Integrated multiple analytes and semi-mechanistic population pharmacokinetic model of tusamitamab ravtansine, a DM4 anti-CEACAM5 antibody-drug conjugate.

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Introduction:
Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is a cell-surface glycoprotein highly expressed in several tumor types [1]. Tusamitamab ravtansine (SAR408701) is an antibody-drug conjugate (ADC), combining a humanized monoclonal antibody (IgG1) targeting CEACAM5 and DM4, a potent cytotoxic payload [2]. SAR408701 is currently tested in clinical trials for the treatment of advanced solid tumors expressing CEACAM5. It is administered as a mixture of conjugated antibodies (species with different payload densities). The drug to antibody ratio (DAR) distribution is heterogeneous and ranges from 0 to 8, with an average DAR in the administered drug of 3.8. During clinical development, four entities were measured in plasma: conjugated antibody (SAR408701), naked antibody (NAB), DM4 and its methylated metabolite (MeDM4, both being active). Average DAR and proportions of individual DAR species were also assessed in a subset of patients.

Objectives:
Developing an integrated and semi-mechanistic population PK model that describes the time-course of all entities in plasma and DAR measurements, to support SAR408701 clinical development.

Methods:
Data from TED13751 study enrolling 254 patients were included in the analysis. A semi-mechanistic integrated model characterizing the kinetics of all entities was developed.

To characterize the PK of SAR408701, species from DAR1 to DAR8 were explicitly represented. Each DAR species was described by a two-compartment PK model and assumed to share with other DAR species the same distribution parameters (V_c, Q and V_p) and the same proteolytic elimination (CL_{ADC}). CL_{ADC} was thus assumed to be DAR independent. Conversion of higher DAR to lower DAR species was modelled as an irreversible first-order process in central compartment.

DM4 disposition was described by a one compartment PK model, with a first order elimination. Each DAR≥1 deconjugation process was assumed to contribute to DM4 formation by releasing one DM4 molecule. MeDM4 was modelled sequentially with a one compartment model and first order formation process directly from DM4 elimination.

All entities data were fitted simultaneously. The estimation of the nonlinear mixed effect model parameters was performed using SAEM algorithm of MONOLIX software (version 2020R1, Lixoft).

Results:
Model parameters were estimated with good precision. Diagnostic plots confirmed good agreement between predicted and observed data for all entities.

Regarding estimated parameters, SAR408701 and NAB distribution volumes were low (as expected for macromolecules) and close to physiological blood volume, with V_c estimated at 3.37 L and V_p at 2.54 L. Apparent DM4 clearance was estimated at 240 L/day with 36.5% IIV and apparent MeDM4 clearance was estimated at 0.256 L/day with 65.4% IIV. F_{NAB} was estimated at 7.1%, with 41.8% IIV.

Deconjugation rate values increased from 0.0565 /day for k_{dec1} to 0.938 /day for k_{dec6}, with higher DAR experiencing higher k_{dec} values. IIV was estimated at 20.2% for all k_{deci}.

Population estimates of SAR408701 and NAB proteolytic clearance were almost equal: SAR408701 proteolytic clearance was estimated at 0.392 L/d and NAB clearance at 0.408 L/day. Combining central deconjugation and proteolytic clearance, SAR408701 global clearance ranged from 0.582 L/d (for DAR1) to 3.55 L/d (for DAR8), with deconjugation clearance being the major elimination pathway for high DAR species.

Conclusions:
We developed a semi-mechanistic model that was able to describe the PK profiles of SAR408701 conjugated antibody and its derivatives (DM4, MeDM4 and NAB). Additionally, the model predicted the PK profiles of all the DAR species. This model, built with clinical data, integrated DAR measurements and specific NAB concentrations thanks to new bioanalytical methods [3,4,5,6]. It aimed to improve understanding of the complex PK behaviour

of DM4 conjugated ADCs. This model may be further used to explore sources of PK variabilities and define potential safety or efficacy PK drivers. As illustrated by many [7,8,9], this type of mechanistic framework is applicable to other ADCs formats, with different payloads or linker properties and can support any step of drug development.

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