Population Pharmacokinetics of Siplizumab (MEDI-507) Implications for Dosing

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Abstract

Objective: Siplizumab (MEDI-507), a humanized IgG1k class monoclonal antibody, targets CD2 expressing T- and NK-cells, is being evaluated in an ongoing open-label phase I dose-escalation trial in patients with CD2-positive lymphoproliferative disease. The aim of this report is to describe a population pharmacokinetic model of sipilzumab and simulations of alternative dosing regimens performed for optimization of dosing.

Methods: 400 serum sipilzumab samples were collected from 25 patients who received 0.4-4.8 mg/kg of sipilzumab as 1-3 consecutive daily doses every 14 days for 1-8 cycles. The population pharmacokinetic analysis was performed using NONMEM. Linear and nonlinear 1- and 2-compartment models were evaluated. Simulations were performed to identify doses and dosing regimens that would maintain drug concentrations above target levels necessary for saturation of CD2 receptors.

Results: Siplizumab pharmacokinetics was described by a 1-compartment model with 2 parallel mechanisms of clearance, linear and Michaelis-Menten (MM) elimination. The half-life of the linear portion of elimination (presumably, FcRn mediated) was 51 days, consistent with expectations, while MM elimination (target-mediated clearance) had a short half-life (38 hours at concentrations below \( K_c \) of 15 µg/mL) suggesting suboptimal target saturation. Pharmacokinetics did not change over time, which was expected, since no immunogenicity was observed. Simulations of various dosing regimens suggested that doses >4.8 mg/kg weekly are necessary to maintain drug concentrations above target level (2 \( >4.8 \) mg/kg weekly are necessary to maintain drug concentrations above target level (2

Conclusions: Siplizumab concentrations follow a 1-compartment kinetics with linear FcRn-mediated and nonlinear target-mediated clearance. The short half-life of target-mediated clearance suggests that tissue target saturation is suboptimal at doses/regimens studied thus far. Dose escalation was accelerated based on simulations, with weekly doses 2.4-8 mg/kg, to maintain concentrations above the target level and to possibly increase target saturation in the tissues.

Background

- Siplizumab is a humanized IgG1k-class anti-CD2 monoclonal antibody.
- Binds to CD2 on human T-lymphocytes (T-cells), natural killer (NK) cells, and thymocytes.
- Mechanism of action via targeted T-cell toxicity.
- CD2 binding region derived from rat monoclonal antibody.
- CD2 is entire human origin (FcRn).
- Linear and nonlinear elimination expected for sipilzumab.
- FcRn mechanism (half-life \( t_1/2 \) = 26 days).
- Target-mediated elimination.
- Linear at low drug concentrations.
- Saturable at high drug concentrations.
- Ongoing (as of December 2006) phase 1 trial demonstrated activity (27% RR) and safety (no maximal tolerated dose reached).
- No dose response.

Methods

Study

- Phase 1, open-label, dose-escalation study in patients with CD2-positive relapsed/refractory T-cell NHL (ATL, LGL, PTCL, CTCL).

Dosing

- Cohorts 1-7: 0.4, 0.6, 0.8, 1.2, 2, 3, 4, and 4.8 mg/kg Q14D, total dose administered over 3-5 days (2-6 infusions).
- Cohorts 6-8: 0.8 or 3.4 mg/kg weekly, dose every other single day (no pharmacokinetic (PK) data for 3.4 mg/kg dose).

Treatment

- Until progression, but no more than 16 weeks in cohorts 1-5.

Pharmacokinetic Data

- 400 serum samples from 25 patients in cohorts 1-8.
- Most patients' trough values below limit of quantitation and no accumulation.
- Only trough and peak samples for treatment cycles >1.

Pharmacokinetic Analysis

- Population PK using NONMEM V.

T-Cell Depletion Data

- Data too sparse for pharmacokinetic/pharmacodynamic (PK/PD) modeling.
- Efficient depletion of CD8+ and CD4+ T-cells in peripheral blood at both doses.
- No PD measurements at trough or between doses.

Results

Pharmacokinetic Data

- One-compartment population PK model.
- Two mechanisms of elimination.
- Linear (presumably FcRn).
- Nonlinear (CD2-mediated).

Dosing Recommendation

- At least 4.8-9.6 mg/kg dose once a week to assure that most patients maintain high concentration levels above 30 or 75 µg/mL.

Conclusions

- Siplizumab follows a 1-compartment model with parallel linear and saturable elimination.
- Half-life of the saturable pathway is 38 hours at low concentrations.
- Rapid elimination in the absence of target cells in peripheral blood suggests the presence of target cells in tissues and distribution of drug to these tissues.
- Weekly dosing achieves desired concentrations at lower doses than Q14D dosing.
- Dosing recommendation: At least 4.8 mg/kg weekly (and preferably higher), if safety allows.

Later Developments

- During trial continuation with intensified dosing, several cases of Epstein-Barr Virus lymphoproliferative disease occurred leading to suspension of enrolment for safety evaluation.

References