

Population Pharmacokinetics Study of a New Humanized Anti-CD20 Monoclonal Antibody AME-133v (LY2469298) in Patients with Previously Treated Follicular Lymphoma (FL)

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ABSTRACT

Background: AME-133v is a humanized monoclonal antibody that was engineered to have increased affinity to CD20 and mediate antibody-dependent cell-mediated cytotoxicity (ADCC) better than rituximab *in vitro*. The safety, pharmacokinetics (PK) and preliminary efficacy of AME-133v were assessed in a Phase 1/2 clinical trial in patients with previously treated follicular lymphoma (FL). The objective of this study is to characterize the pharmacokinetics (PK) of AME-133v in the target patient population.

Methods: 5 dose levels of AME-133v (2, 7.5, 30, 100, and 375 mg/m²) were tested in a total of 67 patients with previously treated CD20+ FL. AME-133v was administered intravenously in four weekly infusions. Blood samples were obtained pre-dose and 1, 3-5 days after infusion 1, pre-dose and post-dose during infusions 2, 3 and 4, and 1, 5 and 9 weeks after infusion 4. The PK database (399 data points) collected from the patients was analyzed by using the nonlinear mixed-effect model (NONMEM) program. A number of covariates including demographic characteristics and the FcγRIIIa receptor genotype were evaluated for their influence on the AME-133v population PK parameters.

Results: Owing to serum concentrations values falling below the limit of detection, the 2 mg/m2 dose group was not included in the analysis. The basic model selected was a two-compartment pharmacokinetic model with first-order elimination. However, a different typical value had to be determined for CL in each dose group. The typical values of V1, Q and V2 were 2.99 L, 0.94 L/day, and 3.31 L, respectively. The typical value for CL was 0.70, 0.53, 0.26, 0.27 L/day-1 for 7.5, 30, 100 and 375 mg/m², respectively, which indicates a linearization of the elimination rate of AME-133v at doses of 100 mg/m² and above. Inter-individual variability was moderate to high with CVs of 45.9, 34.1 and 50.0% on CL, V1 and V2, respectively. The only covariate found to influence the PK of AME-133v was BSA which explained 9.6% of the variability observed on V1. The form of the FcγRIIIa receptor was not found to have a significant effect on the PK of AME-133v.

Conclusions: The PK of AME-133v were best described by a 2-compartment model. Clearance was found to be dose-dependent with a linearization of the elimination rate at doses of 100 mg/m² and above. BSA has a statistically significant influence on V1 whereas the FcγRIIIa genotype does not seem to influence the disposition of AME-133v.

BACKGROUND

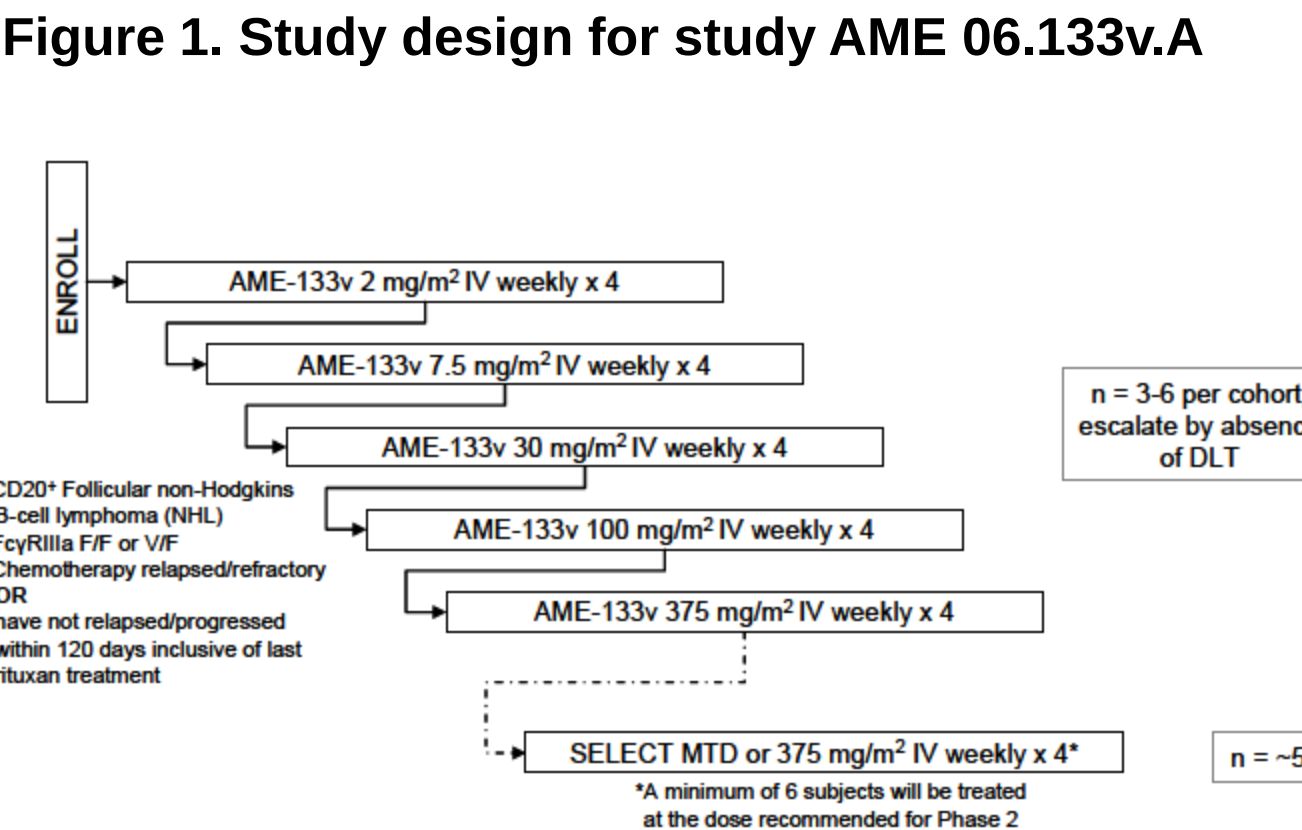
AME-133v is a humanized monoclonal antibody that was engineered to have increased affinity to CD20 and mediate antibody-dependent cell-mediated cytotoxicity (ADCC) better than rituximab *in vitro*.

Study AME 06.133v.A

The safety, pharmacokinetics (PK) and preliminary efficacy of AME-133v were assessed in a Phase 1/2 clinical trial in patients with previously treated follicular lymphoma (FL).

AME-133v was tested at 5 dose levels (Figure 1) in the phase 1 part of the study.

Subsequently, the highest dose of 375 mg/m² was tested in an additional 50 patients in the phase 2 part of the study.



OBJECTIVES [H1]

Primary objective

To characterize the PK of AME-133v in patients with previously treated follicular lymphoma

Secondary objective

To measure the effect of potential covariates on the PK of AME-133v in the target population

METHODS

Structural model development

The pharmacokinetic model was developed in NONMEM (version VII) for AME-133v serum concentrations from study AME 06.133v.A.

- A two-compartment model with first-order elimination rate was selected to describe the data and used as the base structural model for the pharmacokinetic analysis. This two-compartment model was parameterized in terms of clearance and volume of distribution (CL, V1, Q, V2).
- Inter-subject variability was assessed separately on each of the pharmacokinetic parameters assuming a log-normal distribution of individual parameter values.
- The first-order conditional estimation (FOCE) method with interaction was used to estimate the model parameters.

Covariate model development

The covariate model was built by the stepwise selection procedure using a 2-step approach.

- All continuous covariates were tested for relationships with CL and V1 using linear, exponential, and power models as shown in Equations 1 through 3. Sex was tested for relationships with CL and V1 using a categorical model, as shown in Equation 4.
- Categorical covariates were tested using the following relationship

$$P = \Theta_1 \cdot (1 + \Theta_2 \cdot (\text{COV-MED}))$$

Eq. 1

$$P = \Theta_1 \cdot \text{EXP}(\Theta_2 \cdot (\text{COV-MED}))$$

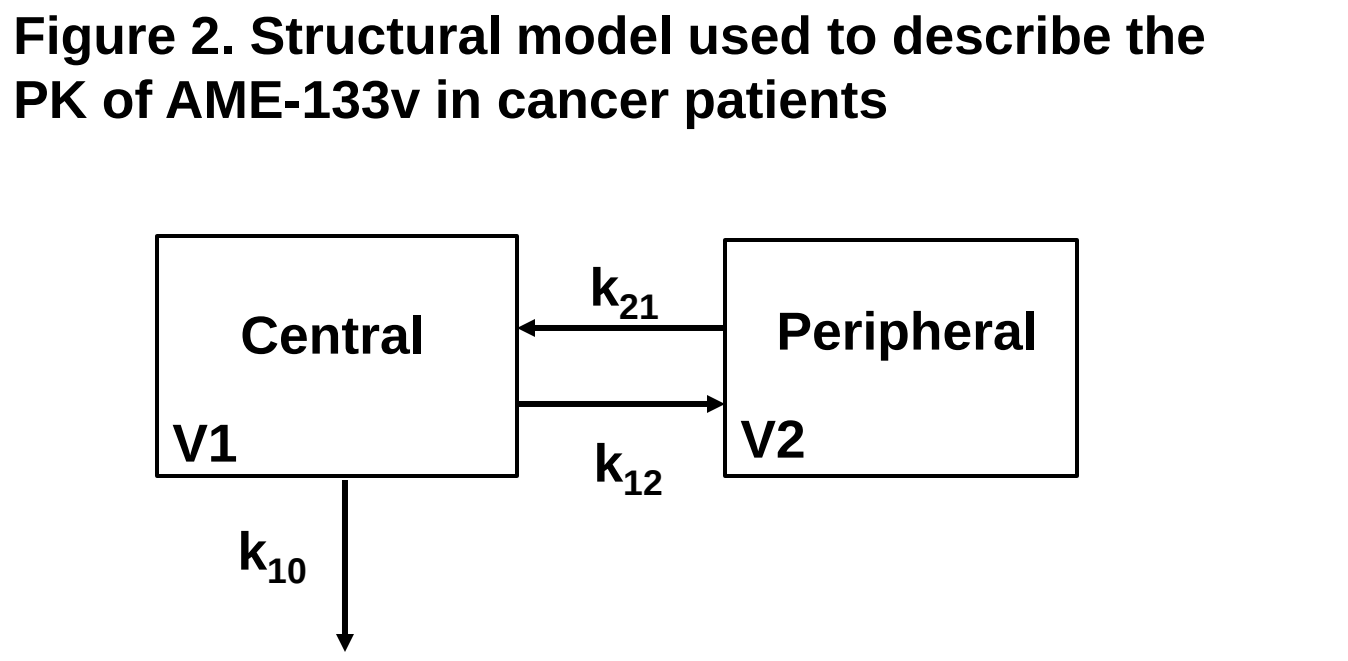
Eq. 2

$$P = \Theta_1 \cdot (\text{COV/MED})^{**\Theta_2}$$

Eq. 3

$$P = \Theta_1 \cdot (1 + \Theta_2 \cdot \text{IND})$$

Eq. 4



RESULTS

Base model

The PK of AME-133v in follicular lymphoma patients were best-described by a 2-compartment model (Figure 2).

The rate of elimination of AME-133v was non linear with respect to dose and a different CL term had to be estimated for each dose level tested (Table 1). The value of CL seemed to stabilise at a dose of 100 mg/m² or greater.

The inter-individual variability was moderate to large with CVs of 40 to 50% on CL, V1 and V2 (Table 1).

Table 1. Parameter estimates of the base PK model		
Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
Clearance		
Parameter for CL at 7.5 mg/m ² (L/day)	0.69 (9.1)	45.9% (24.0)
Parameter for CL at 30 mg/m ² (L/day)	0.52(17.8)	
Parameter for CL at 100 mg/m ² (L/day)	0.26 (14.0)	
Parameter for CL at 375 mg/m ² (L/day)	0.26 (7.8)	
Volume of Distribution		
Parameter for V1 (L)	3.15 (7.6)	43.7% (34.4)
Parameter for V2 (L)	3.31 (9.3)	49.8% (55.6)
Intercompartmental Clearance		
Parameter for Q (L/day)	0.94 (9.4)	-
Residual Error (proportional)		
	32.1% (11.7)	

Covariate model

The following covariates were tested: body surface area (BSA), total body weight (WTE), lean body weight (LBM), body mass index (BMI), gender (GEN), age (AGE) and genotype of the FcγRIIIa receptor (XB7).

Several covariates had a statistically significant effect on V1 but only BSA was retained in the total model (Figure 3, Table 2)

Only BSA had a statistically significant effect on CL but was not retained after inclusion in the complete model (Figure 3)

The genotype of the FcγRIIIa Receptor did not have an effect on the disposition of AME-133v in the target patient population (Figure 4)

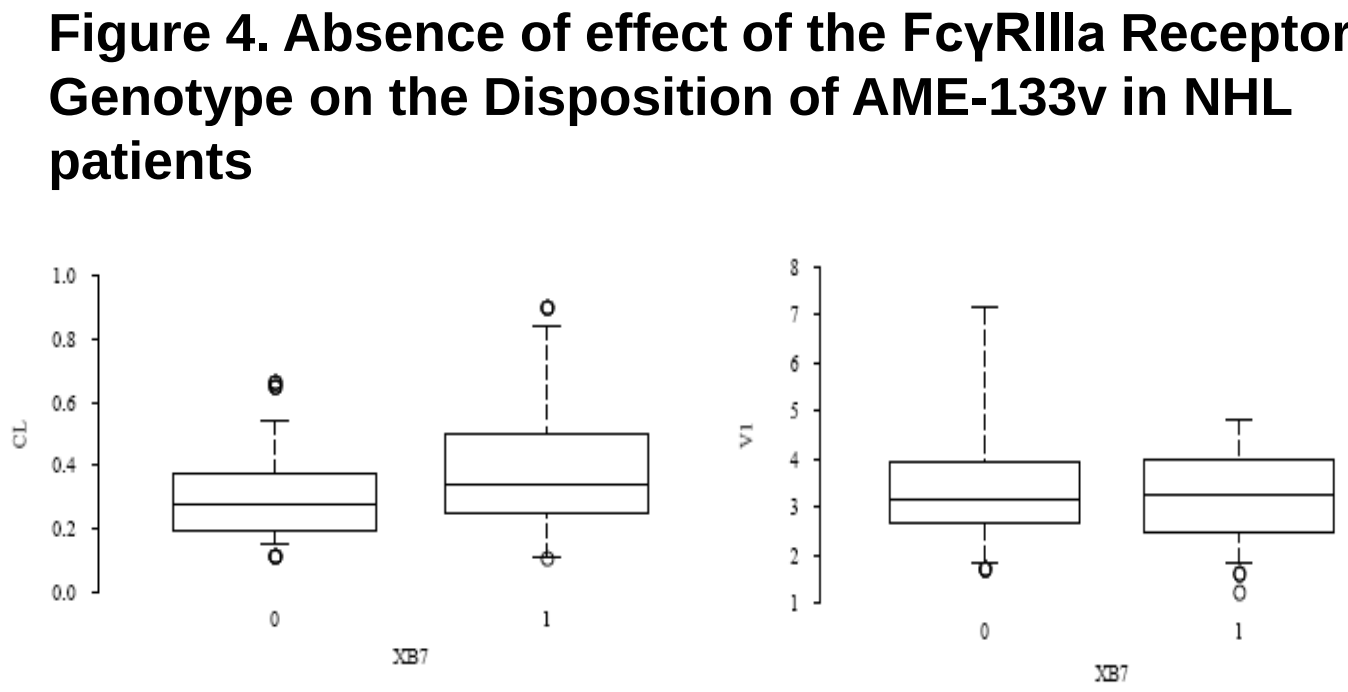
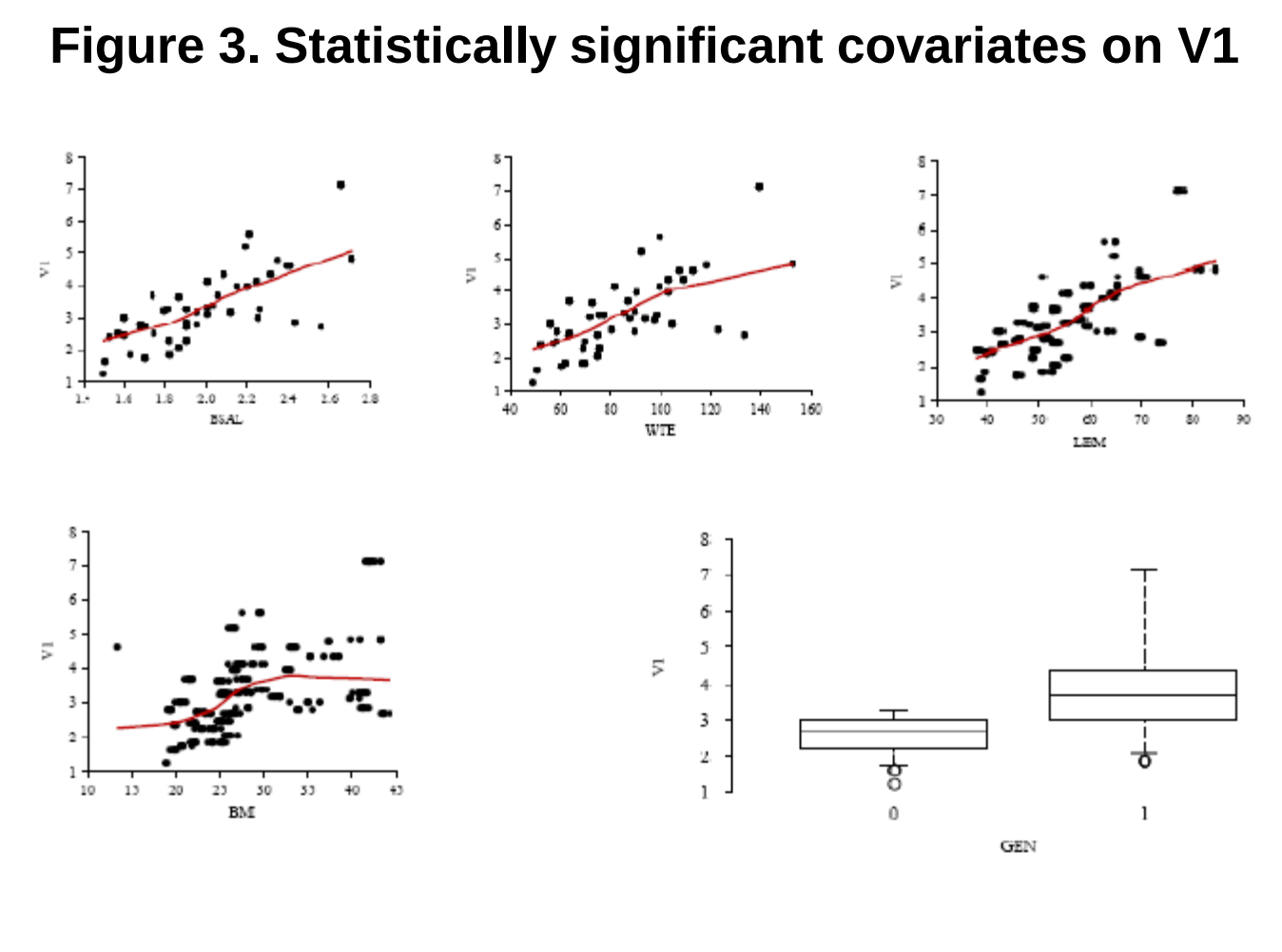
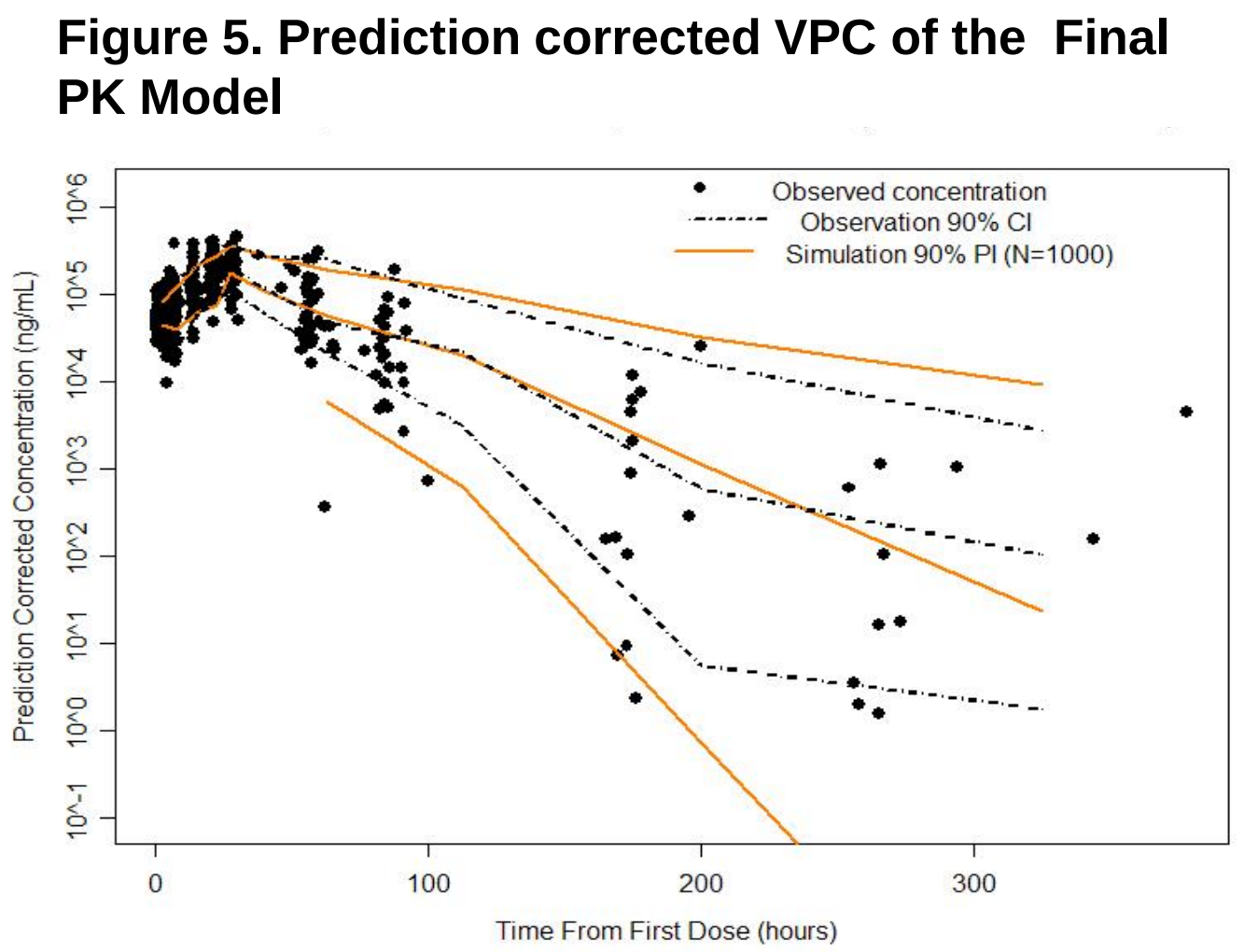


Table 2. Parameter estimates of the final PK model		
Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
Clearance		
Parameter for CL at 7.5 mg/m ² (L/day)	0.70 (8.9)	45.9% (23.6)
Parameter for CL at 30 mg/m ² (L/day)	0.53 (24.4)	
Parameter for CL at 100 mg/m ² (L/day)	0.25 (19.8)	
Parameter for CL at 375 mg/m ² (L/day)	0.26 (7.6)	
Volume of Distribution		
Parameter for V1 (L)	2.99 (5.5)	34.1% (34.2)
Parameter for V2 (L)	3.31 (11.1)	50.0% (57.4)
Intercompartmental Clearance		
Parameter for Q (L/day)	0.94 (9.4)	--
Effect of BSA on V1		
Parameter for BSA-V1	1.69 (27.8)	--
Residual Error (proportional)	32.1% (11.7)	



CONCLUSIONS

- The PK of AME-133v in patients with previously treated follicular lymphoma were best described by a 2-compartment model
 - The CL of AME-133v was non linear and a separate CL term had to be estimated for each dose level
- The only statistically significant covariate retained in the model was BSA with an effect on V1
 - BSA explained 9.6% of the variability observed for V1
- The genotype of the FcγRIIIa Receptor did not have an effect on the disposition of AME-133v in the target patient population