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

E. Gibiansky, PhD[1]; J. Janik, MD[2]; D. Mahony, MD[2]; K. Kaucic, MD[1]; L. Hammershaimb, MD[1]; G. Robbie, PhD[1]

[1] *MedImmune, Inc., Gaithersburg, MD, USA;* [2] *Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*

Abstract

Objectives: Siplizumab (MEDI-507), a humanized IgG1k class monoclonal antibody, which 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 diseases. The aim of this report is to describe a population pharmacokinetic model of siplizumab and simulations of alternative doses/regimens performed for optimization of dosing.

Methods: 490 serum siplizumab samples were collected from 25 patients who received 0.4–4.8 mg/kg of siplizumab 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-Menton (MM) elimination. The half-life of the linear portion of elimination (presumably, FcRn mediated) was 31 days, consistent with expectations, while MM elimination (target-mediated clearance) had a short half-life (38 hours at concentrations below K_m 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 ($2 \times K_m$, 30 µg/mL, the level at which half-life of target-mediated clearance increases 3 times) for 90% of patients.

Conclusions: Siplizumab concentrations follow 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 ≥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.[1]
- CD2 binding region derived from rat monoclonal antibody.[2]
- Fc region is entirely of human origin (FcRn).
- Linear and nonlinear elimination expected for siplizumab.
  - 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 maximum 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, 2.4, 3.4, and 4.8 mg/kg Q14Days, total dose administered over 2–3 days (~2-h infusions).
- Cohorts 8–9: 0.8 or 3.4 mg/kg once weekly, dose over 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

- 490 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.

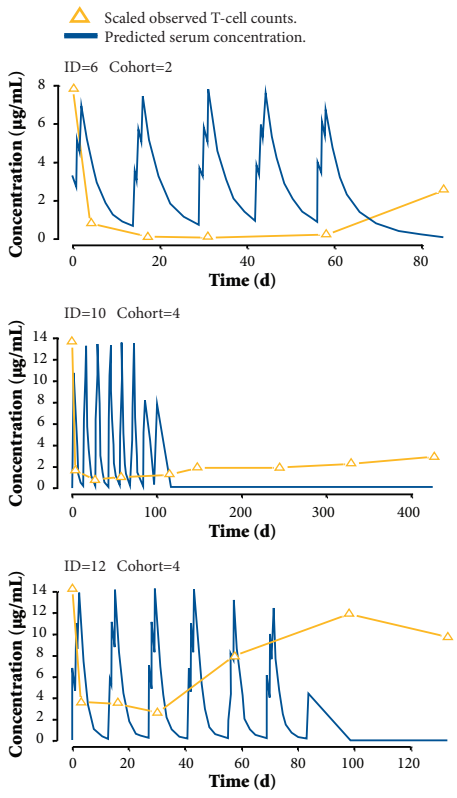
Pharmacokinetic Analysis

- Population PK using NONMEM V.

MedImmune

T-Cell Depletion Data

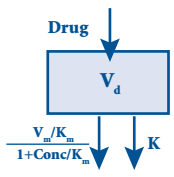
- Data too sparse for pharmacokinetic/pharmacokinetic (PK/PD) modeling.
  - Efficient depetion of CD4+ and CD8+ T cells in peripheral blood at all doses
  - All PD measurements collected at peak effect
  - No PD measurements at trough or between doses



Results

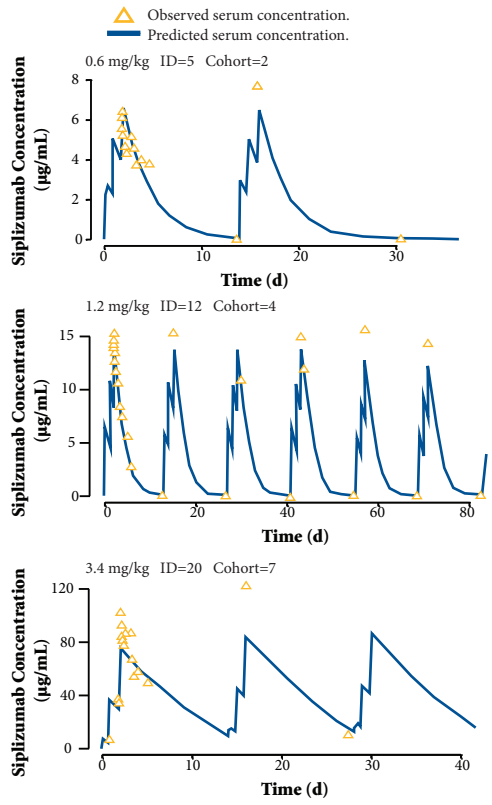
Pharmacokinetics

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



Parameter	Est Value	90% CI	Variability % CV
V_d (L/77 kg)	4.7	4.2–5.3	25
K (L/d)	0.022	0.006–0.07	
K_m (µg/mL)	15	10–37	84
V_m (µg/mL/d)	6.6	4.7–10	

- FcRn elimination
  - $t_{1/2}$ **31 days**
- "Target-mediated" elimination
  - $t_{1/2}$ **38 hours** (very short!!) at concentrations below K_m (<15 µg/mL)
- Saturation of elimination at concentrations above K_m.



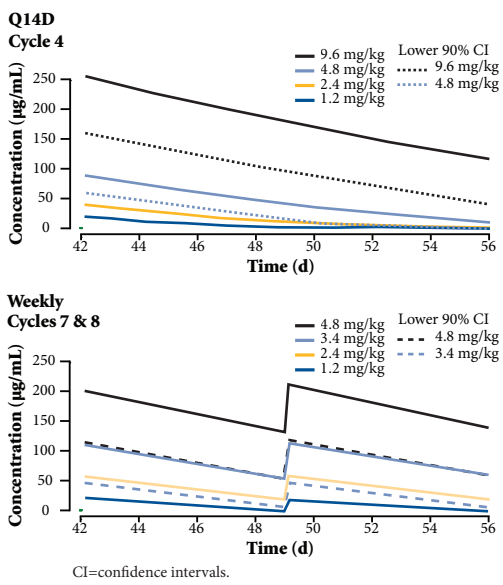
Implications For Dosing

- "Target-mediated" elimination is governed by
  - Availability and affinity to target
  - Distribution of drug to target outside blood
- According to T-cell depletion data drug rapidly kills cells in blood.
- Continued rapid elimination in the absence of target cells in blood suggests
  - presence of target cells in tissues
  - distribution/elimination of drug outside of blood

IMPLICATION
To maximize drug effect, maintain serum concentrations ALWAYS above saturation, ie, several times above 15 µg/mL.

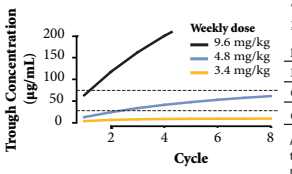
Simulated Concentrations for Different Dosing Regimens

Q14D and Weekly Dosing



CI=confidence intervals.

Weekly Dosing



% of time spent at concentration ≥30 or 75 µg/mL

Level (µg/mL)	30			75		
Dose (mg/kg)	3.4	4.8	9.6	3.4	4.8	9.6
Cycle 1	31	77	100	0	1	89
Cycle 7	46	100	100	0	73	100

At levels of 30 and 75 µg/mL, target-mediated $t_{1/2}$ of siplizumab (38 h) increases 3- and 6-fold, respectively.

Predicted trough levels at lower band of 90% confidence intervals.

Dosing Recommendation

- At least 4.8–9.0 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 enrollment for safety evaluation.

References

1. Xu Y, et al. *Clin Exp Immunol.* 2004;138:476-483.
2. de la Parra B, et al. *Belg J Zool.* 1991;121(suppl 1):13

Population Approach Group in Europe
Sixteenth Annual Meeting
June 13–15, 2007
Copenhagen, Denmark

Research supported by MedImmune, Inc.