Determination of Susceptibility Breakpoints for the Novel Oxazolidinone Tedizolid

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INTRODUCTION

- Tedizolid is a novel oxazolidinone antibacterial with potent *in vitro* activity against a wide range of Gram-positive pathogens, such as *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group, and *Enterococcus faecalis*.[1-3]
- The prodrug tedizolid phosphate is rapidly and extensively converted by phosphatases to its active moiety tedizolid after administration.[4,5]
- The pharmacokinetic/pharmacodynamic (PK/PD) parameter that best predicts the efficacy of tedizolid is the free area under the concentration-time curve/minimum inhibitory concentration (*f*AUC/MIC); target ratio is 3 for *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]).[6]
  - Tedizolid phosphate has been approved for the treatment of ABSSSI in the United States, the European Union, and Canada.[7,8]
  - Two Phase 3 trials, ESTABLISH-1 and ESTABLISH-2 , demonstrated the noninferior efficacy of tedizolid (200 mg once daily for 6 days) to linezolid (600 mg twice daily for 10 days) in patients with ABSSSI.[9,10]
- Tedizolid phosphate is available in oral and intravenous (IV) formulations, and the approved dosage for treatment of ABSSSI with either formulation is 200 mg once daily for 6 days.[7]
- The U.S. Food and Drug Administration approved the following tedizolid breakpoints: ≤0.5 mg/L (susceptible), 1 mg/L (intermediate), and ≥2 mg/L (resistant) for *S. aureus* (including MRSA); ≤0.5 mg/L (susceptible) for *S. pyogenes*, *S. agalactiae,* and *E. faecalis*; and ≤0.25 mg/L (susceptible) for *S. anginosus* Group.[7]
- To establish breakpoints, current European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidance requires analysis of (1) PK/PD and Monte Carlo simulation data, (2) clinical data relating MIC to outcomes, and (3) *in vitro* MIC distributions.[11]
- We present here the analyses conducted to establish antibacterial susceptibility breakpoints for tedizolid according to the current EUCAST guidelines.

METHODS

Determination of PK/PD Breakpoints

- PK/PD breakpoints were determined by target attainment analysis.
- The probability of attaining the *f*AUC/MIC ratio of 3 against *S. aureus* was estimated by Monte Carlo simulation of individual estimates of $AUC_{(0\text{-}24)}$ on Day 1 for a total of 100 000 virtual patients, each administered tedizolid 200 mg once daily for 6 days.
- The analysis considered discrete MIC values between 0.06 and 16 mg/L, and the proportion of simulated patients who had an *f*AUC/MIC ratio of 3 at each MIC value was determined.
- The MIC susceptibility breakpoint was predefined as the highest MIC value with a 90% probability of attaining the PK/PD target.
- Sensitivity analyses were performed to determine target attainment at an *f*AUC/MIC ratio of 2 and an *f*AUC/MIC ratio of 4.

Determination of Clinical Breakpoints

- Efficacy outcomes from one Phase 2 (clinicaltrials.gov identifier, NCT00761215) and two Phase 3 clinical trials (ESTABLISH-1, NCT01170221; ESTABLISH-2, NCT01421511) were arranged according to MIC values of the causative organisms in the microbiologically evaluable (ME) patient population.
- Efficacy outcomes included the following:
  - Early clinical response, defined as ≥20% decrease in lesion area at 48 to 72 hours after administration of the first dose
  - Microbiologic response by pathogen or pathogen group at the end of therapy in the ME patient population

Microbiologic Breakpoints and Epidemiologic Cut-off (ECOFF) Values

- MIC distribution data were obtained from *in vitro* studies, recent surveillance (2009-2012 in the United States and Europe), and Phase 2/3 clinical trials (conducted between August 2010 and January 2013).
  - MIC values were determined by broth micro-dilution techniques established by the Clinical and Laboratory Standards Institute (CLSI).[12]
  - These data were used to define the proposed ECOFF values and give an indication of the MIC values for organisms with acquired or mutational resistance mechanisms.
- Collective MIC data were used to establish the susceptibility breakpoints for tedizolid.

RESULTS

PK/PD Breakpoints

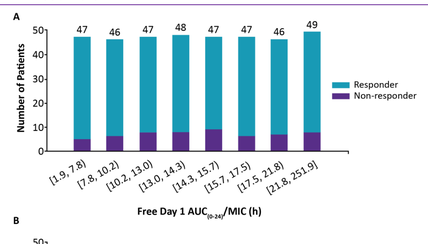
- The Monte Carlo simulation showed that the probability of attaining the PK/PD target (*f*$AUC_{(0\text{-}24)}$/MIC ratio of 3) with a tedizolid phosphate dose of 200 mg was 98.3% in patients with infection caused by strains with tedizolid MIC ≤0.5 mg/L. Probabilities for attaining target ratios a third lower (i.e., ratio of 2) or higher (i.e., ratio of 4) were very similar, thus illustrating the lack of sensitivity around the proposed breakpoint of ≤0.5 mg/L (**Table 1**).
- There was no apparent decrease in efficacy across the range of actual *f*AUC/MIC ratios for all Gram-positive isolates observed in Phase 3 studies (**Figure 1**).
- The data support a susceptibility breakpoint of 0.5 mg/L for tedizolid.
- The probability of target attainment (*f*$AUC_{(0\text{-}24)}$/MIC ratio of 3) is 70.7% at an MIC value of 1 mg/L and, therefore, supports a susceptibility category of intermediate.

Table 1. PK/PD Target Attainment Rates (*f*$AUC_{(0\text{-}24)}$/MIC) for Baseline Pathogens at Potential MIC Susceptibility Breakpoints (Monte Carlo Simulation of Patients Receiving Tedizolid Phosphate 200 mg Once Daily)

	Probability of Attaining Day 1 *f*$AUC_{(0\text{-}24)}$/MIC Target Ratio		
MIC, mg/L	2, Mean % Above	3, Mean % Above	4, Mean % Above
0.06	100	100	100
0.12	100	100	100
0.25	100	99.8	99.5
0.5	99.5	98.3	95.5
1	95.5	70.7	28.8
2	28.8	1.1	0.1
4	0.1	0	0
8	0	0	0

*f*AUC, free drug area under the concentration-time curve; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic.

Figure 1. Frequency Distribution of Day 1 Free AUC/MIC Ratios in the Phase 2/3 Studies by (A) Early Clinical Response (≥20% Decrease in Lesion Area) and (B) Microbiologic Response at End of Therapy (ME population)



AUC, area under the concentration-time curve; ME, microbiologically evaluable; MIC, minimum inhibitory concentration.
Opening or closing bracket indicates that the respective endpoint is included in the interval; opening or closing parentheses indicates that the respective endpoint is not included in the interval.

Clinical Breakpoints

- All clinical isolates had MIC ≤0.5 mg/L; hence, no clinical data were available for strains with MIC >0.5 mg/L.
- Rates of early clinical response, defined as ≥20% decrease from baseline in lesion area, were similar at all MIC values ≤0.5 mg/L; the response rate was 87.0% for an MIC value of 0.5 mg/L and 84.4% at MIC values <0.5 mg/L (**Table 2**).

Table 2. Early Clinical Response According to Pathogen MIC

	Non-responder, N = 57		Responder, N = 320	
MIC, mg/L	N	%	n	%
≤ 0.06	3	33.3	6	66.7
0.125	6	18.2	27	81.8
0.25	39	14.7	227	85.3
0.5	9	13.0	60	87.0
Overall	57	15.1	320	84.9

MIC, minimum inhibitory concentration.

- Microbiologic response data for staphylococci, streptococci, and enterococci indicated little difference in eradication rates for strains with different MIC values up to 0.5 mg/L (**Table 3**).

Table 3. Correlation of Tedizolid MIC Values with Favourable Microbiologic Response (n/N1)[a] at PTE (ME Population)

MIC, mg/L	*Staphylococcus aureus* (All)	MRSA	MSSA	*Staphylococcus haemolyticus*	*Staphylococcus lugdunensis*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Streptococcus anginosus* Group[b]	*Enterococcus faecalis*
≤ 0.06	–	–	–	–	–	3/3 (100)	–	7/7 (100)	–
0.12	4/5 (80)	4/5 (80)	–	2/2 (100)	3/3 (100)	19/20 (95.0)	2/2 (100)	7/7 (100)	–
0.25	212/225 (94.2)	100/109 (91.7)	112/116 (96.6)	3/3 (100)	1/1 (100)	5/7 (71.4)	5/5 (100)	4/4 (100)	4/4 (100)
0.5	54/55 (98.2)	6/6 (100)	48/49 (98.0)	–	–	–	–	–	2/3 (66.7)
Total	**270/285 (94.7)**	**110/120 (91.7)**	**160/165 (96.9)**	**5/5 (100)**	**4/4 (100)**	**27/30 (90.0)**	**7/7 (100)**	**18/18 (100)**	**6/7 (85.7)**

ME, microbiologically evaluable (patients with at least 1 Gram-positive ABSSSI pathogen at baseline who completed end-of-therapy and post-therapy evaluation assessments); MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; PTE, post-therapy evaluation.
[a]n/N1, number of favourable microbiologic outcomes in the specific category/number of pathogens in the specific category; percentages are calculated as 100 × (n/N1).
[b]*Streptococcus anginosus* Group consists of *S. anginosus, S. constellatus,* and *S. intermedius*.

Microbiologic Breakpoints and ECOFF Values

- MIC distributions from multiple sources obtained over the time period from 2009 to 2012 are shown in **Table 4**.
- ECOFF values were 0.5 mg/L for *S. aureus* (MRSA and MSSA), *E. faecalis*, *E. faecium,* and *Peptostreptococcus* spp and 0.25 mg/L for *S. lugdunensis*, *S. haemolyticus*, *S. pyogenes*, *S. agalactiae*, and *S. anginosus* Group.

Table 4. MIC Distribution and ECOFF Values

		Number of Isolates with Indicated MIC																		
Organism	N	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512	ECOFF
Staphylococcus aureus	7787	0	0	0	4	2	11	539	4754	2450	15	4	5	2	1	0	0	0	0	0	0.5
MRSA	3244	0	0	0	2	0	7	264	2028	922	11	3	5	1	1	0	0	0	0	0	0.5
MSSA	4543	0	0	0	2	2	4	275	2726	1528	4	1	0	1	0	0	0	0	0	0	0.5
Staphylococcus haemolyticus	155	0	0	0	0	0	0	27	122	5	1	0	0	0	0	0	0	0	0	0	0.25
Staphylococcus lugdunensis	145	0	0	0	0	0	0	68	74	3	0	0	0	0	0	0	0	0	0	0	0.25
Streptococcus pyogenes	712	0	0	0	2	1	21	386	301	1	0	0	0	0	0	0	0	0	0	0	0.25
Streptococcus agalactiae	708	0	0	0	1	0	3	238	459	7	0	0	0	0	0	0	0	0	0	0	0.25
Streptococcus anginosus Group[a]	91	0	0	0	11	11	13	40	16	0	0	0	0	0	0	0	0	0	0	0	0.25
Enterococcus faecalis	822	0	0	0	4	0	3	33	430	345	5	1	0	1	0	0	0	0	0	0	0.5
Enterococcus faecium	397	0	0	0	0	1	0	23	190	172	8	2	1	0	0	0	0	0	0	0	0.5
Peptostreptococcus spp	41	0	0	0	2	4	3	7	3	12	6	3	1	0	0	0	0	0	0	0	0.5

ECOFF, epidemiologic cut-off; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.
[a]*Streptococcus anginosus* Group consists of *S. anginosus, S. constellatus,* and *S. intermedius*.

EUCAST Clinical Breakpoints for Tedizolid

- For the treatment of ABSSSI, the following clinical breakpoints were determined for a regimen of tedizolid phosphate 200 mg once daily for 6 days (**Table 5**).[8]

Table 5. EUCAST Breakpoints for Tedizolid[8]

	MIC breakpoints, mg/L	
Organism Group	≤ S	R >
Staphylococcus spp	0.5	0.5
β-haemolytic streptococci of Groups A, B, C, G	0.5	0.5
Viridans Group streptococci (*S. anginosus* Group only)	0.25	0.25

EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; S, susceptible; R, resistant.

CONCLUSIONS

- PK/PD data suggest non–species-related susceptibility breakpoints of susceptible (≤0.5 mg/L) and resistant (>1 mg/L).
- ECOFF values, based on MIC distributions for isolates from multiple sources, were 0.25 mg/L for *S. lugdunensis* and *S. haemolyticus* (coagulase-negative staphylococci), β-haemolytic streptococci, and *S. anginosus* Group and 0.5 mg/L for *S. aureus* (MRSA and MSSA), enterococci, and *Peptostreptococcus* spp.
- Clinical and microbiologic response rates for all Gram-positive pathogen groups were similarly high at MIC values of ≤0.5 mg/L.
- Using PK/PD analysis, evaluation of clinical outcomes from Ph2/3 trials, and *in vitro* susceptibility results, tedizolid breakpoints according to EUCAST guidelines were established, with minor differences from FDA-approved breakpoints.[7,8]

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