Modification of the Fc Region of CNTO 1119, a Human Anti-Oncostatin M Monoclonal Antibody for Higher Affinity to FcRn and Half-Life Extension in Cynomolgus Monkeys

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**Purpose**
To evaluate the pharmacokinetics (PK) of anti-oncostatin M (OSM) IgG1 monoclonal antibodies (mAbs), CNTO 1119 and its Fc variant (CNTO 8212) after a single intravenous (IV) and subcutaneous (SC) administration in cynomolgus monkeys. CNTO 8212 incorporates the LS(Xtend) mutations (M428L/N434S) into the IgG1 scaffold and demonstrates higher affinity to human FcRn.

**Methods**
Twelve cynomolgus monkeys that were randomly assigned to four treatment groups (n = 3 per group) received a single intravenous (IV) or subcutaneous (SC) administration of CNTO 1119 or CNTO 8212 at 3 mg/kg. Blood samples were collected for up to 61 days post dose for the measurement of serum concentrations of CNTO 1119 and CNTO 8212. PK parameters were calculated using non-compartmental analysis in WinNonlin (version 5.2.1).

**Results**
The mean ± SD CL, Vz, and T1/2 were 2.84 ± 0.37 mL/day/kg, 61.46 ± 12.04 mL/kg, and 15.14 ± 2.93 days, respectively, after a single IV administration of CNTO 1119, and were 2.13 ± 0.69 mL/day/kg, 91.61 ± 22.10 mL/kg, and 30.33 ± 3.10 days, respectively, after a single IV administration of CNTO 8212. After IV administration, the mean CL of CNTO 8212 was 25% lower, and mean Vz was 49% higher compared with CNTO 1119. For both mAbs, the mean T1/2 after SC administration was similar to the mean T1/2 after IV administration. The estimated absolute bioavailability for CNTO 1119 and CNTO 8212 was 90% and 74%, respectively. Higher FcRn binding affinity of CNTO 8212 resulted in approximately 2-fold longer T1/2 compared to CNTO 1119.

**Conclusion**
The modification of the Fc portion of CNTO 1119 for higher FcRn binding affinity resulted in significantly lower systemic clearance and prolongation of the terminal half-life in cynomolgus monkeys.