A semi-mechanistic population pharmacokinetic model for trastuzumab emtansine (T-DM1) antibody-drug conjugate and total antibody in patients with metastatic breast cancer (mBC)

Franziska Schaedeli Stark1, Vaishali L. Chudasama2, Manish Gupta3, Jay Tibbitts4, Nicolas Frey5, Donald E. Mager2

1Translational Research Sciences, F. Hoffman-La Roche Ltd, Basel, Switzerland, 2Department of Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, NY, 3Pharmacokinetics and Pharmacodynamics, Genentech Inc., South San Francisco, CA

Introduction
Antibody-drug conjugates (ADC) are a class of targeted drugs with antibodies bearing covalently bound cytotoxic agents designed to target antigen-specific cells to enhance efficacy and reduce the toxicity associated with the cytotoxic agent alone.

Trastuzumab-emptansine (T-DM1) is an ADC with the antimicrotubule agent DM1 conjugated to trastuzumab through a stable thioether linker. The drug-antibody ratio (DAR), i.e. the number of DM1 molecules attached to trastuzumab, can range from 0 to 8 (average DAR = 3.5).

This modeling framework may be useful to further investigate the release kinetics of DM1, and to characterize the PK of other ADC systems.

The proposed pharmacokinetic model (Figure 2) is based on the semi-mechanistic model developed for T-DM1 kinetics in monkeys [1].

The number of individual T-DM1 DAR compartments was optimized, from originally eight to five, by removing one compartment at a time and comparing model-fitting criteria.

T-DM1 elimination was described as the net effect of transition from higher to lower DAR species (deconjugation), and elimination from each DAR compartment (antibody degradation). The slower transition kinetics from DAR1 to DAR0 (0.05d−1) is consistent with pre-clinical observations [1].

Methods
Patient population and study design
Pharmacokinetic data from a phase I dose escalation study (TDM180bg) in 52 patients [2], and from a phase II study (TDM208bg) in 111 patients with heavily pre-treated HER2+ metastatic breast cancer [3] were available for model building.

In the phase I study, dosages ranged from 1.2 to 2.9 mg/kg (1.2, 1.6, 2.0, 2.4, and 2.9 mg/kg) in the once-weekly arm (n=28) and from 0.3 to 4.8 mg/kg (0.3, 0.6, 1.2, 2.4, 3.6 and 4.8 mg/kg) in the Q2W regimen (n=24). In the phase II study, 3.6 mg/kg of T-DM1 was given Q3W. T-DM1 was administered via intravenous (IV) infusion.

Concentrations of T-DM1 and TT were measured throughout the treatment course, with a frequent sampling schedule in cycles 1 and 4, and pre- and post-infusion in all other cycles (see [23] for details).

Pharmacokinetic model
The proposed pharmacokinetic model (Figure 2) is based on the semi-mechanistic model developed for T-DM1 kinetics in monkeys [1].

The proposed model successfully described the time-courses of T-DM1 and TT concentrations simultaneously using transit compartments to emulate the deconjugation of higher DAR levels to low DAR levels and unconjugated trastuzumab, combined with a common elimination process for all DAR species.

This model supports the hypothesis that the extended terminal half-life of TT relative to T-DM1 is a consequence of the T-DM1 deconjugation process from higher to lower DAR species (Figure 5).

Model development and qualification were guided by goodness of fit plots and the precision of parameter estimates. A visual predictive check (VPC) was done for further model qualification.

Conclusions
Preclinical pharmacokinetic modeling efforts in monkeys were utilized as an initial approach to developing a clinical semi-mechanistic model.

The proposed model successfully described the time-courses of T-DM1 and TT concentrations simultaneously using transit compartments to emulate the deconjugation of higher DAR levels to low DAR levels and unconjugated trastuzumab, combined with a common elimination process for all DAR species.

This model supports the hypothesis that the extended terminal half-life of TT relative to T-DM1 is a consequence of the T-DM1 deconjugation process from higher to lower DAR species (Figure 5).

This modeling framework may be useful to further investigate the release kinetics of DM1, and to characterize the PK of other ADC systems.