TARGET ATTAINMENT OF EXEBACASE, A FIRST-IN-CLASS ANTIBACTERIAL LYSIN, TO DETERMINE OPTIMAL DOSES FOR ADULT PATIENTS WITH STAPHYLOCOCCUS AUREUS (S. AUREUS) BLOODSTREAM INFECTIONS (BACTEREMIA) INCLUDING ENDOCARDITIS

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Abstract

Background: Exebacase, a novel, antibacterial direct lytic agent for the treatment of *S. aureus* bacteremia and endocarditis, studied in Phase 1 and 2 trials, demonstrated potential to improve clinical outcomes when used in addition to conventional antibiotics. Objectives were to develop population PK (PPK) model and perform target attainment (TA) simulations to determine optimal clinical doses.

Methods: PPK model was developed with data from 72 patients receiving Exebacase, in addition to the standard of care, as single 2-hr intravenous infusion of 0.25 mg/kg (0.12 mg/kg for patients with creatinine clearance (CrCL) < 60 mL/min). PPK model was used for TA simulations of various IV regimens.

Results: 3-compartment model best fit the data, parameters were well estimated (CL=4.2 L/hr (RSE=5.5%), Vc=4.5 L (RSE=8.2%)). Total volume of distribution (V) was 20.2 L. Values were lower than estimated previously in healthy subjects, CL=7.1 L/hr and V =27.7 L. CrCL was the only clinically meaningful covariate. Patients with moderate and severe renal impairment are expected to have 1.3 to 2-fold higher AUC or C_{max} than patients with normal renal function. Age was statistically significant on peripheral clearance but was not clinically meaningful (≤4% effect on exposure). TA simulations were stratified by renal function across a range of fixed as well as weight-based doses (all simulated as 2-hr infusion). In patients with normal renal function or mild impairment, 18 mg dose result in C_{max} and $AUC_{0\text{-}24}$ of 1254 ng/mL and 3026 ng*hr/mL, respectively. In patients with moderate or severe renal impairment, 12 mg dose result in C_{max} and AUC of 1107 ng/mL and 3099 ng*hr/mL, respectively. In ESRD patients including hemodialysis, 8 mg dose result in C_{max} and AUC of 910 ng/mL and 3109 ng*hr/mL, respectively. These exposures place >99% patients above efficacious thresholds of AUC/MIC >0.2 established in animals.

Conclusion: PPK model described exebacase PK in patients adequately. CL and V were estimated to be 40% and 17% lower, respectively, than healthy subjects. CrCL was the only clinically meaningful covariate requiring dose adjustment. TA assessments identified doses that achieve minimum efficacy target (AUC/MIC≥0.2) in >99% of patients with *S. aureus*. Based on these simulations, fixed dosing schedule was recommended.

INTRODUCTION

Exebacase is a first-in-class lysin with activity against *Staphylococcus aureus* (*S. aureus*). Exebacase is manufactured as a purified enzymatic protein that has 2 functional domains: a binding domain that binds to peptidoglycan structures that comprise the bacterial cell wall and a catalytic domain that cleaves peptidoglycan structures found in the cell wall, thereby causing the bacterial cell to lyse.

Several features distinguish exebacase from small molecule antibiotics, which include: (1) a novel mechanism of action; (2) bactericidal activity against antibiotic-resistant *S. aureus*; (3) rapidity of antibacterial activity both *in vitro* and *in vivo (scan the QR code below)*; (4) narrow lytic spectrum of action; (5) potent activity against biofilms; (6) synergistic activity with standard of care antibiotics (e.g. daptomycin); and (7) low propensity for developing bacterial resistance, because the binding and cleavage sites on the bacteria are in the highly conserved peptidoglycan structures essential for viability.

Scan this QR code to see the video of exebacase in action killing bacteria in real time scale

OBJECTIVES

The objectives of the analyses described in this report are as follows:

a) Using the data from Study CF-301-102 develop the population pharmacokinetic (PK) model to describe pharmacokinetics of exebacase in patients

b) Based on the population PK model, perform simulation to enable selection/confirmation of the doses of exebacase in Phase 3 study such that the exposures, C_{max} and $AUC_{0\text{-}24}$, match those observed in Study CF-301-102 (the Phase 2 study).

c) Build pharmacokinetic pharmacodynamic (PKPD) model to explore the relationship between exebacase exposures and probability of patients being Responders

d) Build population PKPD models to explore the relationship between exebacase exposures and death, common Adverse Events (AEs) and pre-dose antidrug (exebacase) antibodies (ADA)

DATA

The population PK and PKPD analyses were conducted using data from patients that participated in Study CF-301-102, a Phase 2 Proof of Concept study which compared the clinical response of patients with *S. aureus* bloodstream infections (BSI) including infective endocarditis (IE) who were treated with exebacase in addition to standard of care antibiotics (SOCA) vs those that were treated with SOCA alone.

A total of 119 patients in Study CF-301-102 that received any amount of study drug; 72 of those patients received exebacase treatment, and the other 47 were on placebo. All 72 patients that received exebacase treatment had PK samples collected and were included in the population PK analysis, 30 of those were administered a dose of 0.25 mg/kg dose, while 42 patients were dose-adjusted to 0.12 mg/kg based on renal function. 13 patients were part of serial PK sampling. The PK data consisted of 348 exebacase plasma concentration records; 15 observations were found to be below LLOQ, 13 of which were measured prior to the first dose. Additionally, 4 records were identified as outliers and removed from the final analyses.

The AE analyses were based on 119 patients that received any amount of the study drug (Safety population per Study CF-301-102 Protocol): 72 exebacase-treated patients and 47 placebo patients. Analysis of the baseline (pre-dose) ADA was based only on 72 patients that were treated with exebacase.

The PKPD analysis of the probability of being a Responder was based on Microbiological Intent-to-Treat (mITT) population (as defined by Study CF-301-102 Protocol): 116 patients, of which 71 patients were on exebacase treatment, and 45 patients were on placebo. Three patients (one from exebacase treatment arm and 2 from placebo) were excluded from the mITT population because the central laboratory did not confirm the isolates as *S. aureus* prior to randomization.

METHODS

Population PK modeling

Two- and three-compartmental models with zero-order infusion were evaluated to characterize the concentration-time profiles of exebacase in patients. Inter-individual variability (IIV) was investigated on all the relevant PK parameters. Proportional, additive, combination of proportional and additive, as well as log-error models were evaluated to describe the intra-individual (residual) variability. Baseline creatinine clearance (CrCL), dialysis status, body weight, ideal body weight (IBW), lean body mass (LBM), baseline ADA, baseline APACHE II Scores, age, race, and sex were tested for their influence on exebacase pharmacokinetics. Model diagnostic plots were used to evaluate the fit of each population PK model. The prediction-corrected visual predictive check was applied to the final population PK model to assess whether the model described the data adequately and was appropriate to be used for simulation. Final population PK model was used to predict C_{max} and $AUC_{0\text{-}24}$ for each patient in the study and to conduct Monte Carlo simulation to identify the dose associated with exposures (C_{max} and $AUC_{0\text{-}24}$) that are expected to match median exposures identified in patients from Study CF-301-102. Figure 1 support the population PK model is adequate in describing the PK of exebacase.

PKPD Modeling

Generalized linear model with the logit link was fit to estimate probabilities of the following events:

- being a Responder
- death in the study (though Test of Cure visit and though Day 180 [long-term follow up] visit)
- having at least one SAE of any kind
- at least one SAE in cardiac disorders system organ class through Test of Cure and Day 180 (long-term follow-up)
- at least one TEAE in infections and infestations system organ class
- at least one TEAEs in cardiac disorders system organ class
- at least one TEAEs in GI disorders system organ class
- at least one TEAEs in respiratory, thoracic and mediastinal disorders system organ class

Stepwise model selection approach was used for all the PKPD analyses. The following variables were tested for their influence on models described above: C_{max}, $AUC_{0\text{-}24}$, AUC/MIC for Responder analysis, CrCL, baseline APACHE II Scores, age, sex, region (US vs. non-US), infection type (MRSA vs. non-MRSA [MSSA]), diagnosis (left-sided endocarditis vs. others [right-sided endocarditis, complicated bloodstream infection [BSI], uncomplicated BSI]). These variables were added to each model one at the time and were kept in the model if they were significant at 5% level (p≤0.05). Likelihood ratio test was used for determination of the significance.

T-test was used to evaluate whether patients that had positive baseline ADA also had statistically different exposures. Linear, log-linear and Emax models were tested to determine whether baseline ADA titer was a significant predictor of $AUC_{0\text{-}24}$.

RESULTS

Population PK Modeling

The final population PK model was a three-compartment model with zero-order infusion with a proportional residual error and IIV terms on CL, central volume of distribution V1 and peripheral clearance Q2. CrCL and age were found to be statistically significant predictors of CL and Q2, respectively. Based on the model diagnostic plots and predictive check (Figure 1), the final population PK model fit adequately the PK data from patients in Study CF-301-102. PK parameters were well estimated: CL=4.2 L/hr (RSE=5.5%) and V1=4.5 L (RSE=8.2%), while the total Volume of distribution (Vd) was 20.2 L. CrCL was the only clinically meaningful parameter. For a given dose, patients with mild renal impairment are expected to have up to 20% higher C_{max} and up to 30% higher $AUC_{0\text{-}24}$, patients with moderate renal impairment are expected to have up to 40% higher C_{max} and up to 70% higher $AUC_{0\text{-}24}$, patients with severe renal impairment are expected to have up to 60% higher C_{max} and up to 2-fold higher $AUC_{0\text{-}24}$, patients with the end-stage renal disease (ESRD) are expected to have up to 90% higher C_{max} and up to 3-fold higher $AUC_{0\text{-}24}$ than patients with normal renal function. Age alone was not a clinically meaningful predictor of exebacase exposures (≤4% effect on $AUC_{0\text{-}24}$ or Cmax). Weight, IBW, LBM, baseline ADA, baseline APACHE II Score, race, and sex were tested for their influence on exebacase pharmacokinetics but were not included in the model because they were not statistically significant.

Weight-based dosing such as 0.5 mg/kg provided on average the desired mean concentrations. However there was still a significant relationship between exposure and body weight.

Individual exebacase exposures for Patients from Study CF-301-102

Based on the population PK analysis, the median C_{max} and $AUC_{0\text{-}24}$ achieved by CF-301-102 patients is estimated to be 1056 ng/mL and 3108 ng*hr/mL, respectively. All the study patients achieved efficacy target of AUC/MIC≥0.5.

Dose recommendation for Future Clinical Studies

The recommended dosing regimen for future clinical studies were such that the expected $AUC_{0\text{-}24}$ would be similar to the median $AUC_{0\text{-}24}$ of 3108 ng*hr/mL observed in Study CF-301-102 (the Phase 2 study). To account for influence or renal function and also remove the trend introduced by weight-based dosing, a fixed dose regimen (as opposed to weight-based dosing of mg/kg) is suggested as follows:

- For patients with normal renal function (CRCL≥90 mL/min) and mild renal impairment (60≤CRCL<90 mL/min), , a dose of 18 mg 2-hr IV infusion. This would result in median C_{max} and $AUC_{0\text{-}24}$ values of 1254 ng/hr and 3026 ng*hr/mL, respectively.
- For patients with moderate (30≤CRCL<60 mL/min), and severe renal impairment (15≤CRCL<30 mL/min) , a dose of 12 mg 2-hr IV infusion. This would result in median C_{max} and $AUC_{0\text{-}24}$ values of 1107 ng/mL and 3099 ng*hr/mL, respectively.
- For patients with ESRD (CrCL<15 mL/min), including those on dialysis, a dose of 8 mg 2-hr IV infusion. This would result in median C_{max} and $AUC_{0\text{-}24}$ values of 910 ng/hr and 3109 ng*hr/mL, respectively.

For the dosing regimen recommended above, 99% of patients would be expected to have $AUC_{0\text{-}24}$ ≤7200 ng*hr /mL ($AUC_{0\text{-}24}$ associated with 5 mg/kg dose administered to rats as a 2-hr infusion) and 69% of patients would be expected to have $AUC_{0\text{-}24}$ ≤3600 ng*hr/mL ($AUC_{0\text{-}24}$ associated with 2.5 mg/kg dose administered to rats as a 2-hr infusion).

The dosing regimen above achieves similar exposures regardless of renal function status (Table 1).

Population PKPD Modeling of Probability of being a Responder

The PKPD models for the Responder analysis identified that probability of clinical response in MRSA patients receiving exebacase in addition to standard of care is statistically higher than those receiving placebo in addition to standard of care group. The factors that were identified as statistically significant predictors of probability of Response were left-sided endocarditis and whether a patient had an MRSA infection. There was no exebacase exposure difference between responders and non-responders (Figure 2).

Population PKPD Modeling of Adverse Events

Separate PKPD models were developed for probability of death in the study, as well as experiencing at least one adverse event of interest: SAE of any kind, SAE in cardiac disorders system organ class, TEAE in infections and infestations system organ class, TEAEs in cardiac disorders system organ class, TEAEs in GI disorders system organ class, TEAEs in respiratory, thoracic and mediastinal disorders system organ class. These PKPD models showed no significant relationship between the exposures of exebacase (C_{max} and $AUC_{0\text{-}24}$) and death in the study or any of SAEs or TEAEs listed above.

Population PKPD Modeling of Baseline Anti-drug Antibodies (ADA)

20.8% (N=15) of exebacase treated patients had positive baseline ADA; however, the differences in $AUC_{0\text{-}24}$ or C_{max} between the two groups of patients were not statistically significant (Figure 3). This was in agreement with the population PK analysis, where baseline ADA was tested as a covariate on exebacase CL and was not found to be of statistical significance. The relationship between baseline ADA titer and $AUC_{0\text{-}24}$ showed that while the relationship between the two was positive, it was not statistically significant.

Figure 1. *Plots of the population (left) and individual predicted (middle) exebacase plasma concentrations against observed values and the figure on the right shows Prediction-corrected Visual Predictive Check of the final population PK model for exebacase with median (solid line) and 90th percentiles (dashed line) overlaid with credible regions (shades around each line).*

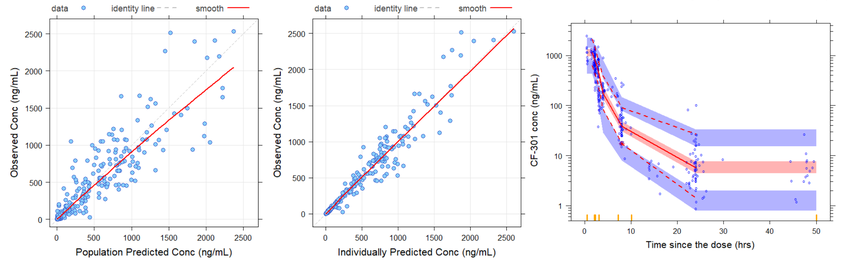


Table 1. *Selected dose exebacase based on renal function that achieve target attainment.*

Renal function	Exebacase Dose (2 hr i.v. infusion)	Median AUC (ng.hr/mL)	95% CI for AUC (ng.hr/mL)	% Subjects achieving AUC/MIC ratio ≥0.2 i.e., attain exebacase AUC >1000 ng.hr/mL for *S. aureus* strains with MIC≤2 and
Normal renal function and mild renal impairment (CrCL≥60 mL/min)	18 mg	3026	(1547; 6074)	0.1
Moderate and severe renal impairment (15≤CrCL<60 mL/min)	12 mg	3099	(1551; 6056)	0.1
ESRD and Dialysis	8 mg	3109	(1667; 5903)	0.1

Figure 2. *Boxplots (overlaid with dot plots) of the population PK model-predicted $AUC_{0\text{-}24}$ and C_{max} for exebacase treated patients stratified by Responders and non-Responders.*

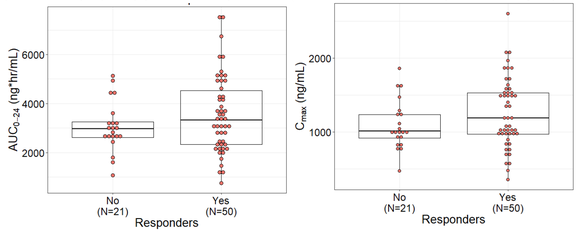
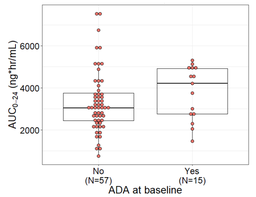


Figure 3. *Boxplots (overlaid with dot plots) of the population PK model-predicted $AUC_{0\text{-}24}$ for exebacase treated patients stratified by patients that had positive ADA at baseline vs. patients with negative ADA*



Conclusions

- Exebacase plasma concentrations were best described by a three-compartment population PK model. CrCL and age were identified as statistically significant covariates affecting exebacase PK. Only effect of CrCL was found to be clinically relevant. The median C_{max} and $AUC_{0\text{-}24}$ estimated for patients in the Phase 2 study (Study CF-301-102) were 1056 ng/mL and 3108 ng*hr/mL, respectively. All patients in Phase 2 study (CF-301-102) receiving exebacase achieved efficacy target of AUC/MIC≥0.5.
- Monte Carlo simulation was used to determine exposures across various dosing and renal function scenarios. For patients with normal renal function (CRCL≥90 mL/min) and mild renal impairment (60≤CRCL<90 mL/min), a dose of 18 mg 2-hr IV infusion would result in C_{max} and $AUC_{0\text{-}24}$ values of 1254 ng/hr and 3026 ng*hr/mL, respectively. For patients with moderate (30≤CRCL<60 mL/min) and severe renal impairment (15≤CRCL<30 mL/min), a dose of 12 mg 2-hr IV infusion would result in C_{max} and $AUC_{0\text{-}24}$ values of 1107 ng/mL and 3099 ng*hr/mL, respectively. For patients with ESRD (CrCL<15 mL/min), including patients on hemodialysis, a dose of 8 mg 2-hr IV infusion would result in C_{max} and $AUC_{0\text{-}24}$ values of 910 ng/mL and 3109 ng*hr/mL, respectively, The selected dosing regimen is expected to attain efficacious exposure in >99% of patients.
- The PKPD models for the Responder analysis identified that the probability of clinical Response in patients receiving in addition to standard of care is statistically higher than those receiving placebo in addition to standard of care. The PKPD models for the probability of being a Responder identified two factors as predictors of higher probability of Response: having a diagnosis other than left-sided endocarditis and having an MRSA infection.
- No statistically significant differences in $AUC_{0\text{-}24}$ was found between patients with positive baseline (pre-dose) ADA and those with negative baseline ADA. This finding was in agreement with the population PK analysis, where baseline ADA was tested as a covariate on CF-exebacase and was not found to be of statistical significance.