ABSTRACT

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BACKGROUND

AME-133v

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).

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).

Study AME 06.133v.A 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.

Figure 2. Structural model used to describe the PK of AME-133v in cancer patients

Parameter Description
Population Estimate (95%BE)
Inter-Patient Variability (%VBE)

Clearance
Parameter for CL at 7.5 mg/m² (L/day)
0.70 (8.9)
Parameter for CL at 30 mg/m² (L/day)
0.53 (24.4)
Parameter for CL at 100 mg/m² (L/day)
0.25 (19.6)
Parameter for CL at 375 mg/m² (L/day)
0.26 (7.6)

Volume of Distribution
Parameter for V1 (L)
2.29 (29.5)
34.1% (34.2)
Parameter for V2 (L)
3.11 (11.1)
50.5% (57.4)

Intercompartmental Clearance
Parameter for Q (L/day)
0.94 (9.4)
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Residual Error (proportional)
32.1% (11.7)

Figure 3. Statistically significant covariates on V1

Figure 4. Absence of effect of the FcγRlla Receptor Genotype on the Disposition of AME-133v in NHL patients

Parameter Description
Population Estimate (95%BE)

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

Objectives [H1]

The structural model developed was 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 basic structural model for the pharmacokinetic analysis. This two-compartment model was parameterized in terms of clearance and volume of distribution (CL, V1, 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 used was 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.

Figure 5. Prediction corrected VPC of the Final PK Model

- 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 FcγRlla Receptor did not have an effect on the disposition of AME-133v in the target patient population

Figure 1. Study design for study AME 06.133v.A

Figure 2. Structural model used to describe the PK of AME-133v in cancer patients

Table 1. Parameter estimates of the base PK model

Table 2. Parameter estimates of the final PK model

- The PK of AME-133v was best described by a 2-compartment model – Clearance was found to be dose dependent with a linearmization of the elimination rate at doses of 100 mg/m² and above. BSA has a statistically significant influence on V1. The model of the FcγRlla Receptor was not found to have a significant effect on the PK of AME-133v.

Conclusions:

- The PK of AME-133v was best described by a 2-compartment model.
- Clearance was found to be dose dependent with a linearmization of the elimination rate at doses of 100 mg/m² and above. BSA has a statistically significant influence on V1. The model of the FcγRlla Receptor was not found to have a significant effect on the PK of AME-133v.

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 0.70 L, respectively. The typical value for CL was 0.70, 0.53, 0.26, 0.27 L/day for 7.5, 30, 100 and 375 mg/m², respectively, which indicates a linearmization 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 45.3, 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 FcγRlla receptor was not found to have a significant effect on the disposition of AME-133v.

AME-133v

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).
- Study AME 06.133v.A 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.

- The following covariates were tested: body surface area (BSA), total body weight (TBW), lean body weight (LBW), body mass index (BMI), gender (GEN), age (AGE) and genotype of the FcγRlla Receptor

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