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Allometric Scaling of Preclinical Pharmacokinetic and Toxicokinetic Parameters to Predict Clinical Pharmacokinetics of BXQ-350 Saposin C Protein-Phosphatidylserine Nanovesicles.

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Background: Interspecies allometric scaling is used to extrapolate pharmacokinetics (PK) from preclinical data to human PK and dosing. Efficacy of BXQ-350, a novel Saposin C phosphatidylserine lipid nanovesicle therapy that targets tumor cell phospholipids, has been demonstrated in murine tumors, and pharmacokinetic and toxicokinetic (PK/TK) parameters have been derived in animal models. This study compares predictions based on allometric scaling of animal PK/TK data with FIH data for BXQ-350.

Methods: PK was assessed over 24 hr after IV BXQ-350 doses in mice (30 mg/m2) and rats/monkeys (60 mg/m2). TK was assessed at day 1 and 24 in rats/monkeys (24, 72 and 240 mg/m2 5 days/wk). Saposin C was analyzed by ELISA, and noncompartmental PK methods were used. Preclinical PK/TK was allometrically scaled to predict human PK and exposure (AUC) at 0.7-2.4 mg/kg therapeutic doses. Values were compared to actual FIH Phase 1 data (NCT02859857).

Results: Human clearance, terminal volume of distribution (Vz), half-life, and AUC (at 0.7 and 2.4 mg/kg doses) were within predicted ranges, though human ranges were somewhat narrower for clearance (63-114 vs 81-102 mL/kg/hr), Vz (135-650 vs 285-380 mL/kg), and half-life (0.8-4.5 vs 2.0-3.4 hr). Notably, actual vs predicted AUC hr*ng/mL at 0.7 and 2.4 mg/kg were not significantly different (7,100 vs 6,100 and 38,000 vs 36,000, respectively). Efficacy occurred in murine models at 4-16 mg/kg (AUC 7,400-29,600), aligned with human exposure at 0.7-2.4 mg/kg doses.

Conclusions: Allometric scaling of animal PK/TK data provided reasonable estimates of human PK and exposure (AUC) for BXQ-350 and can thus be expected to have good predictive utility for extrapolating drug dose and pharmacokinetic parameters.

Table. Predicted vs Actual PK/TK

	Predicted[1]	Actual[2]
Clearance, mL/kg/hr	**63-114**	**81-102**
Volume of distribution (Vz), mL/kg	**135-650**	**285-380**
Half-life, hrs	**0.8-4.5**	**2-3.4**
AUC at 0.7 mg/kg, hr*ng/mL	**6100**	**7100**

AUC at 2.4 mg/kg, hr*ng/mL	**36000**	**38000**
Murine Efficacy-associated AUC (~4-16 mg/kg), hr*ng/mL	**7,400-29,600**	**-**

[1]3-animal composite PK/TK models

[2]High/low geometric mean for 0.7-2.4 mg/kg Phase 1 cohorts

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