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Analyses Supporting Phase 2 Clinical Trial Dose Selection for Zabofloxacin in Community-acquired Pneumonia

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ABSTRACT

Objective: To conduct analyses in support of dose selection for zabofloxacin in Phase 2 community acquired pneumonia (CAP) studies. Phase 2 clinical trials will be initiated for zabofloxacin, a new antimicrobial agent belonging to the fluoroquinolone class. Zabofloxacin has high *in vitro* activity against pathogens associated with community-acquired respiratory tract infections, including penicillin- and levofloxacin-non-susceptible strains of *Streptococcus pneumoniae*.

Methods: Monte Carlo simulation (5,000 iterations) using Phase 1 pharmacokinetic (PK), protein binding, and non-clinical PK-PD data were utilized to determine the probability of attaining free-drug (*f*) AUC:MIC target thresholds for daily doses of zabofloxacin ranging from 50 to 800 mg. PK data were derived from a randomized, placebo-controlled, ascending multiple-dose (dose range 200-800 mg daily orally for 7 days) study in 24 healthy volunteers. Zabofloxacin clearance (CL/F) was linear over the dose range studied, with a mean (SD) of 36.3 (12.8) L/hour. A point estimate of zabofloxacin binding to serum proteins of 77%, as estimated by ultra-filtration methodology, was used in the simulations. *f*AUC:MIC was calculated as the product of *f*, where *f* is the fraction unbound, and dose/CL/F. A log normal distribution for CL/F was assumed. Resultant *f*AUC values were divided by fixed clinically relevant MIC values for zabofloxacin against pneumococci ranging from 0.008 to 0.5 mg/L ($MIC_{50/90/99}$ for zabofloxacin against *S. pneumoniae*: 0.015/0.03/0.06 mg/L). The *f*AUC:MIC target threshold evaluated in these analyses was 30, which was associated with complete eradication of *S. pneumoniae* from the lungs of immuno-competent mice (inoculated with 10^6 CFU) after treatment with zabofloxacin.

Results: The probabilities of PK-PD target attainment are presented in the Table. Note that for daily doses of 300 mg or greater, the probability of PK-PD target attainment approaches 1.0 for MIC values as high as 0.03 mg/L, the MIC_{90} for zabofloxacin against *S. pneumoniae*.

	MIC Range (mg/L)					
Daily dose (mg)	0.008	0.015	0.03	0.06	0.125	0.25
50	0.884	0.201	0	0	0	0
100	0.999	0.876	0.195	0	0	0
200	1.0	0.998	0.880	0.190	0	0
300	1.0	1.0	0.991	0.626	0.045	0
600	1.0	1.0	1.0	1.0	0.579	0.034
800	1.0	1.0	1.0	1.0	0.852	0.167

Conclusion: These analyses support a 300 mg (or greater) once-daily dose-regimen for zabofloxacin for the treatment of CAP associated with *S. pneumoniae*.

INTRODUCTION

Zabofloxacin is an oral fluoroquinolone with a broad-spectrum of *in vitro* antimicrobial activity against the pathogens commonly associated with community-acquired pneumonia (CAP, including penicillin- and levofloxacin-non susceptible strains of *Streptococcus pneumoniae*). Dose justification for late-phase clinical trials is critical for successful drug development. 50% of Phase 3 trials do not succeed, often due to poor dose selection. The integration of Phase 1 pharmacokinetic and non-clinical infection model data can be used to form the basis for identification of safe and effective dosing regimens for Phase 2-3 studies. As Phase 2 studies evaluating the safety and efficacy of zabofloxacin for the treatment of CAP will soon be initiated, analyses integrating Phase 1 pharmacokinetic and non-clinical infection model data were conducted to support dose regimen selection.

MATERIALS AND METHODS

Monte Carlo Simulation

Monte Carlo simulation was utilized to determine the probability of attaining various free-drug (*f*) $AUC_{0\text{-}24}$:MIC ratio targets derived from mouse-thigh infection models involving fluoroquinolones and *S. pneumoniae* as described below.

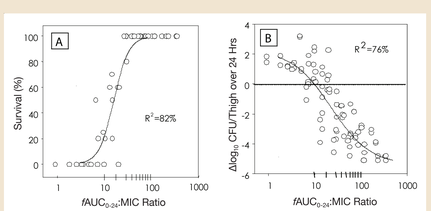
Zabofloxacin pharmacokinetic and protein binding data, which are provided below, were used to simulate 5,000 free-drug $AUC_{0\text{-}24}$ values using Crystal Ball® version 7.3 simulation software (Decisioneering, Inc., Denver, Colorado). Free-drug $AUC_{0\text{-}24}$ was calculated as dose/clearance • *f*, where *f* is the fraction unbound. A log-normal distribution for clearance was assumed. Resultant *f*$AUC_{0\text{-}24}$ values were divided by fixed MIC values ranging from 0.008 to 0.5 mg/L.

Pharmacokinetic-Pharmacodynamic (PK/PD) Target Thresholds

The PK-PD measure and magnitude of the measure used as a target for simulation was based upon two information sources. The first information source was historical data for fluoroquinolones against *S. pneumoniae* in murine-thigh infection models. The second information source was the results from a recent murine-pneumonia model involving zabofloxacin and *S. pneumoniae*.

Historically, the PK/PD index that has been shown to best describe quinolone efficacy is the *f*$AUC_{0\text{-}24}$:MIC ratio. Figure 1 shows the relationship between the *f*$AUC_{0\text{-}24}$:MIC ratio for various quinolones and survival or bacterial density in the thighs of immuno-competent mice infected with *S. pneumoniae*. Note that the *f*$AUC_{0\text{-}24}$:MIC ratio required to achieve approximately 90% animal survival or a 99% reduction in bacterial density for quinolones against pneumococci was approximately 30.

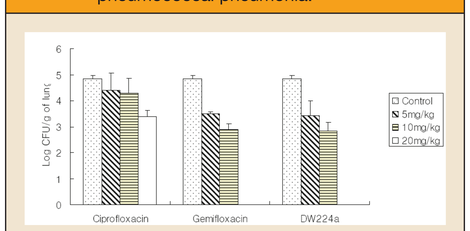
Figure 1. The relationship between the free-drug (*f*) $AUC_{0\text{-}24}$:MIC ratio for six quinolones (ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, and sitafloxacin) and survival (A) and bacterial density (B) in immuno-competent mice infected with *S. pneumoniae*. The dashed line in Figure 1B represents the initial bacterial inoculum.



Recently, zabofloxacin was studied in a murine-pneumonia infection model. Immuno- competent ICR mice were infected intra-nasally with 10^6 CFL/mouse of *S. pneumoniae* ATCC 6305. One day after inoculation, groups of three animals were treated with zabofloxacin (DW-224a, MIC = 0.008 mg/L), gemifloxacin (MIC = 0.015 mg/L) or ciprofloxacin (MIC = 0.5 mg/L) orally at doses of 5, 10 or 20 mg/kg for three days. Three animals per group served as untreated controls. One day after the final dose, mice were euthanized, their lungs aseptically removed, weighed, homogenized and plated for CFU determination using standard techniques. The pharmacokinetics of zabofloxacin was determined in a study using non-neutropenic ICR mice.

Figure 2 shows the bacterial density in the lungs of mice after 3 days of treatment. As zabofloxacin dose increased, so too did the reduction in bacterial burden; the 20 mg/kg cohort had no bacteria recovered. $AUC_{0\text{-}24}$:MIC ratios associated with the 5, 10 and 20 mg/kg cohorts were 9.4, 18.7 and 37.5, respectively. Note that an $AUC_{0\text{-}24}$:MIC ratio of 18.7 was associated with a 2 log unit reduction in bacterial burden.

Figure 2. Dose-response relationship for the efficacy of zabofloxacin, gemifloxacin and ciprofloxacin in immuno-competent mice with pneumococcal pneumonia.



Based upon the cumulative historical and recent zabofloxacin animal model data, a *f*$AUC_{0\text{-}24}$:MIC ratio of 30 was selected as the PK-PD threshold for these analyses.

Zabofloxacin In Vitro Microbiological Activity

The zabofloxacin MIC distribution for 225 isolates of *S. pneumoniae* tested by reference CLSI broth micro-dilution method are presented in Table 1.

Table 1. MIC distribution of zabofloxacin against *S. pneumoniae*.

	Occurrences at MIC (mg/L)												
Organism groups (no. tested)	≤0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
S. pneumoniae													
All (225)	2	20	147	30	3	11	6	3	1	1	0	1	0
Penicillin-S (99)	2	9	76	12	0	0	0	0	0	0	0	0	0
Penicillin-NS (101)	0	11	71	18	1	0	0	0	0	0	0	0	0
Levofloxacin-NS (25)	0	0	0	0	2	11	6	3	1	1	0	1	0

Zabofloxacin Pharmacokinetic and Protein Binding Data

The zabofloxacin pharmacokinetic data utilized in these analyses were obtained from a randomized, placebo-controlled, ascending multiple-dose study in healthy volunteers. 24 patients were enrolled in the trial, 18 of which received active treatment. Cohorts of six patients received by mouth either 200, 400 or 800 mg doses of zabofloxacin daily for seven days. Zabofloxacin exhibited dose proportionality and pharmacokinetic linearity over the dose range studied.

Table 2 shows descriptive statistics of the pharmacokinetic results for Day 1.

Table 2. Zabofloxacin plasma pharmacokinetic results for Day 1

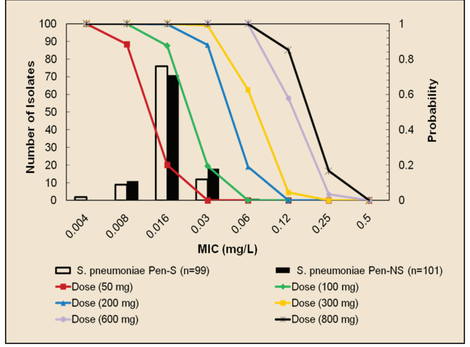
Parameter	200 mg	400 mg	800 mg
Geometric Mean (CV%)			
AUC0-t(ng•h/mL)	5412 (36.5)	11810 (22.0)	23869 (14.0)
AUCinf (ng•h/mL)	5786 (35.5	12591 (21.4)	25012 (15.5)
Cmax (ng/mL)	695 (51.8)	1590 (34.5)	3583 (25.2)
Arithmetic Mean (±SD)			
$t_{1/2}$ (h)	6.24 (0.748)	6.34 (0.597)	5.51 (0.453)
CL/F (L/h)	36.3 (12.8)	32.4 (7.41)	32.3 (4.71)
CL/F (L/h/kg)	0.497 (0.206)	0.445 (0.087)	0.423 (0.0748)
Varea/F (L)	330 (133)	297 (80.1)	256 (36.8)
Varea/F (L/kg)	4.48 (1.93)	4.06 (0.893)	3.34 (0.458)
Median (Min-Max)			
tmax (h)	2.00 (1.53 – 4.00)	1.75 (0.75 – 2.00)	3.50 (1.00 – 4.00)

Zabofloxacin protein binding in human serum has been estimated to be approximately 77% using ultrafiltration methodology and 72% using ultracentrifugation. This minor between-method difference is likely due to non-specific binding. In these simulations, the more conservative (higher, 77%) protein-binding estimate was utilized.

RESULTS

- Figure 3 shows the probability of PK-PD target (*f*$AUC_{0\text{-}24}$:MIC ratio of 30) attainment for daily doses ranging from 50 to 800 mg over the zabofloxacin *S. pneumoniae* MIC distribution. The probability of PK-PD target attainment increases with dose and decreasing MIC.

Figure 3.



- Note that for doses of 300 mg per day, the probability of PK-PD target attainment (*f*$AUC_{0\text{-}24}$:MIC ratio of 30) is essentially 1.0 for MIC values of 0.03 mg/L or less. Of the 200 wild-type pneumococci in Table 1, 199 (99.5%) have MIC values of 0.03 mg/L or less.
- For doses of 800 mg per day, the probability of PK-PD target attainment (*f*$AUC_{0\text{-}24}$:MIC ratio of 30) for levofloxacin-non-susceptible pneumococci approaches 0.9 for MIC values as high as 0.12 mg/L.
- Of the 25 levofloxacin-non-susceptible pneumococci in Table 1, 13 (52%) have MIC values of 0.12 mg/ or less.

CONCLUSIONS

- Zabofloxacin is an oral fluoroquinolone with a broad-spectrum of activity against the pathogens commonly associated with CAP, including penicillin- and levofloxacin-non susceptible strains of *S. pneumoniae*.
- These PK-PD target attainment analyses were conducted to support dose regimen selection for upcoming Phase 2 studies evaluating the safety and efficacy of zabofloxacin for the treatment of CAP.
- A zabofloxacin dosing regimen of 300 mg once daily provides a probability of PK-PD target attainment approaching 1.0 for MIC values of 0.03 mg/L and less, which comprised essentially the entire wild-type MIC distribution for *S. pneumoniae*.
- These analyses support a 300 mg (or greater) once-daily dose-regimen for zabofloxacin for the treatment of CAP associated with *S. pneumoniae*.

SELECTED REFERENCES

1. Bhavnani SM, Hammel JP, Cirincione BB, Wikler MA, Ambrose PG. Use of Pharmacokinetic-Pharmacodynamic Target Attainment Analyses To Support Phase 2 and 3 Dosing Strategies for Doripenem. *Antimicrob. Agents Chemother.* 2005 49: 3944-3947.
2. Craig WA, Andes DR. Correlation of the Magnitude of the AUC_{24}/MIC for 6 Fluoroquinolones against *Streptococcus pneumoniae* with survival and bactericidal activity in an animal model. In Abstracts of the 40th ICAAC, Toronto, Canada, Sept. 17-20th, 2000. Abstract A-289.