The Impact of Anti-drug Antibodies on the Pharmacokinetics of a Human Therapeutic Monoclonal Antibody in Non-naïve Monkeys
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Purpose
Pharmacokinetics (PK) in non-human primates presents the most relevant information for pre-clinical prediction of human PK behaviors for human monoclonal antibodies (mAbs). However, human mAbs are, in part, immunologically foreign in non-human primates and may induce anti-drug antibody (ADA) responses uncharacteristic in incidence and impact of those induced in clinical subjects. Hence, naïve monkeys have been extensively used for preclinical PK studies for biologics therapeutics to minimize potential interference from pre-existing cross-reactive ADAs. If, instead, monkeys previously treated with an unrelated human mAb could be re-deployed for further testing with a different human mAb, then the ethical desire to reduce the number of non-human primates for medical research could be partially realized in this setting. To this end, we investigated the use of non-naïve monkeys in a PK study.

Methods
The PK of mAb A, a human therapeutic mAb was studied in a non-naive cynomolgus monkey colony that had previously received different human mAbs. Prior to the study start, one sample collected from each animal was screened for pre-existing cross-reactive anti-mAb A antibodies. The colony was then grouped according to ADA positive or negative results. The PK of mAb A was assessed following a single dose administered at 1, 3, 10 mg/kg intravenously or 3 mg/kg subcutaneously. Serum samples were collected prior to mAb A administration and up to 50 days post-treatment for the determination of mAb A concentrations and ADA status using validated immunoassays.

Results
High occurrence rate of post-dose ADA development and more pronounced impact on PK were observed in non-naïve animals with pre-existing cross-reactive anti-mAb A antibodies. Nonetheless, the PK of mAb A was successfully characterized in the monkeys without pre-existing cross-reactive anti-mAb A antibodies. The PK parameters calculated from these animals were similar to the ones from naïve monkeys.

Conclusion
The results indicate a potential approach for utilization of non-naïve monkeys to study the PK of human therapeutic mAbs.