Poster # A1-1932

Population Pharmacokinetics of CEM-102 in Healthy Subjects

J.B. Bulitta,[1] O.O. Okusanya,[1] A. Forrest,[1] S.M. Bhavnani,[1] D.K. Reynolds,[1] M.P. Pai,[1] J.G. Still,[2] P. Fernandes,[2] P.G. Ambrose[1]

[1]Institute for Clinical Pharmacodynamics/Ordway Research Institute, Latham, NY; [2]Cempra Pharmaceuticals, Chapel Hill, NC

Jurgen Bulitta, Ph.D.
Institute for Clinical Pharmacodynamics
Ordway Research Institute
43 British American Blvd.
Latham, NY 12110
Telephone: 518 429-2600
E-mail: JBulitta@ordwayresearch.org

Abstract

Background: CEM-102, an oral antibiotic with activity against methicillin-resistant *Staphylococcus aureus* (MRSA), is being developed for the treatment of complicated skin and skin-structure infections. Using Phase 1 data, population pharmacokinetics (PPK) analysis was conducted to characterize the disposition of CEM-102 with and without food.

Methods: Healthy subjects (n = 69) enrolled in 3 Phase 1 clinical studies received 500–2200 mg of CEM-102 orally as either single or multiple doses, with or without food. Food effect was assessed after a single 500 mg dose in a crossover study with 14 subjects. Serial pharmacokinetic (PK) samples were collected and assayed for CEM-102 using LC/MS/MS. Candidate PPK models were fit to the data using the Monte Carlo parametric expectation maximization algorithm in S-ADAPT 1.56.

Results: The final PPK model, comprised of 2 disposition compartments, described the PK of CEM-102 well (overall r^2 was 0.96 for individual and 0.84 for population fits). This model included an auto-inhibition of clearance by a hypothetical inhibition compartment. Mean total clearance was 1.36 L/h (39% CV for between subject variability). Maximum extent of inhibition of clearance by the effect of the inhibition compartment was 45.9% and the associated IC_{50} was 46.8 mg/L (37% CV). The slower rate of absorption for evening vs. morning doses and slower rate of absorption in the fed state was modeled by a slower gastric release. The bioavailable fraction of dose was ~18.4% lower in the fed compared to fasting state. Front-loaded dose regimens achieved steady-state more rapidly than regimens without front-loading.

Conclusions: The saturable elimination of CEM-102 was best described by an auto-inhibition of clearance. Extent of bioavailability was ~18% lower in the fed than in the fasted state. The PPK model described herein, in combination with a mechanism-based PK-PD model, will allow prediction of the effectiveness of different CEM-102 dosing regimens.

Introduction

- CEM-102, also known as sodium fusidate, is an oral antibiotic with activity against *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA).
- Cempra Pharmaceuticals is developing CEM-102 for the treatment of acute bacterial skin-structure infections in the US.
- This analysis describes the development of a population PK model for CEM-102 using available data from 3 Phase 1 studies.

Methods

Study Design and Dose Administration

- Data from 3 Phase 1 studies (Studies 102-A, 102-B, and 103) in healthy subjects were pooled for the population PK analysis.

Methods

Study Design and Dose Administration (continued)

- Study 102-A was a bioequivalence study in which 28 subjects were randomized to receive a single 500 mg oral dose of CEM-102 without food. After a washout period, a subset of 14 subjects were randomly selected to receive CEM-102 with food.
- In Study 102-B, 18 subjects were enrolled and randomized to receive 500 mg of CEM-102 three times daily for 13 doses.
- In Study 103, 30 subjects were enrolled and randomized to receive doses ranging from 550 mg to 2200 mg of CEM-102 as a single dose followed by multiple doses of 550 to 1650 mg.
- Serial blood samples were collected at various times during the study after the administration of a single dose and multiple doses.
- CEM-102 concentrations in plasma samples were determined using a validated LC/MS/MS method with a lower limit of quantification of 0.02 mg/L and an inter-day coefficient of variation (%CV) of ≤ 11.6%.

Population PK Analysis

- Candidate population PK model selection was based on both a review of the exploratory data analysis results and prior knowledge of the PK of fusidic acid.
- Inter-individual variability was estimated for each PK parameter, where possible, using an exponential between subject variability model (assuming log-normal distributions) or a logistic transform where appropriate (to constrain estimates to the allowed domain).
- Residual variability was described using an additive plus proportional residual error variance model.
- All population PK analyses were conducted using Monte Carlo parametric expectation maximization (MC-PEM), as is implemented in the open-source software program, S-ADAPT 1.56.
- Model discrimination was performed by comparison of objective function for nested models or Akaike's Information Criterion for either nested or non-nested models

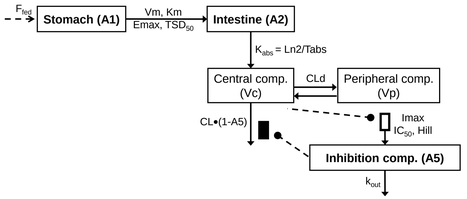
Results

- Preliminary evaluation of the PK data revealed:
  - Modest differences in fed versus fasted profiles in Study 102-A;
  - Marked and highly variable accumulation with time;
  - Differences in rate and extent of accumulation with dose;
  - Apparent half-lives that change moderately with dose and dramatically after single compared to multiple doses;
  - Slower rate of absorption with food and with evening versus morning doses;
  - Multi-phased and variable rates of absorption after a dose, and;
  - Day-to-day variability in rates of absorption within subjects.

Results

- The final model was a two-compartment disposition (central and peripheral) model with a time-dependent mixed-order absorption and auto-inhibition of clearance.
- As shown in **Figure 1**, an initial time-dependent, mixed-order process for absorption was followed by a first-order absorption from the stomach into the central compartment.

Figure 1. Final Population PK model for CEM-102



- In order to accommodate the characteristics observed in the PK data, the models considered included the following:
  - First-order absorption model;
  - First-order absorption model with the dose split into several absorption phases;
  - A time-dependent mixed-order absorption model;
  - Models with first-order or Michaelis-Menten elimination or both, and;
  - Model with auto-inhibition of clearance.
- After absorption from the intestine to the central compartment, drug equilibrated between the central (volume:Vc) and peripheral compartments (volume: Vp) via the distributional clearance (CLd).
- A hypothetical, indirect-effect auto-inhibition process affected clearance from the central compartment.
- Plasma clearance (CL) was modeled as being proportional to (1-A5).
- IC_{50}, for this inhibition of clearance, was estimated to be 46.8 mg/L and Imax was estimated to be 45.9%.
- Inter-occasion variability was allowed for all parameters that describe the rate of absorption (cVmX, cKm, $cTSD_{50}$, dLgEx) and to accommodate the differences in CEM-102 absorption between fed and fasted states (cVm_{Fed}, cKm_{Fed}, $cTSD_{50Fed}$, $dLgEx_{Fed}$).
- The rate of absorption of CEM-102 was slower in the presence of food as compared to the fasted state and the amount of drug absorbed was 18.4% less. This translates to a lower mean AUC of approximately 18% in the fed state compared to the fasted state, since the elimination of CEM-102 was saturable.

Results

- The parameter estimates and associated standard errors for the final population PK model are provided in **Table 1**.

Table 1. Final CEM-102 population PK parameter estimates and standard errors

Parameter[a]	Population mean		Magnitude of inter-individual variability (%CV)	
	Final estimate	%SEM	Final estimate	%SEM
CL (L/hr)	1.36	4.95	38.9	20.5
Vc (L)	14.0	2.26	18.5	21.9
CLd (L/hr)	0.533	5.25	40.0	21.1
Vp (L)	6.85	7.89	53.4	30.5
k_{out} (hr^{-1})	0.664	1.15	8.51	20.8
IC_{50} (mg/L)	46.8	5.95	36.5	30.4
Hill	4.32	5.45	0.00	15.0
LgIM	-0.164	20.2	17.4[b]	34.8
LgEX	-0.290	219	356[b]	23.2
VmKm[c]	6.48	8.92	43.2	26.6
Km[c]	0.0890	17.5	98.6	19.2
Tabs (min)	33.9	9.13	57.8	35.1
TSD_{50} (hr)	0.680	4.67	14.4	94.6
cVmX1, cVmX2, cVmX4, cVmX5	1.00	Fixed	93.4	16.9
cVmX3	0.413	21.7	93.4	16.9
cKm1, cKm2, cKm4, cKm5	1.00	Fixed	8.43	34.9
cKm3	1.91	4.83	8.43	34.9
$cTSD_{50}1$,$cTSD_{50}2$,$cTSD_{50}4$, $cTSD_{50}5$	1.00	Fixed	48.3	16.6
$cTSD_{50}3$	2.49	13.8	48.3	16.6
dLgEx1, dLgEx2, dLgEx4, dLgEx5	0.00	Fixed	264	21.1
dLgEx3	0.548	136	264	21.1
cF_{Fed}	0.816	4.45	11.3	84.4
cVm_{Fed}	2.17	6.41	14.2	82.8
cKm_{Fed}	0.0864	19.5	31.0	54.2
$cTSD_{50Fed}$	1.49	13.7	25.8	54.4
$dLgEx_{Fed}$	14.7	10.4	277	59.5
SDslp	0.156	1.69	—	—
SDint	0.1	Fixed	—	—

Minimum value of the objective function = 7718

a. Vc is the volume of the central compartment; Vp is the volume of the peripheral compartment; Cld is the distributional clearance between the Vc and Vp; K_{out} is the rate of loss from the inhibition compartment; IC_{50} is the total plasma concentration of fusidic acid that results in a 50% of maximum stimulation of the input into the inhibitory effect compartment; LgIM is the logit-transformed of the maximum inhibitory effect on clearance: Imax = 1 / (1 + exp(-LgIM)); Vm(t) is the maximum rate (mg/h) of the study drug absorption at time (t); Km is the value of A1 (mg) at which drug absorption is half-maximal; TSD is the time since last dose; TSD_{50} is the TSD at which there is 50% maximum change in the Vm(t); LgEX is the logit-transform of the maximum fractional change in Vm(t) over time.

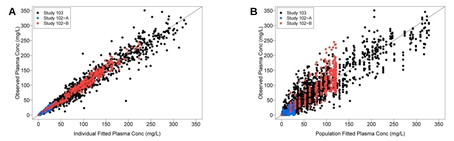
b. Please note that this is the %CV in the transformed domain.

c. Please note that the estimated VmKm and Km have no units, as these parameters were multiplied by the administered dose. This assumption assures that the time of peak concentration is independent of dose.

Results

- The goodness of fit plots demonstrated that the population PK model provided a relatively unbiased fit to the data from all three studies.
- Despite the inherent variability in the absorption process, the model provided excellent fits to the data, as evidenced by the overall r^2 of 0.967 for observed versus individual fitted plasma concentrations (**Figure 2A**) and an overall r^2 of 0.842 for observed versus population fitted plasma concentrations (**Figure 2B**).
- The performance of the model was similar among the three studies, with overall r^2 values for the observed versus individual fitted plasma concentrations of 0.967, 0.964 and 0.955 for Studies 102-A, 102-B and 103, respectively.

Figure 2. Relationship between the observed vs individual fitted plasma concentrations (A) and the observed vs population fitted plasma concentrations (B) based on the final population PK model for CEM-102, with a line of identity through the data



Conclusions

- The population PK model developed can be used to describe the time course of total plasma concentrations of CEM-102 at various dose levels and after single- and multiple-doses.
- Depending on the dose level and the IC_{50} within a subject, the population PK model results suggest the following:
  - Subjects could have a pronounced or less pronounced accumulation of drug exposure after multiple dosing, and
  - Time to steady-state, with no front-loading, could vary from approximately 1 week to over 2 weeks.
- This model can be used to predict plasma concentration-time profiles for various clinical dosage regimens under consideration, including front-loaded regimens.
- Using Monte Carlo simulation, the population PK model described herein will be used together with a mechanism-based PK-PD model[1] to support dose selection decisions for CEM-102 in future clinical studies.

References

1. Tsuji BT, et al. Pharmaockinetics-pharmacodynamics of CEM-102 against methicillin-resistant *Staphylococcus aureus* using an in vitro pharmacodynamic model and mechanism-based modeling. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy. [A1-1933] San Francisco, CA, September, 2009.