Acute Bacterial Skin and Skin Structure Infections

William O’Riordan, a Courtney Tiffany, b Nicole Scangarella-Oman, b Caroline Perry, b Mohammad Hossain, c Teri Ashton, b Etienne Dumont b

eStudySite, San Diego, California, USA; GlaxoSmithKline, Upper Providence, Pennsylvania, USA;
GlaxoSmithKline, King of Prussia, Pennsylvania, USA

GSK2140944 (gepotidacin) – Clinical data

Efficacy, Safety, and Tolerance of GSK2140944, a New Innovative Oral Beta-Lactam, in the Treatment of Patients with Confirmed Gram-Positive Skin and Skin Structure Infections

William O’Riordan, Courtney Tiffany, Nima Nia, Mohammad Hossain, Teri Ashton, Etienne Ettiene

The administration of gepotidacin was generally well tolerated in patients with ABSSSIs in all 3 treatment groups, with no unexpected findings.

These phase 2 data suggest that gepotidacin, a new antimicrobial agent with a novel mechanism of action, has the potential to address a critical need for novel antibacterial agents for the treatment of ABSSSIs caused by targeted drug resistant pathogens.

FabI (Enoyl-[acyl-carrier-protein] reductase) inhibitors


Specifically active on *S. aureus*
Debio1452 (AFN-1252) *in vitro* activity

<table>
<thead>
<tr>
<th>Species or isolate group (no. of isolates)</th>
<th>Agent</th>
<th>MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Methicillin-resistant <em>S. aureus</em> (127)</td>
<td>AFN-1252</td>
<td>≤0.008</td>
</tr>
<tr>
<td></td>
<td>Cefazolin</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>&gt;16</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>&gt;8</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>≤0.5</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>≤0.12</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>1</td>
</tr>
<tr>
<td>Methicillin-resistant <em>S. epidermidis</em> (9)</td>
<td>AFN-1252</td>
<td>≤0.008</td>
</tr>
<tr>
<td></td>
<td>Cefazolin</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>&gt;16</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>&gt;8</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>1</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> (489)</td>
<td>AFN-1252</td>
<td>&gt;4</td>
</tr>
<tr>
<td></td>
<td>Penicillin</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone</td>
<td>≤0.06</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>≤0.12</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>≤0.25</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em> (81)</td>
<td>AFN-1252</td>
<td>&gt;4</td>
</tr>
<tr>
<td></td>
<td>Cefazolin</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>&gt;8</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>≤0.12</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>1</td>
</tr>
</tbody>
</table>

*Karlowsky et al, AAC (2009) 53: 3544-48*
Debio1452 (AFN-1252) *in vitro* activity

Flamm et al. Antimicrob Agents Chemother 2015;59:2583-7 - PMID 25691627

Activity of Debio1452, a FabI Inhibitor with Potent Activity against *Staphylococcus aureus* and Coagulase-Negative *Staphylococcus* spp., Including Multidrug-Resistant Strains

Robert K. Flamm, a Paul R. R homberg, a Nachum Kaplan, b Ronald N. Jones, a David J. Farrell a

JMI Laboratories, North Liberty, Iowa, USA; Nobelex Inc., Toronto, Canada b

Debio1452 demonstrated potent activity against MSSA, MRSA, and CoNS. Debio1452 showed significantly greater activity overall (MIC$_{50}$, 0.004 g/ml) than the other agents tested against these staphylococcal species, which included dominant MRSA clones and strains resistant to currently utilized antimicrobial agents.
Debio1452 (AFN-1252) *in vitro* activity

<table>
<thead>
<tr>
<th>Strain</th>
<th>Antibiotic</th>
<th>MIC (mg/L)</th>
<th>EUCAST categor.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATCC25923</td>
<td>Debio 1452</td>
<td>0.004</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>daptomycin</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>MU50</td>
<td>Debio 1452</td>
<td>0.004</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>8</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>daptomycin</td>
<td>8</td>
<td>R</td>
</tr>
<tr>
<td>SA040 LZR</td>
<td>Debio 1452</td>
<td>0.004</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>NRS119</td>
<td>Debio 1452</td>
<td>0.004</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>64</td>
<td>R</td>
</tr>
</tbody>
</table>

Peyrusson *et al*. 26th ECCMID, 2016 - Poster no. P1134
**Brilacidin**

- membrane depolarisation ~ daptomycin
- cytoplasmic protein misfolding
  - upregulation of chaperones and proteases (genes involved in stress response)
  - ~ defensins

http://en.wikipedia.org/wiki/Antimicrobial_peptides

*Mensa et al, AAC (2014) 58:5136-45*
Brilacidin

http://www.ipharminc.com/stages-of-development/

Drug Candidate | Indication | Preclinical | Phase 1 | Phase 2 | Phase 3
---|---|---|---|---|---
Brilacidin | IBD: UC (UP/UPS)\(^3\) | | | | |
Oral Mucositis\(^4\) | | | | | |
ABSSSI\(^5,6\) | | | | | |

\(^3\) IBD - Inflammatory Bowel Disease; UC - Ulcerative Colitis (UP/UPS - Ulcerative Proctitis/Ulcerative Proctosigmoiditis)

\(^4\) Awarded Fast Track Designation

\(^5\) ABSSSI - Acute Bacterial Skin and Skin Structure Infection

\(^6\) Awarded Qualified Infectious Disease Product (QIDP) Designation (qualifies for Fast Track and Priority Review)
Antibiotic pipeline: the reality today

• Most advanced molecules (Phase III) are new derivatives of existing classes but with improved properties (MIC – resistance – PK- safety)

• BUT there are
  ... many more in preclinical development
  ... some very new *

* I cannot tell you which ones as I’m under confidentiality agreement
Asking the same questions ...

The pipeline is

1. empty
2. has only mee-too's (no interest for the clinician)
3. contains compounds with useful properties compared to old friends…
4. contains truly novel compounds

Did you change your mind?
Antibiotic pipeline: some work ahead

- Susceptibility Breakpoint harmonization

An example with MRSA ...

<table>
<thead>
<tr>
<th>antibiotic</th>
<th>EUCAST</th>
<th></th>
<th>CLSI/FDA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≤</td>
<td>R ≥</td>
</tr>
<tr>
<td>rifampicin</td>
<td>0.06</td>
<td>0.5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>azithromycin</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>doxycycline</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>vancomycin</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>linezolid</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>tedizolid</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>ceftaroline</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>telavancin</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>dalbavancin</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
<td></td>
</tr>
</tbody>
</table>
Antibiotic pipeline: can we do better?

- Equivalence to current options in comparative clinical trials

  ⇒ This will raise issues for reimbursement, especially against the generics of the comparators used in these studies

  ⇒ Need to design superiority trials and to focus pricing and reimbursement for documented cases of infection by resistant organisms
Integrating superiority trials in the process

White Paper: Recommendations on the Conduct of Superiority and Organism-Specific Clinical Trials of Antibacterial Agents for the Treatment of Infections Caused by Drug-Resistant Bacterial Pathogens

Clinical Infectious Diseases 2012;55(8):1031–46

Infectious Diseases Society of America (IDSA)®

Nested Superiority–Noninferiority Trial

Patient with Appropriate Signs and Symptoms Randomized

Comparator Drug Targets XDR/PDR Pathogens

Confirmed XDR/PDR Pathogen

No Confirmed Pathogen

Confirmed Not XDR/PDR Pathogen

Superiority Efficacy Analysis

Noninferiority Efficacy Analysis

Intention to Treat
Safety Population

Narrow Comparator Drug
What will be our future?

Artwork and Photography by DON HONG-OAI
Born in Canton in 1929, Chinese artist Dong Hong-Oai passed away in 2004 at the age of 75. He left behind an incredible volume of work, using a style known as pictorialism to create incredible photographs that look like traditional Chinese paintings.