**Investigation of Body-Size-Based Dosing Regimens for vcMMAE Antibody-Drug Conjugates (ADC)**

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**Objectives**: To compare inter-individual variability of ADC steady state exposure following various body-size-based dosing regimens.

**Methods**: A platform model for eight different ADCs [1] was used to derive individual exposure (acMMAE AUC) following administration of 11 body-size-based dosing regimens, specifically: flat; proportional to weight (WT), body surface area (BSA), lean body weight (LBW), or ideal body weight (IBW). In addition, dosing (flat or proportional to weight) in specific weight ranges were evaluated. Performance of dosing was characterized by the overall variability of exposure (CV%), and percent difference of the mean exposure in patients with low weight (<55 kg), high weight (>100 kg), and high BMI (>40 kg/m²) relative to the exposure of patients with average weight (60-90kg).

**Results**: Flat dosing and weight-proportional dosing both resulted in bodyweight dependent exposure and the highest variability. BSA-proportional dosing provided nearly optimal reduction in weight-related variability. Similar results can be obtained using weight-proportional dosing with bound of 60 and 90 kg, flat dosing with two different dose levels, and dosing based on LBW or IBW. Weight proportional dosing resulted in 41% higher AUC in patients with high BMI relative to patients with average weight. Capping the dose at 100 kg normalized the exposure in obese patients to some extent. With the BSA based dosing and with two flat dose levels, the exposure in obese patients was similar to patients of average weight.

**Conclusions**: Dosing in proportion to body weight does not help reduce the variability over flat dosing. BSA-proportional dosing traditionally used in oncology provides nearly optimal reduction in weight-related inter-patient variability of steady-state acMMAE exposure. Two dose levels for patient above or below 75kg also provides a simple alternative. Both BSA based dosing and 2 flat dose levels normalized the exposure in the obese patients. Both the complexity in dosing and the potential clinical benefit needs to be accounted for when selecting regimen.

Figure 1    Predicted Exposure (Steady-State acMMAE AUC) following 11 Body-Size-Based Dosing Regimens

**Reference:** mean exposure for subjects with weight between 60 and 90 kg.  

- **B1:** percent difference of mean exposure of subjects with weight <55 kg relative to the reference.  
- **B2:** percent difference of mean exposure of subjects with weight >100 kg relative to the reference.  
- **B3:** percent difference of mean exposure of subjects with BMI>40 kg/m² relative to the reference.  
- **CV:** AUC coefficient of variation.