**Evaluation of fixed-dose regimens of seribantumab in patients with solid tumors**

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**Table 1: Seribantumab clinical studies from which data for PK analysis was obtained**

<table>
<thead>
<tr>
<th>Study ID / Indication</th>
<th>N patients</th>
<th>race</th>
<th>age (years)</th>
<th>sex</th>
<th>weight (kg)</th>
<th>bilirubin (umol/L)</th>
<th>albumin (g/L)</th>
<th>BUN (mg/dL)</th>
<th>ALT (IU/L)</th>
<th>ALP (IU/L)</th>
<th>lactate dehydrogenase (R/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM121 , NSCLC, 3 g Q2W+fulvestrant</td>
<td>121</td>
<td>Male</td>
<td>60</td>
<td>12 (15-90)</td>
<td>75.5 (55-85)</td>
<td>39 (7-50)</td>
<td>4.1 (2.7-5.6)</td>
<td>1.2 (1-2)</td>
<td>111 (15-451)</td>
<td>95 (25-198)</td>
<td>422 (108-6077)</td>
</tr>
</tbody>
</table>

**Figure 1:** (A) HER3 molecular signaling (B) Seribantumab mechanism of action

**Methods**

- Pharmacokinetic data were available from a total of 499 adult patients with solid tumors across multiple indications in 7 clinical trials treated with seribantumab alone or in combination with other treatments (Table 1).
- Available plasma concentrations obtained from patients were analyzed by a non-linear mixed effects modeling approach in NONMEM software.
- PK was quantified with the following covariates: sex, race, age, weight, dose, study, and hepatic functions.
- Association between weight-based dosing PK and safety was modeled for grade 1+ and 3+ adverse events (AE) of interest for logistic regression.
- Using the logistic regression model obtained from the weight-based safety data and simulated fixed dosing PK, fixed dose rates of seribantumab were estimated.

**Study Information and baseline demographics**

<table>
<thead>
<tr>
<th>Baseline factors</th>
<th>Subgroups</th>
<th>Statistics</th>
<th>N (%), or median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>MM-121-61-100</td>
<td>50 (25)</td>
<td>50 (25)</td>
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<tr>
<td></td>
<td>MM-121-61-101</td>
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<td>MM-121-62-02-03</td>
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<td></td>
<td>MM-121-65-01-06</td>
<td>50 (25)</td>
<td>50 (25)</td>
</tr>
</tbody>
</table>

**Figure 2:** Impact of baseline factors on seribantumab clearance

**Pharmacokinetics of fixed-dose vs. weight-based doses**

- Fixed and weight-based doses showed similar variability (Figure 3 and Table 3).
- Steady-state C_{ss} were higher with 3 g than with 20 mg; these values were comparable to C_{ss} with 40 mg.
- Steady-state C_{ss} were equal to or higher for fixed dose than comparable weight-based dose.
- All doses tested had minimum concentrations (C_{min}) higher than the nonclinical target concentration of 100 mg/L.
- With higher weight, weight-based dose resulted in higher exposure (average concentration (C_{av} and maximum concentration (C_{max})) and fixed dose resulted in lower exposure (Figure 4).

**Figure 3:** Predicted pharmacokinetics by seribantumab dose regimens

**AE rates of fixed dose vs. weight-based dose**

- Compared to weight-based dosing, fixed dosing tended to increase AE rates in patients with lower weight and reduce AE rates in patients with higher weight (Figure 6).
- In most instances (all except fatigue G1+), the predicted AE rates in lower-weight patients (<70 kg) treated with fixed dosing are still lower than the predicted AE rates in higher-weight patients (>70 kg) treated with weight-based dosing.

**Figure 5:** Association between weight-based dosing PK and adverse events of interest for grade 1+ and grade 3+ with/without logistic regression

**Table 2: Distribution of baseline factors in the population PK dataset**

**Table 3: Predicted PK parameters by seribantumab dose regimens**

**Figure 4:** Relationship between average seribantumab concentrations and weight for alternative dose regimens

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