Xydalba™ 500 mg

(dalbavancin hydrochloride)
powder for infusion

For the Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in adults

Healthcare professionals are asked to report any suspected adverse reactions. Adverse events should be reported. For UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard. For Ireland, Adverse events should be reported to HPRA Pharmacovigilance: Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, E-mail: medsafety@hpra.ie.
Adverse events should also be reported to: Correvio UK Ltd Tel:+44(0)203 0028 114; email: medinfo@correvio.com.

correvio

Xydalba™ - A efficacious full treatment course in one 30-minute infusion[1-4,8]

- **A efficacious therapeutic alternative[3]**
  - ✓ Potent activity against Gram-positive bacteria, including multi-resistant strains[1,4]
  - ✓ A long-half life allowing a treatment coverage up to 2 weeks[1]
  - ✓ Established efficacy (clinical improvement 48-72 hrs) maintained to achieve clinical success (14-28 days)[5,6,12]

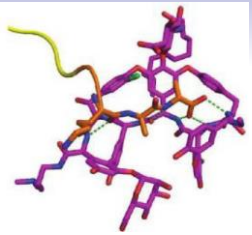
- **Well tolerated[1,6,12]**
  - ✓ Fewer adverse events than comparators[6*,12**], only 3 common AEs[1]
  - ✓ Infrequent late onset events, at a similar rate to comparators[6*,12**]

- **Potential reduction of the length of hospital stay[7-11]**

**Vancomycin/linezolid in Discover studies; **Pooled analysis of dalbavancin-treated patients in phase 2/3 studies vs those receiving comparator agents (vancomycin, linezolid, cefazolin, nafcillin, or oxacillin)*

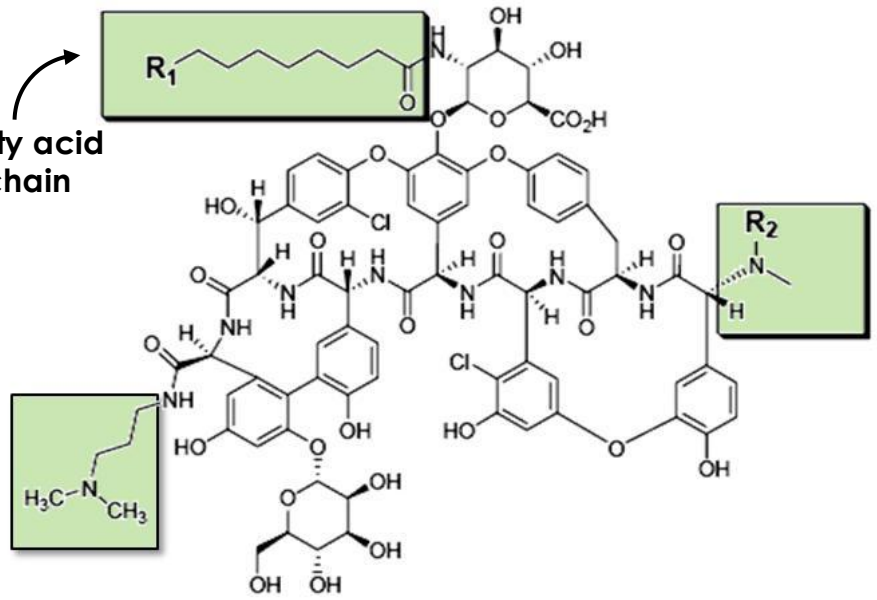
1. Xydalba™ SmPC; **2.** Gonzales PL, *et al*. Drugs Context. 2018; 7: 212559; **3.** Leuthner KD, *et al*. Ther Clin Risk Manag. 2016;12:931-40; **4.** Pfaller MA, *et al*. J Antimicrob Chemother. 2018 Oct 1;73(10):2748-2756; **5.** Dunne MW, *et al.* Clin Infect Dis. 2016;62:545–51; **6.** Boucher HW, *et al.* N Engl J Med. 2014;370:2169-79; **7.** Nair T, *et al.* Infect Dis (Lond). 2018;50(1):75-76; **8.** Galluzzo M, *et al*. Expert Opin Drug Metab Toxicol. 2018 ;14(2) :197-206; **9.** Rappo, *et al*. J Glob Antimicrob Resist. 2019 Feb 20. pii: S2213-7165(19)30047-5; **10.** Keyloun K, *et al*. J Med Econ. 2019 Jul;22(7):652-661; **11.** Marcellusi, *et al*. Expert Rev Pharmacoecon Outcomes Res. 2019 Feb 4:1-19; **12.** Dunne MW, *et al*. Drug Safety. (2016) 39:147–157.

Structure of dalbavancin



Extended half life ($T_{1/2}$) *in vivo*

Fatty acid chain



Define family of homologues, all with antibacterial activity

Enhances antibacterial activity of dalbavancin

3,3-dimethylaminopropyl amide

- Dalbavancin **inhibits the transglycosylation by binding to the terminal** D-ala-D-ala of *S. aureus* and others Gram-positive bacteria.

- The structural changes allowed the dimerization of dalbavancin, enabling:
  - a **stronger affinity towards its target**
  - a **more potent bactericidal activity** than with vancomycin, most notably among the staphylococci species.

Finch RG, *et al*. Safety and efficacy of glycopeptide antibiotics J Antimicrob Chemother 52005) 55, Suppl. S2, ii5–ii13; Leuthner KD, *et al*. Clinical efficacy of dalbavancin for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Therapeutics and Clinical Risk Management 2016:12 931–940; Bennett JW, *et al*. Dalvancin review Therapeutics and Clinical Risk Management 2008 4(1) 31–40.

Xydalba™ 500 mg

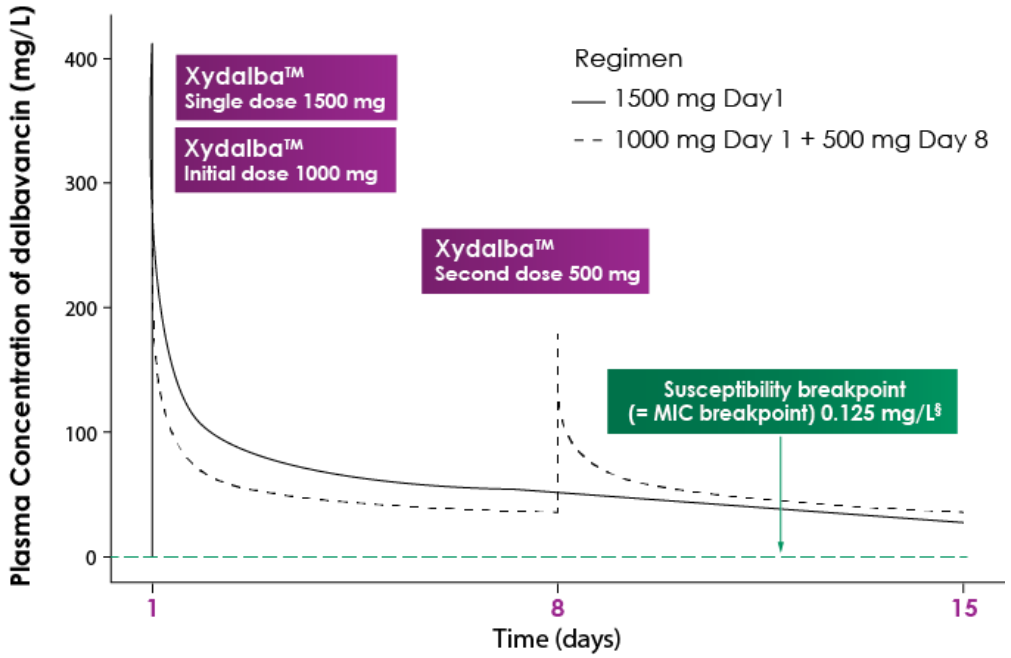
(dalbavancin hydrochloride)
powder for infusion

Pharmacology

Xydalba™ a long half-life

- Mean **terminal elimination half-life** ($T_{1/2}$): 372 h (333 - 405) (= 15,5 days)

Dalbavancin mean Plasma Concentrations *versus* time in a typical ABSSSI patient (simulation using population pharmacokinetic model) for both the single and the two-dose regimens



- Plasma concentrations far above MIC for over 15 days when administered as one 30-minute infusion, or two infusions over two weeks.

§ Determined by EUCAST (European Committee on Antimicrobial Susceptibility Testing): Staphylococcus spp., Beta-haemolytic Streptococci of Groups A, B, C, G, Viridans group Streptococci (Streptococcus anginosus group only).

XYUK220820195K

Xydalba™ SmPC.

Other pharmacokinetic properties

- Drug AUC exposure increased proportionally with dose (range: 140 mg to 1 120 mg)

Mean (SD) dalbavancin pharmacokinetic parameters using population PK analysis[1]

Parameter	Two-dose regimen[2]	Single-dose regimen[3]
C_{max} (mg/L)	Day 1: 281 (52)	Day 1: 411 (86)
	Day 8: 141 (26)	
$AUC_{0\text{-}Day14}$ (mg•h/L)	18100 (4600)	20300 (5300)
CL (L/h)	0.048 (0.0086)	0.049 (0.0096)

[1] Source: DAL-MS-01.
[2] 1000 mg on Day 1 + 500 mg on Day 8; Study DUR001-303 subjects with evaluable PK sample.
[3] 1500 mg Study DUR001-303 subjects with evaluable PK sample.

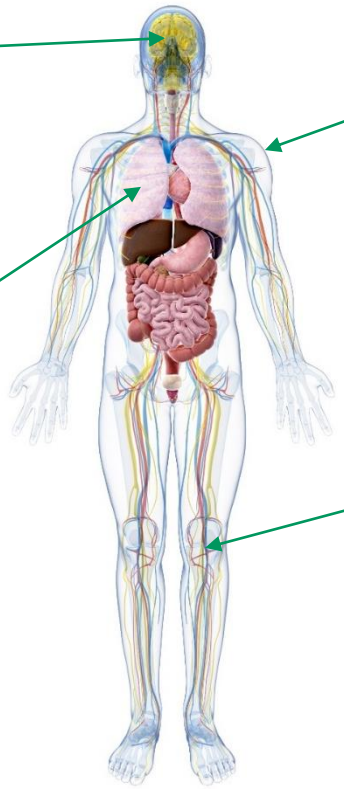
- Distribution:
  93% plasma protein bound: Low mean Volume of Distribution (13.8 ±2.3L)
- Elimination:
  2 elimination routes (following single dose of 1 000 mg to healthy subjects):
  - ✓ 19 -33% of unchanged dalbavancin is excreted in urine (8 -12% excreted as hydroxy-dalbavancin metabolite)
  - ✓ ~20% of administered dose is recovered in stool

Xydalba™ SmPC; Xydalba™ Assessment report EMA/39820/2015.

Tissue Penetration of Xydalba™

CNS:
Dalbavancin does not cross the blood brain barrier[5]

Lung:
36% mean lung epithelial lining fluid (ELF):plasma AUC ratio[4]



Skin and Soft Tissue:
83-110% in skin blister fluid[1]
60% (mean) in skin blister fluid[2]

Bone and Articular Tissue:
13% mean bone: plasma AUC ratio[3]

1. Leighton A , *et al.* Antimicrob Agents Chemother. 2004 Mar;48(3):940-5; 2. Nicolau DP, *et al.* J Antimicrob Chemother. 2007 Sep;60(3):681-4; **3.** Dunne MW, *et al.* Antimicrob Agents Chemother. 2015 Apr;59(4):1849-55; **4.** Dunne M, *et al.* Intrapulmonary and Plasma Concentrations of Dalbavancin in Healthy Adults after a Single 1500 mg Infusion. Poster presented at 26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2016), 9-12April 2016, Amsterdam, Netherlands; P1198; **5.** FDA Medical Review Dalvance.

Xydalba™ 500 mg

(dalbavancin hydrochloride)
powder for infusion

Microbiology

Xydalba™ shows potent activity against 27,208 isolates of Gram-positive cocci from Europe and US (2015-2016)

Organism (No. tested)	MIC_{90} (mg/L)	% Susceptible EUCAST ≤0.125mg/L	% Susceptible CLSI ≤0.25 mg/L
S. aureus (14,319)	0.03	>99.9	100
MSSA (9,111)	0.03	>99.9	100
MRSA (5,208)	0.03	100	100
S. aureus with vancomycin MIC ≥2 mg/L (44)	0.12	95.5	100
CoNS (1,992)	0.06	99.6	-
Vancomycin-susceptible *E. faecalis* (2,022)	0.06	-	100
Vancomycin-susceptible *E. faecium* (531)	0.12	-	-
S. Pneumonaie (3,487)	0.015	-	-
BHS (3,269)	0.03	100	100
VGS (1,063)	0.03	99.7	100

MIC, minimum inhibitory concentration; BHS, beta-hemolytic Streptococci; VGS, Viridans-group Streptococci
- =not applicable since no established breakpoints; Enterococcus is not included in the Xydalba SmPC label and no EUCAST breakpoints are listed; for E. faecalis and VGS, Breakpoints from US FDA Package Insert were used

XYUK2208201 9SK

Pfaller, *et al*. Antimicrob Chemother 2018; 73: 2748–2756.

Xydalba™ shows potent *in vitro* activity against 124 Multi-Drug Resistant (MDR) *S. aureus* strains

Organism (No. tested)	MIC (mg/L) Dalbavancin			
	50%	90%	Range	NS n (%)
MSSA (23)	0.03	0.125	≤0.007-0.125	0
MRSA / VSSA (24)	0.06	0.125	0.06-0.25	1 (4%)
MRSA / hVISA (22)	0.06	0.125	≤0.007-0.125	0
MRSA / DNS (5)	0.06	0.125	0.03-2	1
MRSA / RIF-R (50)	0.125	0.25	0.06 - 0.5	11 (22%)

MSSA, methicillin-susceptible S. aureus; MRSA, methicillin-resistant S. aureus; VSSA, vancomycin-susceptible S. aureus; hVISA, hetero-resistant vancomycin intermediate S. aureus; DNS, daptomycin non-susceptible; RIF-R, rifampicin-resistant.

Dalbavancin exerted a bactericidal activity against all MRSA including the dalbavancin non-susceptible RIF-R.
(Dalbavancin concentration 4x MIC, 3 $\log_{10}$ reduction, at 8 and 24h) and DNS (Dalbavancin concentrations 1x and 2x MIC, 4 $\log_{10}$ reduction, at 24h; Dalbavancin concentration 4x MIC, 5 $\log_{10}$ reduction, at 24h) isolates

Campanile, *et al*. Poster P2061, ECCMID 2018.

Xydalba™ shows *in vitro* activity against *Staphylococcal* biofilms*

	(mg/L)		
	MIC_{90}	$MBIC_{90}$	$MBBC_{90}$
MRSA	0.06	0.25	2
MSSA	0.06	0.12	2
MRSE	0.12	0.5	4
MSSE	0.12	0.25	4

MIC, Minimal inhibitory concentration; MBIC, minimal biofilm inhibitory concentration, MBBC, minimum biofilm bactericidal concentration, MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible S. aureus; MRSE, methicillin-resistance Staphylococcus epidermidis; MSSE, methicillin-susceptible S. epidermidis

** Study included 171 isolates of staphylococci associated with prosthetic joint infection (1996-2014)*

Fernández, *et al*. Diagn Microbiol Infect Dis. 2016;85(4):449-51.

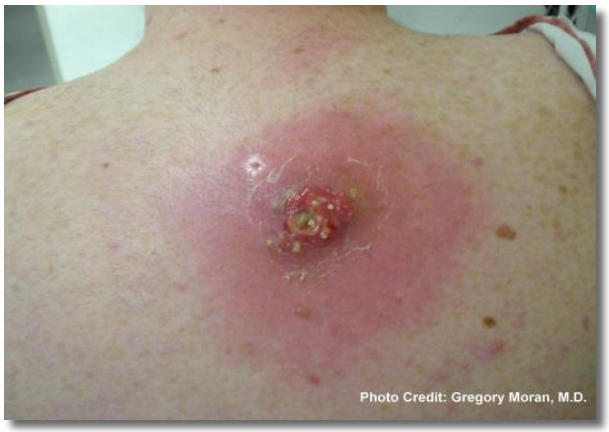
Xydalba™ 500 mg

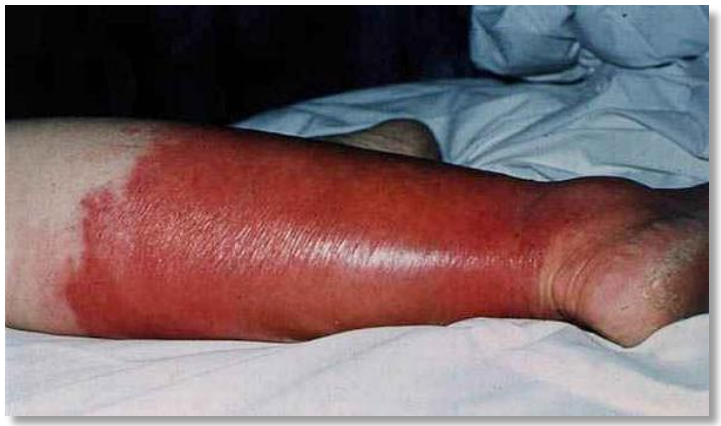
(dalbavancin hydrochloride)
powder for infusion

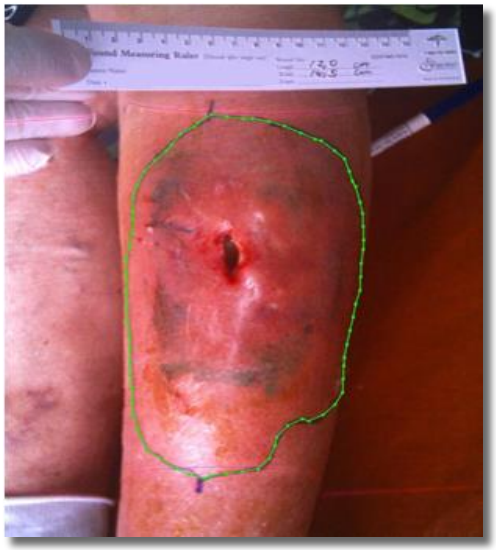
Clinical Context

- ✓ ABSSSI
- ✓ PWID
- ✓ Real World Experience

Acute Bacterial Skin and Skin Structure Infections (ABSSSI)







Major Cutaneous Abscess[1]

Infection characterised by a collection of pus within the dermis or deeper that is accompanied by redness, oedema, and/or induration

Cellulitis/Erysipelas[2]

Diffuse skin infection characterised by spreading areas of redness, oedema, and/or induration

Wound infection[3]

Infection characterised by purulent drainage from a wound with surrounding redness, oedema, and/or induration

Minimum lesion surface area of approx. 75 cm^2

ABSSSI, acute bacterial skin and skin structure infection

1. http://www.anshudentalcare.com/Access-Drainage-surgery-in-Jaipur.html; **2.** http://www.bestonlinemd.com/cellulitis-can-worsen-if-you-have-diabetes/; **3.** FDA Briefing Presentation. Anti-infective Drugs Advisory Committee Meeting. March 31, 2014. NDA 21-883; **4.** FDA. Guidance for Industry. October 2013, https://www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf.

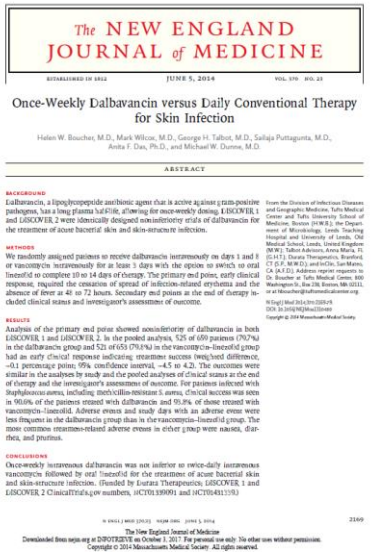
Xydalba™ 500 mg

(dalbavancin hydrochloride)
powder for infusion

Efficacy in ABSSSI

DISCOVER 1 and DISCOVER 2 (n=1,312)

Phase 3, double-blind, double-dummy, international, multicentre, randomized trials aiming to demonstrate non-inferior efficacy and to compare the safety of dalbavancin to vancomycin/linezolid



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 5, 2014 VOL. 370 NO. 23

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.

ABSTRACT

BACKGROUND

Dalbavancin, a lipoglycopeptide antibiotic agent that is active against gram-positive pathogens, has a long plasma half-life, allowing for once-weekly dosing. DISCOVER 1 and DISCOVER 2 were identically designed noninferiority trials of dalbavancin for the treatment of acute bacterial skin and skin-structure infection.

METHODS

We randomly assigned patients to receive dalbavancin intravenously on days 1 and 8 or vancomycin intravenously for at least 3 days with the option to switch to oral linezolid to complete 10 to 14 days of therapy. The primary end point, early clinical response, required the cessation of spread of infection-related erythema and the absence of fever at 48 to 72 hours. Secondary end points at the end of therapy included clinical status and investigator's assessment of outcome.

RESULTS

Analysis of the primary end point showed noninferiority of dalbavancin in both DISCOVER 1 and DISCOVER 2. In the pooled analysis, 525 of 659 patients (79.7%) in the dalbavancin group and 521 of 653 (79.8%) in the vancomycin–linezolid group had an early clinical response indicating treatment success (weighted difference, −0.1 percentage point; 95% confidence interval, −4.5 to 4.2). The outcomes were similar in the analyses by study and the pooled analyses of clinical status at the end of therapy and the investigator's assessment of outcome. For patients infected with *Staphylococcus aureus*, including methicillin-resistant *S. aureus*, clinical success was seen in 90.0% of the patients treated with dalbavancin and 91.8% of those treated with vancomycin–linezolid. Adverse events and study days with an adverse event were less frequent in the dalbavancin group than in the vancomycin–linezolid group. The most common treatment-related adverse events in either group were nausea, diarrhea, and pruritus.

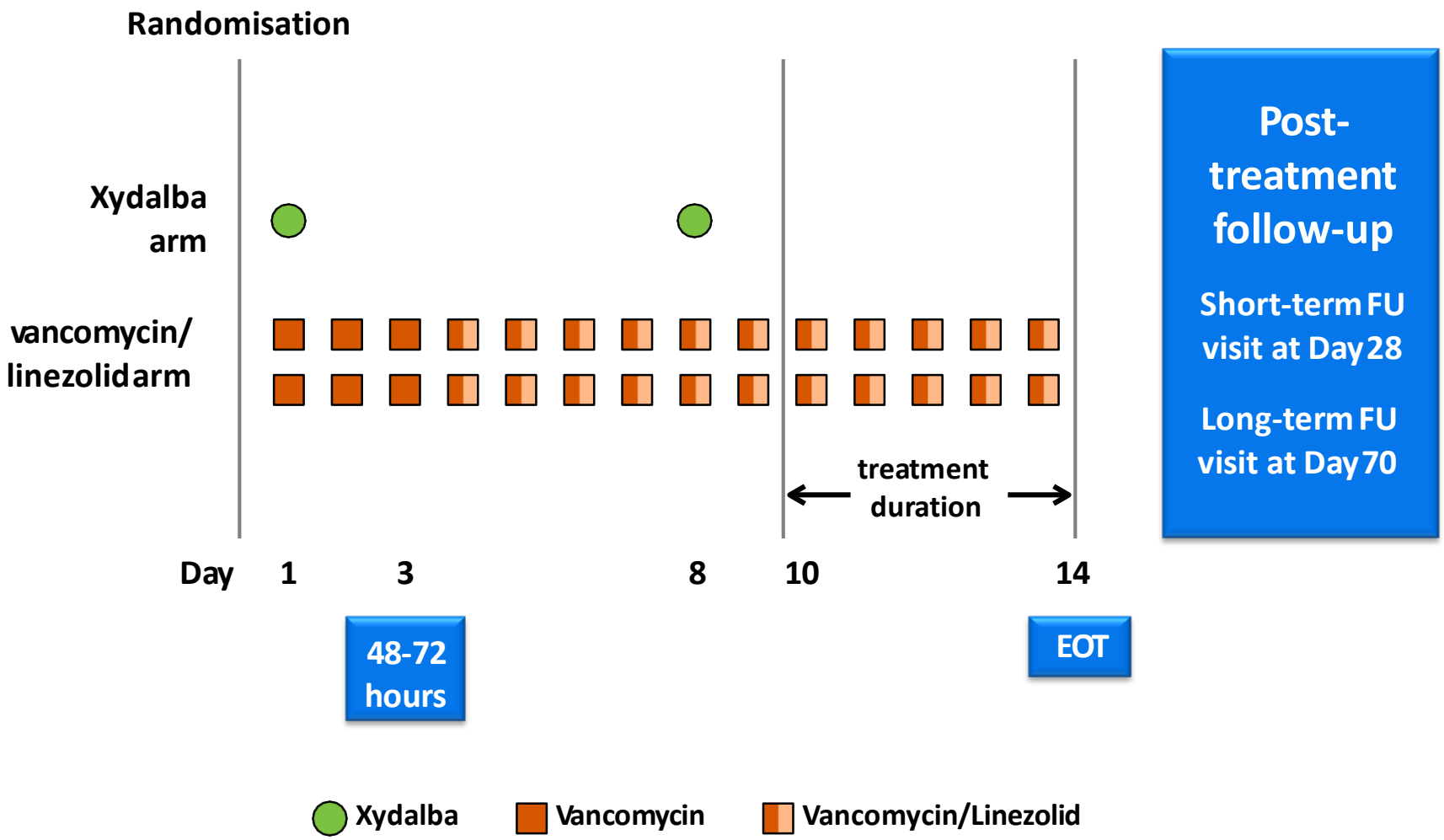
CONCLUSIONS

Once-weekly intravenous dalbavancin was not inferior to twice-daily intravenous vancomycin followed by oral linezolid for the treatment of acute bacterial skin and skin-structure infection. (Funded by Durata Therapeutics; DISCOVER 1 and DISCOVER 2 ClinicalTrials.gov numbers, NCT01139099 and NCT01431378)

2169

Boucher HW, *et al*. Once-Weekly Dalbavancin *versus* Daily Conventional Therapy for Skin Infection. N Engl J Med. 2014;370:2169-79.

Study Design - key features
DISCOVER 1 and DISCOVER 2



EOT: End of Therapy; FU: Follow-up

Boucher HW, *et al*. Once-Weekly Dalbavancin *versus* Daily Conventional Therapy for Skin Infection. N Engl J Med. 2014;370:2169-79.

DISCOVER 1 and DISCOVER 2

Key Inclusion Criteria

- Diagnosis of ABSSSI required the presence of cellulitis, a major abscess, or a wound infection, each associated with at least 75 cm^2 of erythema with at least one of the following systemic signs of infection:
  - ✓ Fever (≥38°C within 24 hours of baseline)
  - ✓ Leucocytosis (WBC count >12,000 cells/mm3)
  - ✓ Left shift (peripheral smear with ≥10% band forms)
- At least two additional local signs of ABSSSI:
  - ✓ Purulent drainage/discharge, fluctuance, heat/localized warmth, tenderness on palpation, swelling/induration
- **Infection severity including systemic signs requiring a minimum of 3 days of IV therapy**

Key Exclusion Criteria*

- Prior antibiotic, systemically or topically administered, within 14 days prior to randomization
- Gram-negative bacteraemia
- Burns
- Diabetic foot infection
- Decubitus ulcer
- Perirectal abscess
- Infected device
- Venous catheter entry-site infection
- Immunocompromised patients
- Necrotizing fasciitis
- Osteomyelitis
- Endovascular infection
- Septic arthritis
- Meningitis

ABSSSI: Acute Bacterial Skin and Skin Structure Infections

**FDA Briefing Document. Anti-infective Drugs Advisory Committee Meeting. March 31, 2014. NDA 21-883. Dalvance (dalbavancin) for injection.*

Boucher HW, *et al*. Once-Weekly Dalbavancin *versus* Daily Conventional Therapy for Skin Infection. N Engl J Med. 2014;370:2169-79.

Selected Demographics
DISCOVER 1 and DISCOVER 2 pooled*

USA/Canada	~37%
EU, South Africa and Asia	~63%
Cellulitis	~54%
Major abscess	~25%
Wound infection	~22%
Median size of infected area	~324 cm^2
IV drug users	~14%
Temperature $\geq 38^{\circ}C$	~85%
SIRS	~52%
MRSA	~45%
Outpatient treatment only	~25%
Total treatment duration	~12 days (~4 days IV)

** Characteristics of the patients in the Intention-to-Treat Population.*

Boucher HW, *et al*. Once-Weekly Dalbavancin *versus* Daily Conventional Therapy for Skin Infection. N Engl J Med. 2014;370:2169-79.

Study Endpoints
DISCOVER 1 and DISCOVER 2

Primary endpoint

- Early response at 48 to 72 hr. post-initiation of therapy
  - Cessation of spread of the erythema of the lesion, and
  - Absence of fever (in 3 consecutive readings performed 6 hours apart)

Secondary endpoints

- Clinical status at end of therapy (Day 14) in CE and ITT
- Prespecified Sensitivity Analyses for Clinical Status at EOT and SFU
- Clinical status at short-term follow-up (Day 28), CE, and ITT populations
- Investigator assessments at EOT and SFU
- Microbiologic outcome

EOT, End of Therapy; CE, Clinically Evaluable; ITT, Intent-to-treat ; SFU, Short-term Follow-up

Boucher HW, *et al*. Once-Weekly Dalbavancin *versus* Daily Conventional Therapy for Skin Infection. N Engl J Med. 2014;370:2169-79.

Study Endpoints
DISCOVER 1 and DISCOVER 2 – Study populations

- **Intention-to-treat population (ITT):** All randomised patients
- **Safety population:** ITT patients who received at least 1 dose of a study drug
- **Clinically Evaluable (CE):** Fulfilled inclusion/exclusion criteria, received the correct study drug, and met minimum dosing requirements
  - CE-EOT: CE population at end of treatment visit (day 14-15)
  - CE-SFU: CE population at short-term follow-up visit (day 28)
  - CE –LFU: CE population at long-term follow-up visit (day 70)
- **Microbiological ITT (micro-ITT):** ITT population with at least 1 gram- positive pathogen isolated at baseline
- **Microbiologically Evaluable (ME):** CE population with at least 1 gram- positive pathogen isolated at baseline

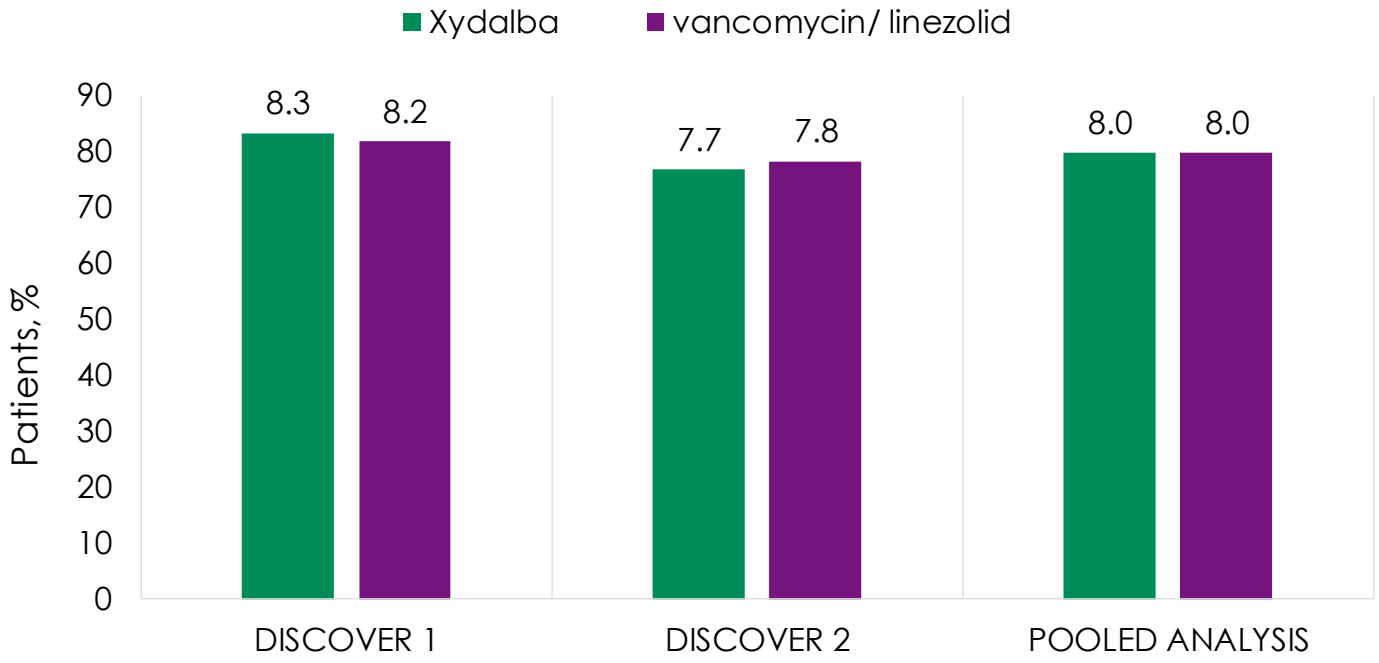
Boucher HW, *et al*. Once-Weekly Dalbavancin *versus* Daily Conventional Therapy for Skin Infection. N Engl J Med. 2014;370:2169-79.

Xydalba™ – Non-inferiority *vs* Vancomycin/Linezolid

EMA secondary endpoint and primary for FDA

Early (48-72 hours) Clinical Response

ITT population



DISCOVER 1 *Absolute Difference (95% CI) Percentage Points [1.5 (–4.6 to 7.9)]*

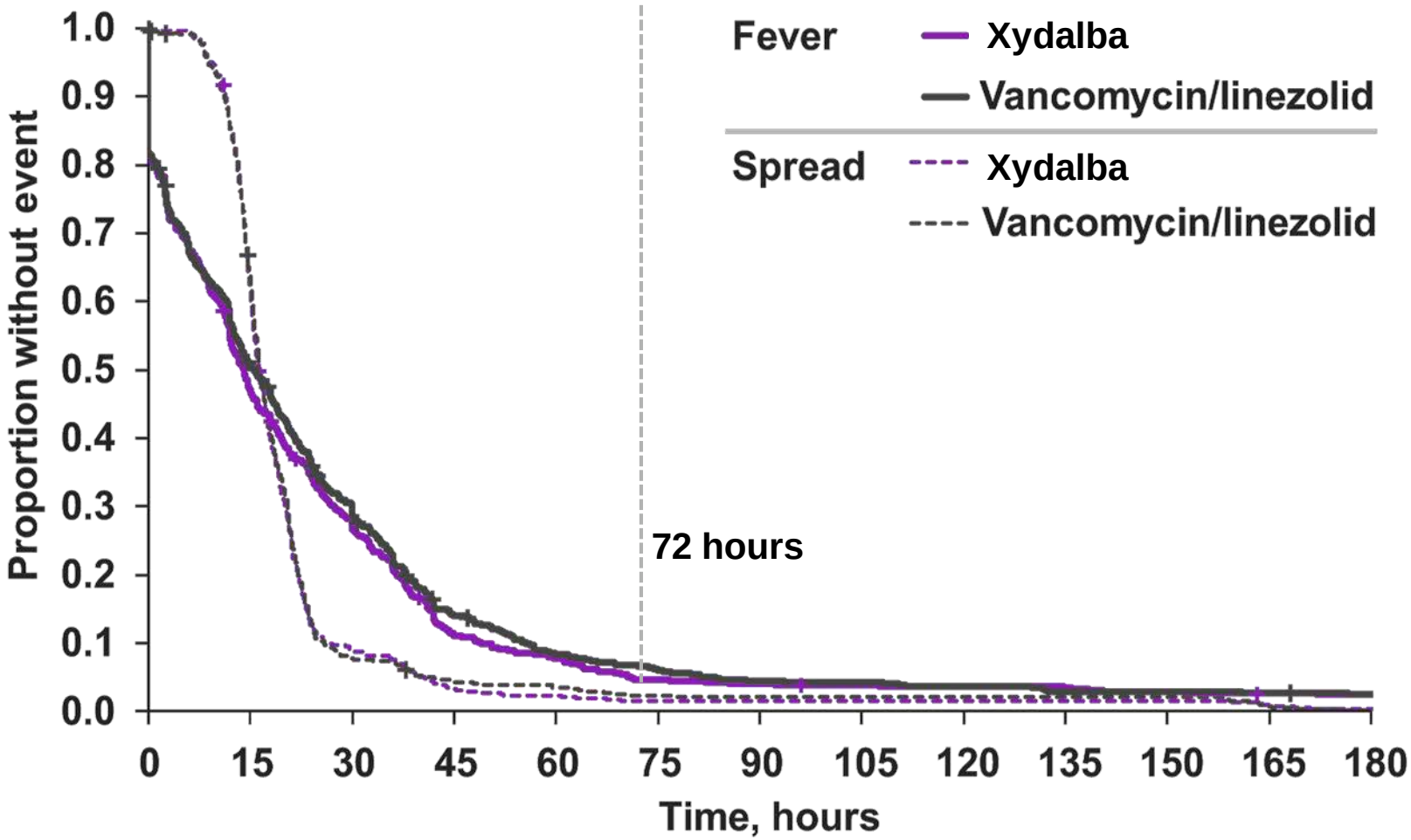
DISCOVER 2 *Absolute Difference (95% CI) Percentage Points [-1.5 (–7.4, 4.6)]*

Pooled Analysis Absolute Difference *(95% CI) Percentage Points [-0.1 (–4.5 to 4.2)].*

XYUK2208201 9SK

Boucher HW, *et al*. Once-Weekly Dalbavancin *versus* Daily Conventional Therapy for Skin Infection. N Engl J Med. 2014;370:2169-79.

Time to Absence of Fever or Cessation of Spread



XYUK220820195K

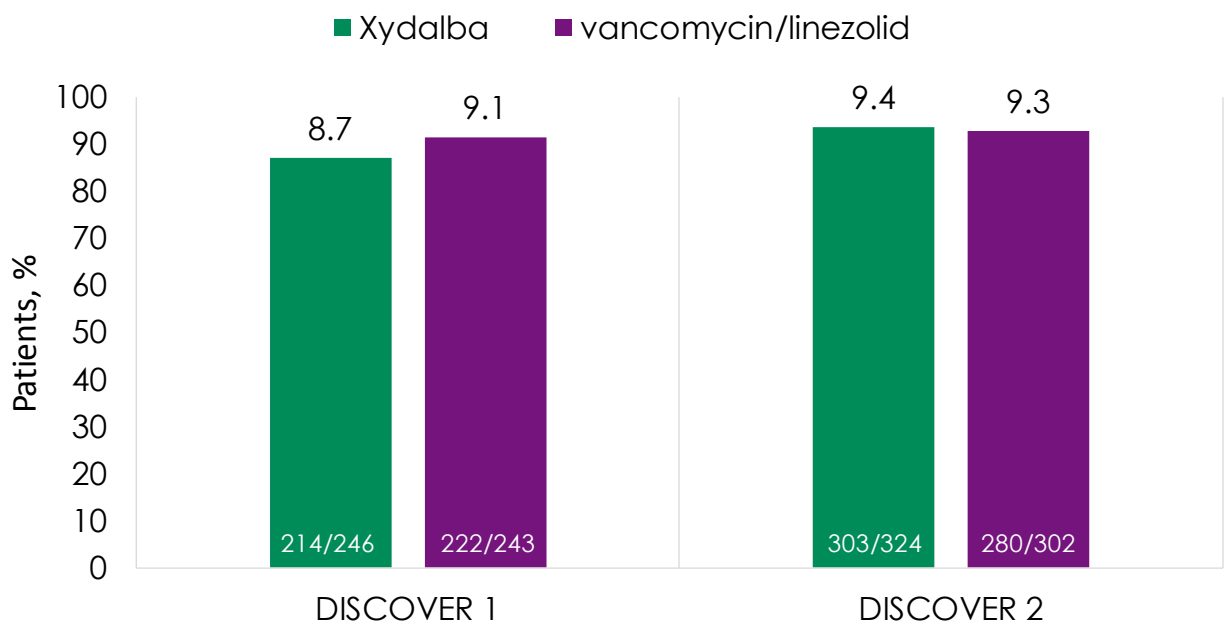
Data on file. FDA Briefing Presentation. Anti-infective Drugs Advisory Committee Meeting. March 31, 2014. NDA 21-883.

Xydalba™ – Non-inferiority *vs* Vancomycin/Linezolid

EMA primary endpoint

Clinical Success at End-of-Treatment (Day 14-15)*

ITT population



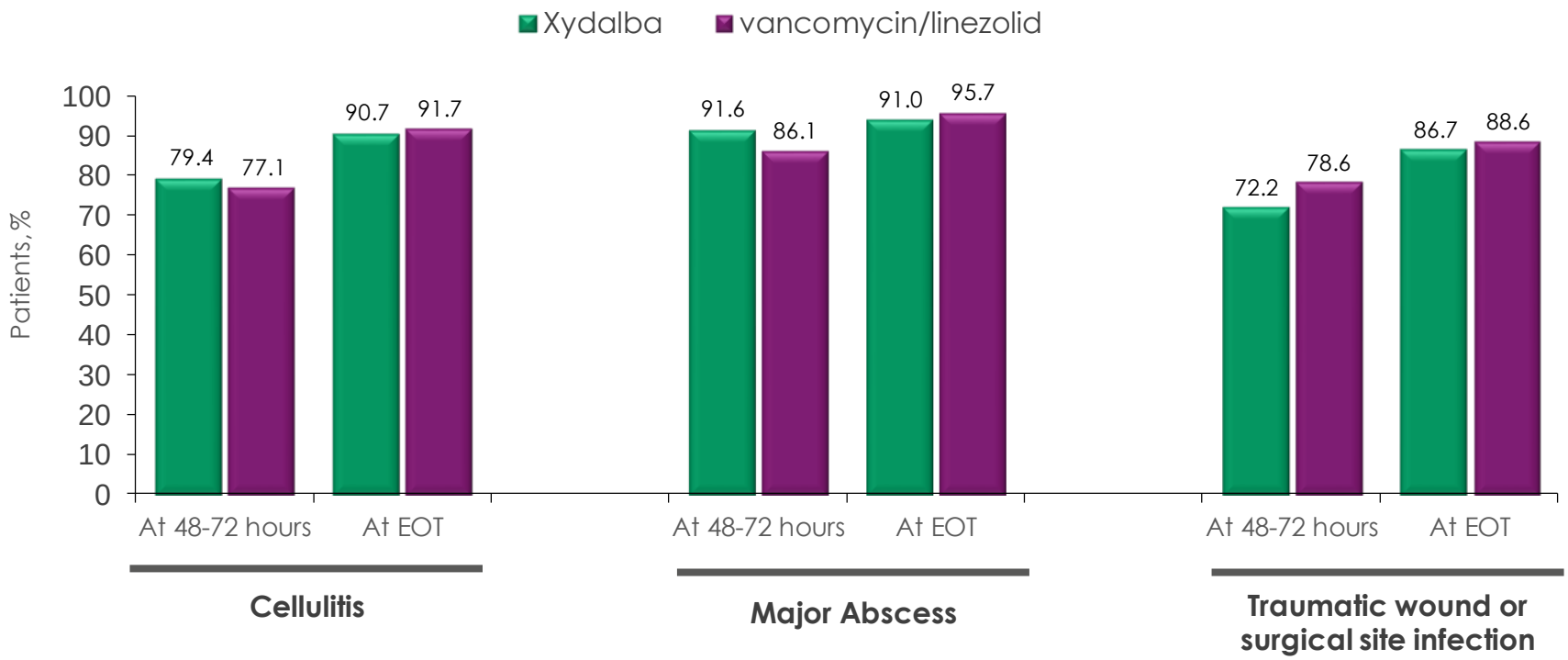
**Clinical success at End-of-treatment (EOT) visit (Day 14-15) in the CE population was defined as decreased lesion size (both length and width measurements), a temperature of ≤37.6°C, Local signs of fluctuance and localized heat/warmth were absent; local signs of tenderness to palpation and swelling/induration were no worse than mild; and for patients with a wound infection, the severity of purulent drainage was improved and no worse than mild relative to baseline; No need for further systemic antibacterial treatment for the SSTI.*

XYUK220820195K

Xydalba™ Assessment report EMA/39820/2015.

Subgroups

Clinical Response by Infection Type
DISCOVER 1 and 2 Pooled

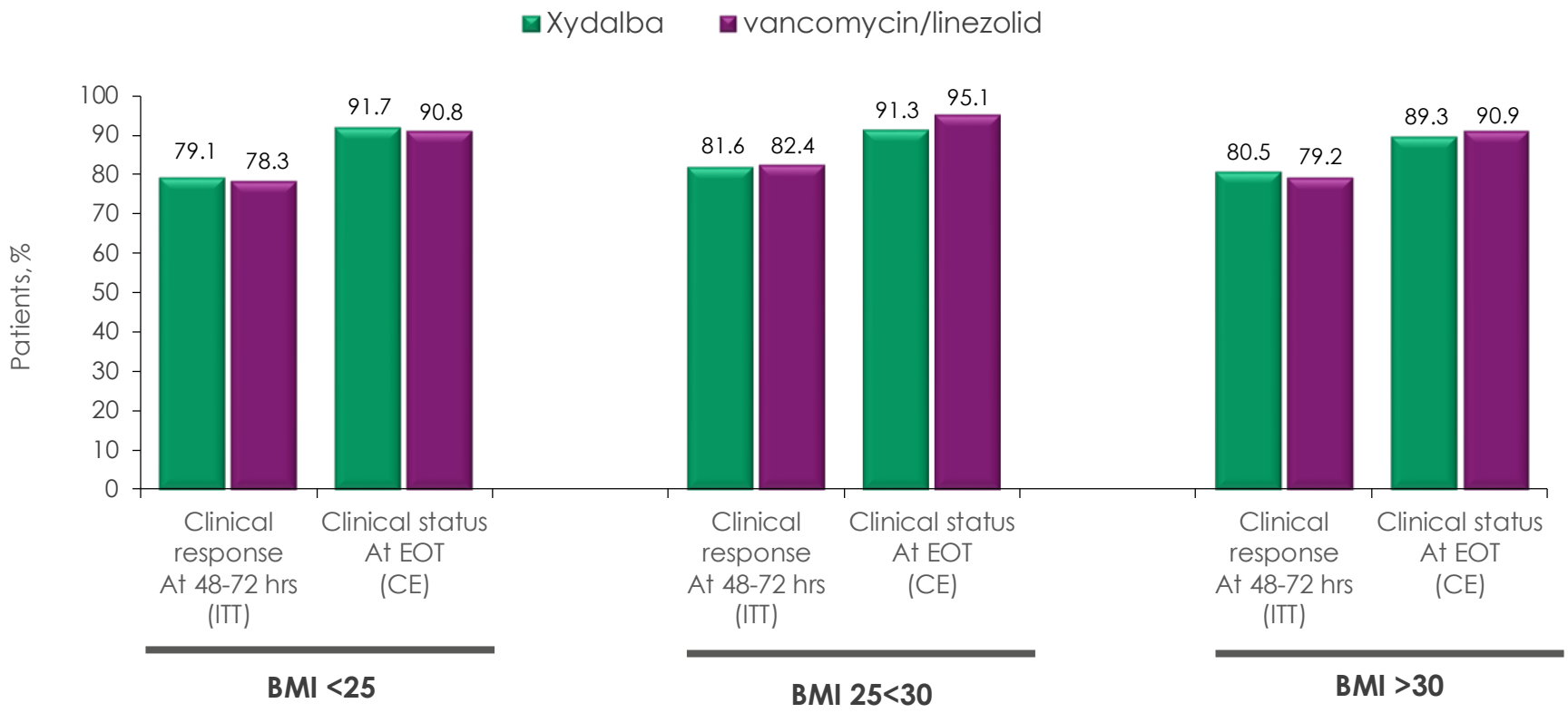


EOT, End of Therapy

XYUK2208201 9SK

Boucher HW, *et al*. Once-Weekly Dalbavancin *versus* Daily Conventional Therapy for Skin Infection. N Engl J Med. 2014;370:2169-79.

Clinical Response by BMI
DISCOVER 1 and 2 Pooled



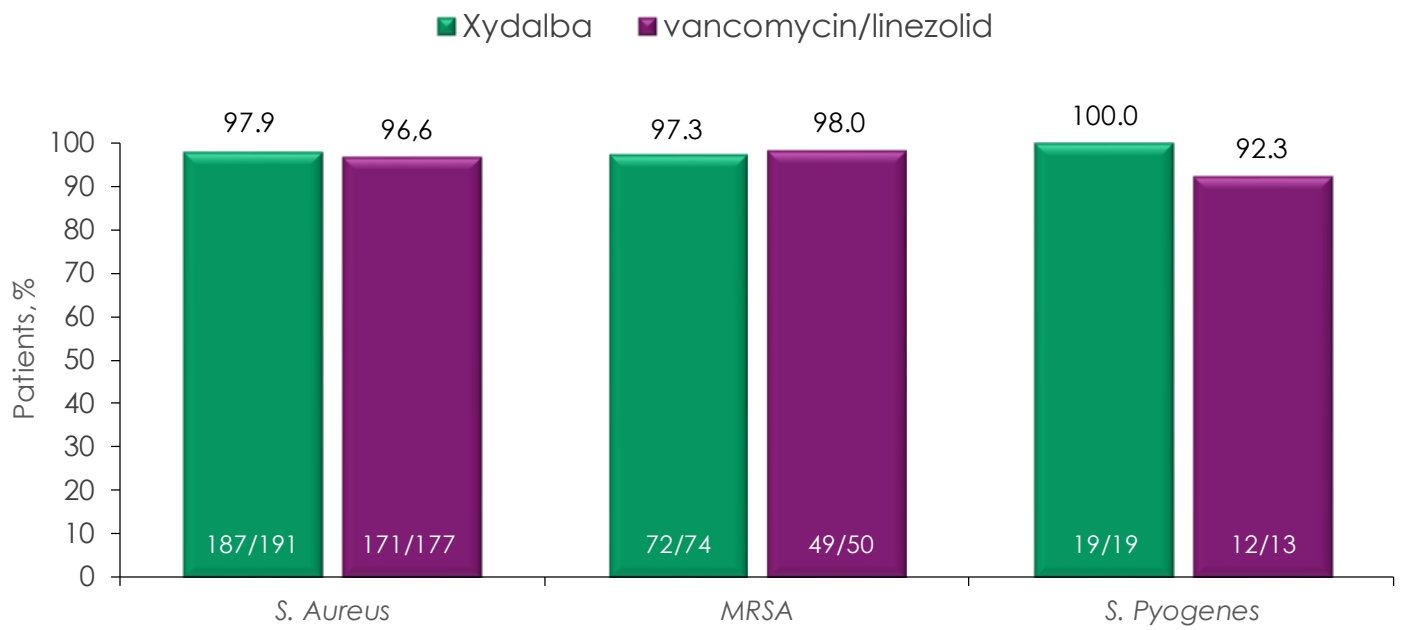
EOT, End of Therapy; CE, Clinically Evaluable

XYUK2208201 9SK

S. Puttagunta. Poster Presented at ECCMID, Copenhagen, Denmark 25-28 April 2015.

Clinical Success by Baseline Pathogen
DISCOVER 1 and 2 Pooled

Investigator-assessed Clinical Response at End of Therapy*

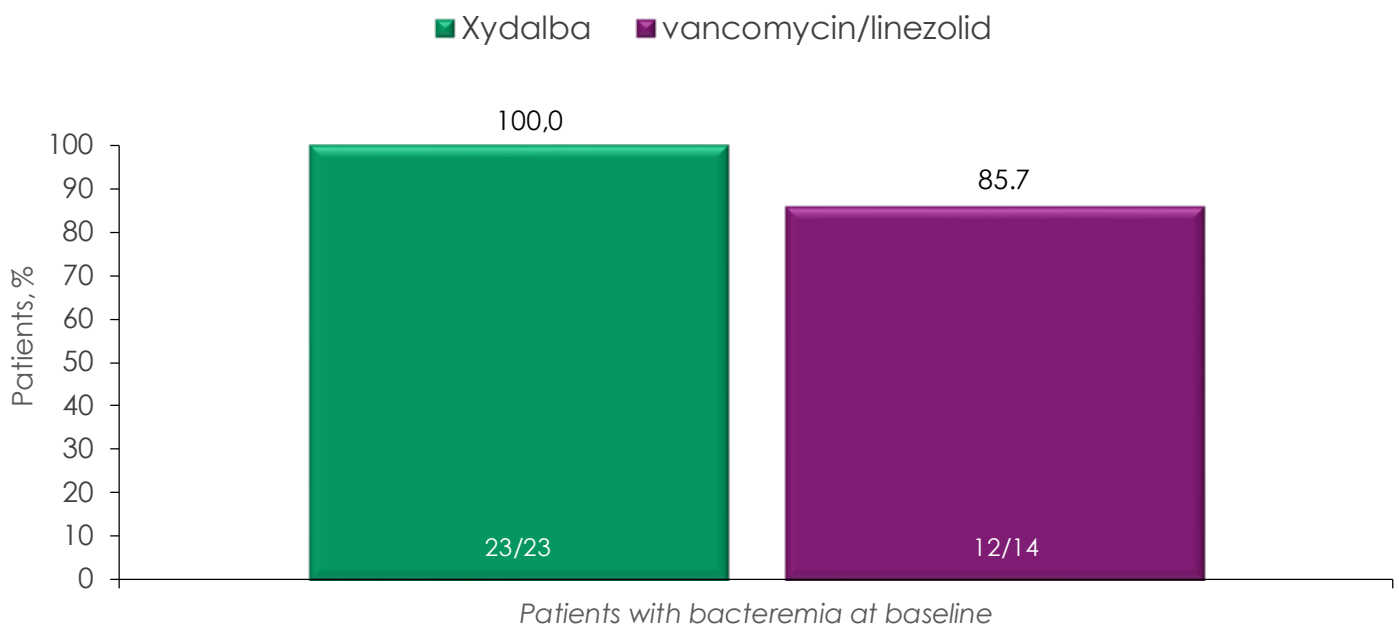


*The success rates at the end of therapy were assessed in the subgroup of patients with monomicrobial infection in the microbiologic per-protocol population.

XYUK220820195K

Boucher HW, *et al*. Once-Weekly Dalbavancin *versus* Daily Conventional Therapy for Skin Infection. N Engl J Med. 2014;370:2169-79.

Clearance of Bacteraemia at End of Therapy
DISCOVER 1 and 2 Pooled



Boucher HW, *et al*. Once-Weekly Dalbavancin *versus* Daily Conventional Therapy for Skin Infection. N Engl J Med. 2014;370:2169-79.

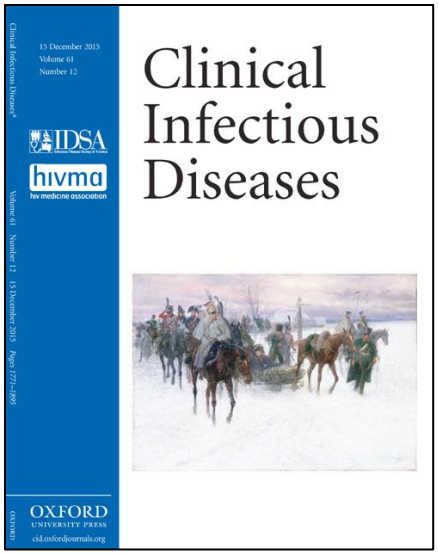
Xydalba™ 500 mg

(dalbavancin hydrochloride)

powder for infusion

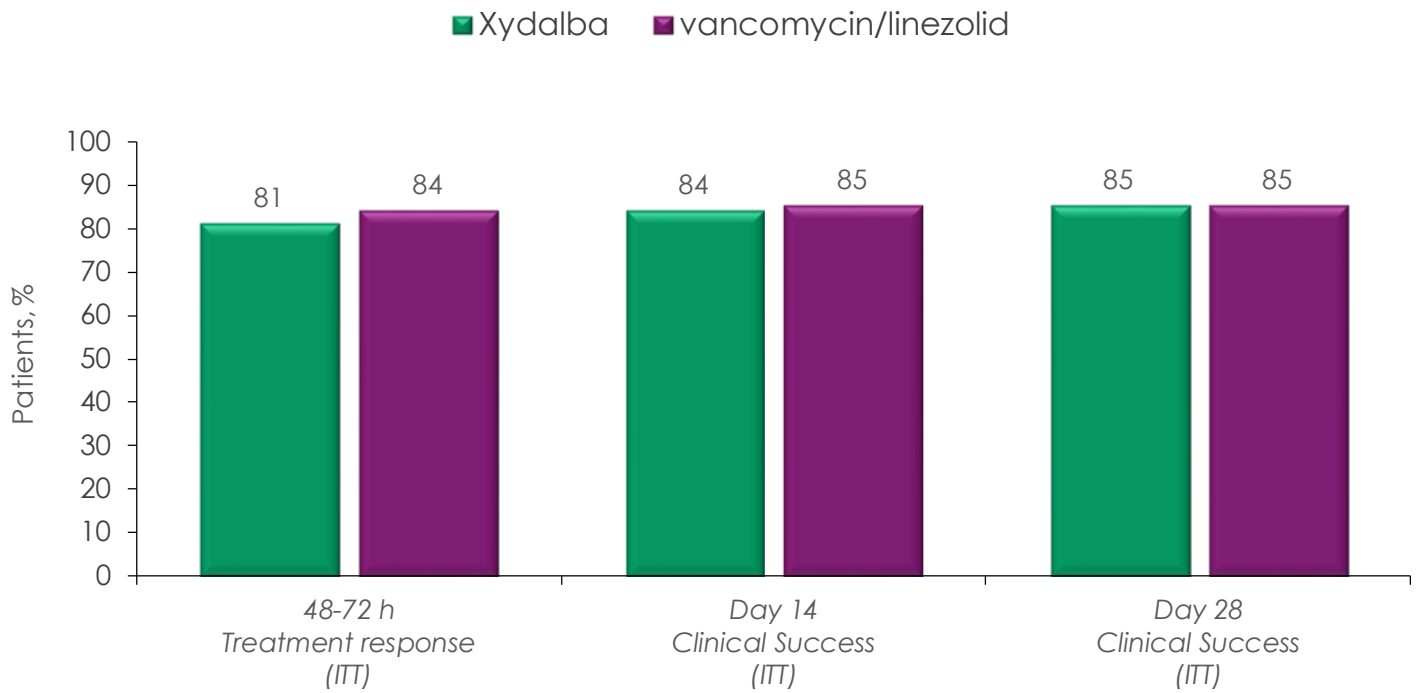
Single dose *vs* two-dose regimen in ABSSSI

Phase 3b, double-blind, pharmacist-unblinded, randomized, multicentre, international, non-inferiority trial
n=698



Dunne, *et al.* A Randomized Clinical Trial of Single Dose *vs* Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection. Clin Infect Dis. 2016 Mar 1;62(5):545-51.

Single-dose Xydalba™ is non-inferior to two-dose regimen



The primary endpoint was a comparison of the proportion of patients in the ITT population who achieved a ≥20% reduction in the size of the erythema 48–72 hours (±3 hours) after initiation of study drug and did not receive rescue antibacterial therapy.

Clinical status, defined as improvement in lesion size as well as resolution or improvement of clinical signs and symptoms, was performed at day 14 and day 28.

ITT, Intent-to-treat

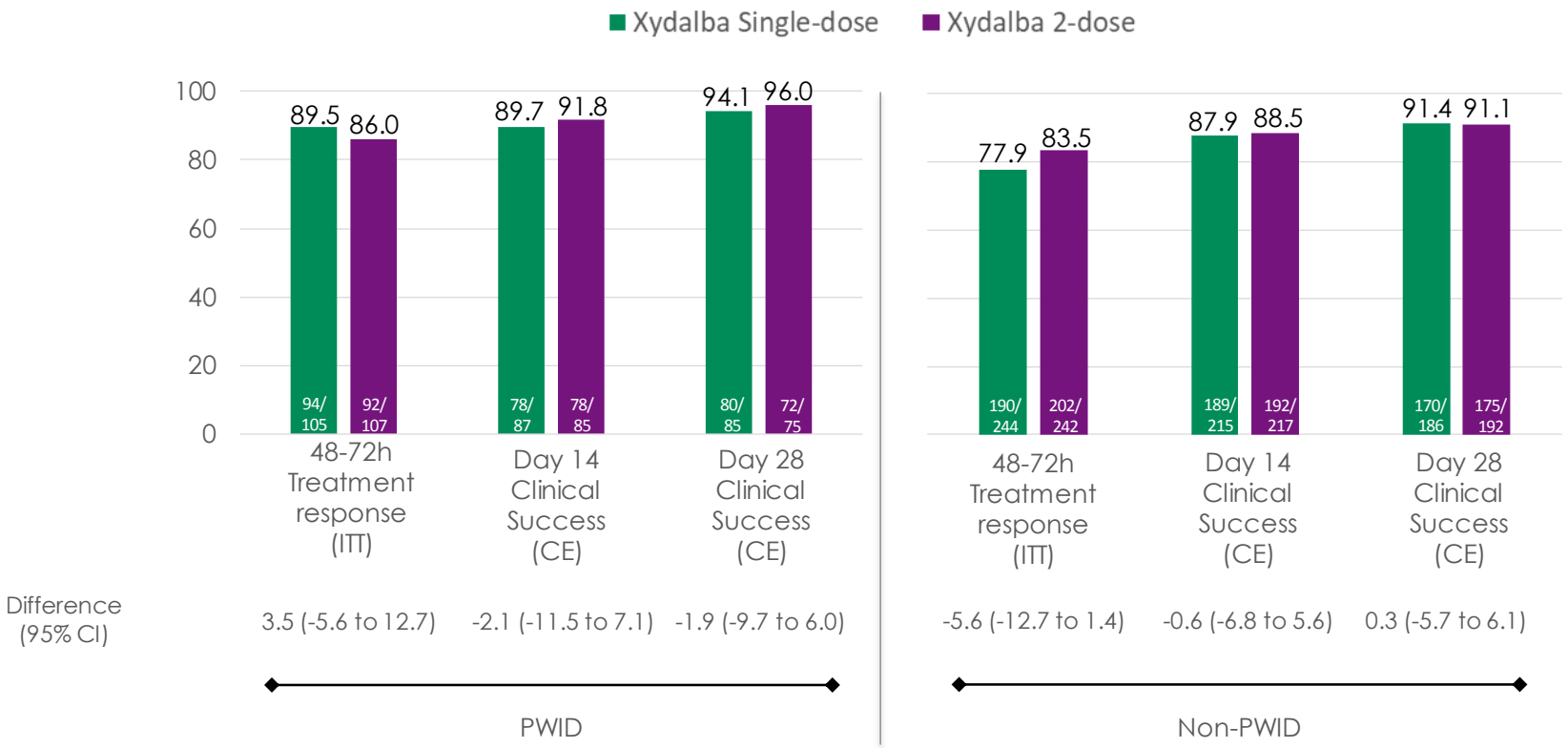
XYUK2208201 9SK

Dunne, *et al.* A Randomized Clinical Trial of Single Dose *vs* Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection. Clin Infect Dis. 2016 Mar 1;62(5):545-51.

PWID

Persons who inject drugs

Xydalba™ convenient for PWID patients



CE, Clinically evaluable population; CI, Confidence interval; ITT, Intent to treat; PWID, Persons who inject drugs.

Gonzales, *et al*. Treatment of acute bacterial skin and skin structure infection with single-dose dalbavancin in persons who inject drugs in Context 2018; 7: 212559.

BSAC OPAT Good Practice Recommendations 2019

New long acting lipoglycopeptide antibiotics may be useful;

- For patients with compliance concerns
- Line care concerns
- Managing OPAT capacity

- Homeless patients and injecting drug users are usually excluded from OPAT services.

Chapman A et al; Updated good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults and children in the UK, JAC-AR, 2019

Xydalba™ 500 mg

(dalbavancin hydrochloride)
powder for infusion

Well tolerated

Xydalba™ SmPC; Xydalba™ Assessment report EMA/39820/2015.

Adverse Reactions having occurred in >1% of Patients* - All Phase 2/3 trials

Most common adverse reactions in Phase 2/3 Studies in ≥1% of Patients Treated With Dalbavancin	n=2,473
Nausea	2.4%
Diarrhoea	1.9%
Headache	1.3%

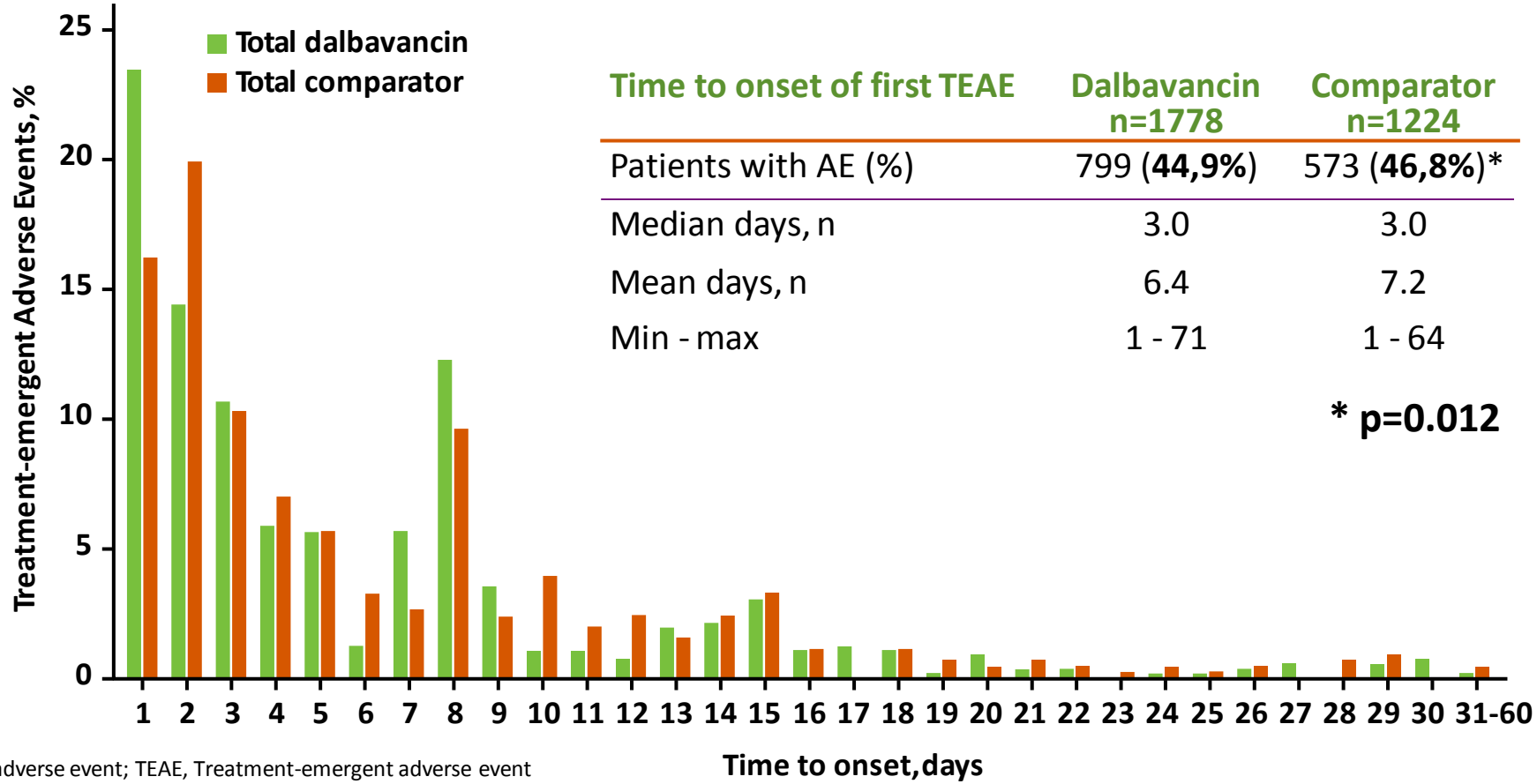
- In Phase 2/3 clinical studies, 2,473 patients received Dalbavancin administered as either a single infusion of 1500 mg or as 1000 mg followed one week later by 500 mg.
- The most common adverse reactions were generally of mild or moderate severity.

* Complete Tabulated list of adverse reactions available in SmPC

Similar Distribution of Day of Onset of Adverse Events between Dalbavancin and Comparator

Phase 2/3 trials

Late onset adverse events were seen at similar rates in patients treated with dalbavancin relative to those receiving comparator agents; vancomycin, linezolid, cefazolin, nafcillin, or oxacillin.



Time to onset of first TEAE	Dalbavancin n=1778	Comparator n=1224
Patients with AE (%)	799 (**44,9%**)	573 (**46,8%**)*
Median days, n	3.0	3.0
Mean days, n	6.4	7.2
Min - max	1 - 71	1 - 64

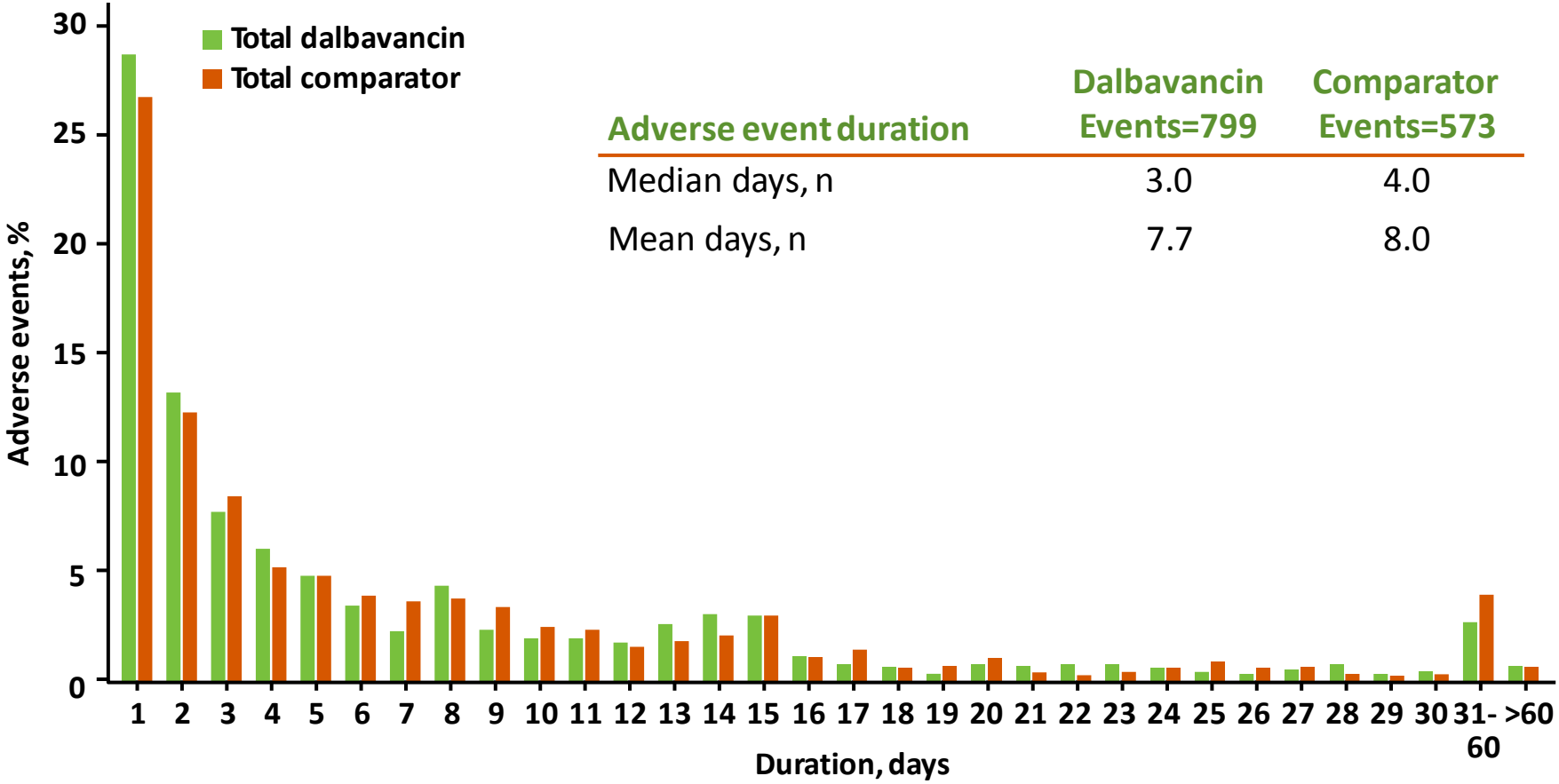
*** p=0.012**

AE, adverse event; TEAE, Treatment-emergent adverse event

Dunne MW et al. Drug Saf (2016) 39:147–157

Similar Distribution of Duration of Adverse Events with Dalbavancin and Comparator

Phase 2/3 trials



Adverse event duration	Dalbavancin Events=799	Comparator Events=573
Median days, n	3.0	4.0
Mean days, n	7.7	8.0

Dunne MW et al. Drug Saf (2016) 39:147–157

Xydalba™ - A efficacious full treatment course in one 30-minute infusion[1-4,8]

- **A efficacious therapeutic alternative[3]**
  - ✓ Potent activity against Gram-positive bacteria, including multi-resistant strains[1,4]
  - ✓ A long-half life allowing a treatment coverage up to 2 weeks[1]
  - ✓ Established efficacy (clinical improvement 48-72 hrs) maintained to achieve clinical success (14-28 days)[5,6,12]

- **Well tolerated[1,6,12]**
  - ✓ Fewer adverse events than comparators[6*,12**], only 3 common AEs[1]
  - ✓ Infrequent late onset events, at a similar rate to comparators[6*,12**]

- **Potential reduction of the length of hospital stay[7-11]**

**Vancomycin/linezolid in Discover studies; **Pooled analysis of dalbavancin-treated patients in phase 2/3 studies vs those receiving comparator agents (vancomycin, linezolid, cefazolin, nafcillin, or oxacillin)*

1. Xydalba™ SmPC; **2.** Gonzales PL, *et al*. Drugs Context. 2018; 7: 212559; **3.** Leuthner KD, *et al*. Ther Clin Risk Manag. 2016;12:931-40; **4.** Pfaller MA, *et al*. J Antimicrob Chemother. 2018 Oct 1;73(10):2748-2756; **5.** Dunne MW, *et al.* Clin Infect Dis. 2016;62:545–51; **6.** Boucher HW, *et al.* N Engl J Med. 2014;370:2169-79; **7.** Nair T, *et al.* Infect Dis (Lond). 2018;50(1):75-76; **8.** Galluzzo M, *et al*. Expert Opin Drug Metab Toxicol. 2018 ;14(2) :197-206; **9.** Rappo, *et al*. J Glob Antimicrob Resist. 2019 Feb 20. pii: S2213-7165(19)30047-5; **10.** Keyloun K, *et al*. J Med Econ. 2019 Jul;22(7):652-661; **11.** Marcellusi, *et al*. Expert Rev Pharmacoecon Outcomes Res. 2019 Feb 4:1-19; **12.** Dunne MW, *et al*. Drug Safety. (2016) 39:147–157.