Population Pharmacokinetic-Pharmacodynamic Assessment of Cardiac Safety Endpoints for CF-301, a First-In-Class Antibacterial Lysin

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INTRODUCTION

Lysins are enzymes derived from naturally occurring bacteriophage, viruses which infect bacteria. When produced in recombinant form and applied to bacteria, lysins cleave a key component in the structure of the bacterial peptidoglycan cell wall which results in clearing biofilms and in rapid killing of the dormant bacteria within the biofilm.

CF-301, the first bacteriophage-derived recombinant lysin to complete Phase 1 trial in the US, is being developed for treatment of *Staphylococcus aureus (S. aureus)* bacteremia. It exhibits rapid *S. aureus* specific bacteriolysis, anti-biofilm activity, has low propensity for resistance and pronounced synergy with antibiotics. CF-301 is being developed for the treatment of methicillin-resistant and susceptible *S. aureus* (MRSA and MSSA) bloodstream infections (BSI; bacteremia), including endocarditis. New drug-resistant strains of *S. aureus* have been identified which demonstrate resistance against vancomycin and daptomycin, the only two standard-of-care (SOC) antibiotics indicated for the treatment of MRSA BSI in the US. CF-301 has the potential to be a first-in-class treatment for *S. aureus* bacteremia. CF-301 is proposed to be used as single 2-hr intravenous infusion. Addition of CF-301 to sub-therapeutic doses of vancomycin or daptomycin significantly increased survival and reduce tissue burdens in multiple animal efficacy models when compared to anti-staphylococcal antibiotics or CF-301 alone. CF-301 targets a highly conserved region of the cell wall that is vital to bacteria, thus making resistance less likely to develop. Addition of CF-301 to existing anti-staphylococcal antibiotics is a novel combination therapy that has the potential to combat the high unmet clinical need of *S. aureus* infections.[1]

OBJECTIVES

To assess the pharmacokinetic (PK) – pharmacodynamic (PD) relationship between CF-301 plasma concentrations and cardiac safety endpoints: heart rate (HR), QT interval, systolic and diastolic blood pressure (SBP and DBP).

DATA

Data from a first-in-man Phase 1, placebo-controlled, dose-escalating study to examine the safety and tolerability of single intravenous dose of CF-301 in healthy male and female subjects were used for population PK-PD analyses. The study was designed to dose subjects in 4 dosing cohorts (0.04, 0.12, 0.25, and 0.4 mg/kg/dose single 2-hour intravenous infusion), with 6 subjects in each cohort randomized to CF-301 (4 subjects) or placebo (2 subjects). PK-PD analyses of HR and QT were based on 98 baseline-corrected readings across baseline and active treatment days and across 17 subjects for each of the HR and QT analyses. PK-PD analyses of blood pressure were based on the 299 SBP and 299 DBP measurements taken in sitting position from 20 subjects at baseline (one measurement only), during active treatment phase and during the follow-up.

METHODS

A population PK model that adequately described the plasma concentrations observed in the Phase 1 study with <10% error in prediction of these values, was developed and used to predict individual CF-301 concentrations matching the time of cardiac safety assessments.[2] Separate PK-PD models were developed for SBP, DBP, and QTcI. A nonlinear mixed-effects approach was used for all the models.

Figure 1. Relationship between uncorrected (QT), Fridericia-corrected (QTcF), Bazett-corrected (QTcB) and Individually-corrected (QTcI) QT (stratified by each study subject) and RR intervals (a time between beats on ECG that is used to calculate HR) overlaid with the data smooth

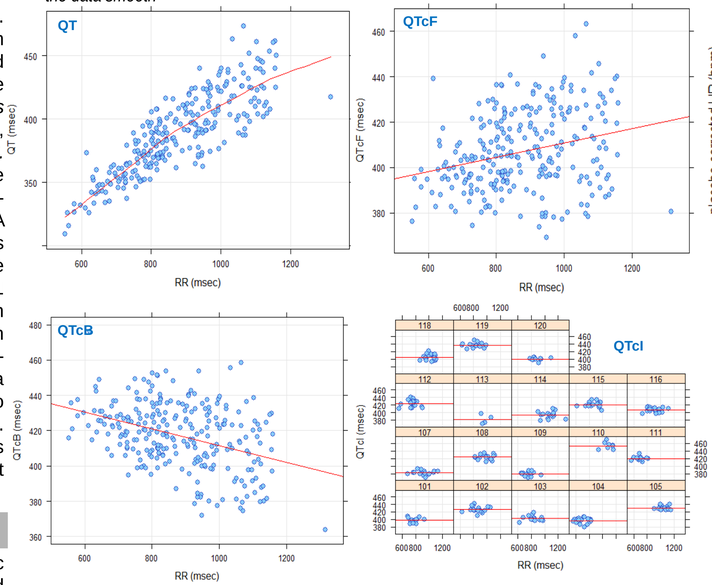

Figure 2. Relationship between placebo-model corrected HR and CF-301 plasma concentrations overlaid with the model fit

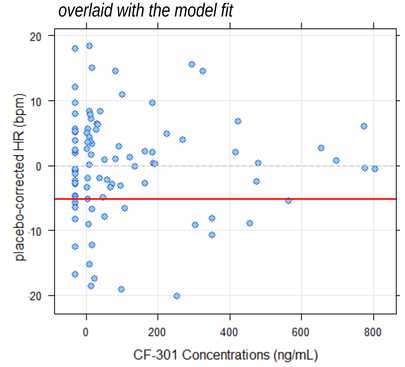

Figure 3. Relationship between placebo-model corrected QTcI and CF-301 plasma concentrations overlaid with the model fit

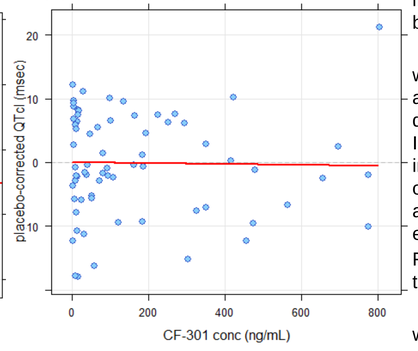

Figure 4. Relationship between placebo-model-corrected SBP measurements and CF-301 plasma concentrations overlaid with the linear model fit

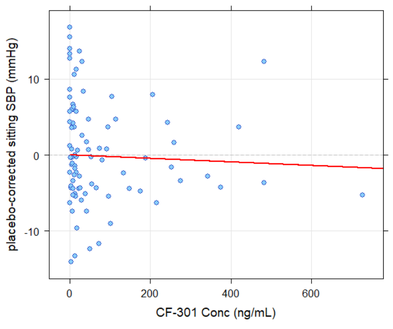

Figure 5. Relationship between placebo-model-corrected DBP measurements and CF-301 plasma concentrations overlaid with the linear model fit

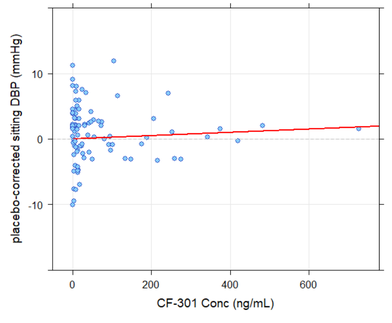

Table 1. Population PK-PD model parameter estimates for final HR model

Parameter	Estimate	St. Error	p-value	
Placebo	-5.8	3.4	0.09	
Effect of weight on placebo (θ*(Weight-77))	-0.2	0.1	0.18	
Additive effect of 2.5 hr timepoint on placebo	7.9	2.8	0.01	
Additive effect of 3 hr timepoint on placebo	5.9	2.7	0.03	
Additive effect of 6 hr timepoint on placebo	15.8	2.7	0.00	
Additive effect of 14 hr timepoint on placebo	11.4	2.7	0.00	
Effect of CF-301 exposure (on-off switch)	-5.2	3.8	0.19	NOT statistically significant drug effect
IIV on placebo (additive) (SD)	5.73			
Residual error (additive) (SD)	8.44			

Table 2. Population PK-PD model parameter estimates for final QTcI model

Parameter	Estimate	St. Error	p-value	
Placebo	-7.52	1.35	0.00	
Effect of age on placebo (θ*(Age-33))	-0.21	0.07	0.00	
Magnitude of the diurnal term for 24-hr period	6.63	2.40	0.00	
Shift of the diurnal term for 24-hr period o	16.76	0.85	0.00	
Slope for CF-301 concentrations	-0.0007	0.005	0.89	NOT statistically significant drug effect
IIV on placebo (additive) (SD)	1.44			
Residual error (additive) (SD)	8.08			

Table 3. Population PK-PD model parameter estimates for final SBP model

Parameter	Estimate	St. Error	p-value	
Baseline/placebo	120.08	1.86	0.00	
Change in baseline/placebo for females	-13.65	2.76	0.00	
Slope for CF-301 concentrations	-0.002	0.005	0.67	NOT statistically significant drug effect
IIV on baseline/placebo (additive) (SD)	5.84			
Residual error (additive) (SD)	6.96			

Table 4. Population PK-PD model parameter estimates for final DBP model

Parameter	Estimate	St. Error	p-value	
Baseline/placebo	75.94	1.29	0.00	
Change in baseline/placebo for females	-5.84	1.92	0.00	
Slope for CF-301 concentrations	0.003	0.004	0.18	NOT statistically significant drug effect
IIV on baseline/placebo (additive) (SD)	4.07			
Residual error (additive) (SD)	4.68			

METHODS (cont'd)

Individual correction of QT interval for HR (or RR interval, a time between beats on ECG that is used to calculate HR):

$$QTcI = QT + b*(1-RR)$$

was derived prior to the start of the PK-PD modeling of QTcI. For PK-PD models of HR and QTcI, the structural model of the following form was applied to the change from baseline data:

$$\hat{Y} = Placebo + Drug\ Effect$$

where, $\hat{Y}$ is the change from baseline either in HR or QTcI, and *Placebo* and *Drug Effect* are the statistical models describing placebo and drug effect responses, respectively. Inter-individual variability (IIV) term was fit on placebo effect in both models. Change from baseline was fit instead of the observed values as the diurnal pattern was quite variable among the subjects and none of the models tested explained the baseline data adequately.

For PK-PD models of SBP and DBP, the structural model of the following form was applied:

$$\hat{Y} = Baseline/Placebo + Drug\ Effect$$

where, $\hat{Y}$ is the predicted random variable (SBP or DBP), and *Baseline/Placebo* is the shared effect of baseline and placebo, as only one measurement of BP was taken on baseline day.

RESULTS

The model describing the relationship between CF-301 plasma concentrations and HR is shown in Table 1 and Figure 2. There was no significant drug effect (i.e., CF-301 conc.) on HR (average effect of -5 bpm, p=0.19). The placebo effect was -6 bpm.

Linear correction method of QT for HR (i.e., QTcI) was adequate and removed correlation between QTcI and HR (Figure 1). PK-PD model for QTcI can be found in Table 2 and Figure 3. Mean placebo effect was -8 msec, age and diurnal variations showed a statistically significant effect on QTcI ($p<0.01$), but there was no significant relationship between QTcI and CF-301 conc. (slope -0.0007, p=0.89).

PK-PD models for SBP and DBP can be found in Tables 3 and 4, and Figures 4 and 5, respectively. The combined mean baseline/placebo SBP effect was 120 mmHg with females having lower SBP by 14 mmHg. There was no significant relationship between SBP and CF-301 conc. (slope -0.002, p=0.67). The combined mean baseline/placebo DBP effect was 76 mmHg with females having lower DBP by 6 mmHg. There was no significant relationship between DBP and CF-301 conc. (slope 0.003, p=0.18).

CONCLUSIONS

No significant change in SBP, DBP, heart rate or HR-corrected QT intervals was detected with increases in CF-301 plasma concentration. Therefore, it can be concluded that at doses ranging from 0.04 to 0.4 mg/kg administered as a 2-hour infusion, CF-301 is not expected to result in clinically relevant changes in SBP, DBP, HR or QT.

REFERENCES

[1] http://www.contrafect.com/

[2] Khariton T, Chiu J, Cassino C, Ghahramani P (2016) Population PK in humans and Target Attainment Simulations for CF-301 - a First-In-Class Antibacterial Lysin. ACoP.