Interspecies Scaling and Estimation of First-in-Human Starting Dose of JNJ-42721458, a Modified Human Stresscopin Peptide Linked to a Polyethyleneglycol (PEG) Moiety

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Purpose
The purpose of this study was to predict apparent clearance (CL/F), apparent volume of distribution (Vd/F) and terminal half-life (T1/2) of JNJ-42721458, a pegylated variant of human stresscopin, and to project the first-in-human (FIH) starting dose. JNJ-42721458 is a potent and selective agonist of corticotropin-releasing factor type 2 (CRF2) receptor, and may have potential for the treatment of chronic heart failure (CHF).

Methods
Pharmacokinetic (PK) studies were conducted in mice, rats, dogs, and cynomolgus monkeys after intravenous (IV) and subcutaneous (SC) administration. The PK parameters CL/F and Vd/F derived from SC dosing were used for allometric scaling because the SC dosing dataset was more complete and consistent. JNJ-42721458 CL/F, Vd/F and T1/2 in humans were predicted using both multiple species and single species allometric scaling methods. Based on the estimated primary PK parameters, systemic exposure in human was predicted at single SC doses and multiple SC doses (up to 20 mg daily) for a 70 kg subject using a 2 compartment linear kinetics model with bioavailability (F) of 50% and absorption rate constant (ka) of 0.4 h⁻¹ determined from the monkey PK data. The FIH starting dose was estimated from the PK/PD data after SC administration of JNJ-42721458 in Mongrel dog heart failure (HF) model based on the MABEL approach.

Results
After SC administration of 5 or 15 μg/kg of JNJ-42721458 in monkeys, JNJ42721458 achieved a Cmax at 2-8 h. The AUCinf increased in a dose proportional fashion, and the F was 55-56%. JNJ-42721458 exhibited a T1/2 of 28.2 ± 26.2 h and 18.7 ± 4.7 h after SC administration of 5 or 15 μg/kg in monkeys, respectively. Based on multiple species allometric scaling, CL/F versus body weight was poorly correlated (r² = 0.66) with an allometric coefficient of 10.9 mL/h and an exponent of 0.69 with all species included in the analysis. The Vd/F versus body weight was well correlated (r² = 0.88) with an allometric coefficient of 245 mL and an exponent of 0.86. Based on multiple species allometric scaling, the predicted CL/F and Vd/F in a 70 kg human were 2.89 mL/h/kg and 132.73 mL/kg, respectively, and the estimated T1/2 in humans was 31.80 h. Based on the multiple species allometric scaling, CL/F is likely to be underestimated since the exponent is less than 0.75. Another allometric scaling method based on observed PK data from a single species (monkeys) was used to predict the PK of JNJ-42721458 in humans. Based on the single species scaling after SC administration of JNJ-42721458 in monkeys, the predicted CL/F, inter-compartmental clearance (CLD2/F), the apparent volume of the central compartment (V1/F) and the apparent volume of the peripheral compartment (V2/F) in humans were 8.93 ± 2.17 mL/h/kg, 0.98 ± 1.15 mL/h/kg, 173.23 ± 81.41 mL/kg and 46.87 ± 42.88 mL/kg, respectively. The estimated T1/2 in human based on the single species approach was 44.66 ± 9.79 h. In the dog HF study, the minimum effective plasma concentration of JNJ-42721458 was identified as 40 ng/mL. Based on single species allometric scaling from monkeys, a mean JNJ-42721458 peak plasma concentration of 40 ng/mL was projected to be achieved transiently following a single SC dose of 0.7 mg in a 70 kg human. Thus, a starting dose 0.1 mg was anticipated to have a minimal effect on cardiac function in humans. Following multiple daily dosing with 10 mg JNJ42721458, the pre-dose plasma concentration of JNJ42721458 at Day 10 for the majority of subjects was similar to or greater than the steady-state plasma concentration associated with pharmacological activity observed in the dog HF study. Therefore, a potential clinical dose in patients with CHF may be 10 mg/day. In the FIH study of JNJ-42721458, the mean CL/F, mean Vz/F and mean T1/2 values ranged from 0.05 to 0.23 L/hr/kg, 1.95 to 13 L/kg, and 16.80 to 68.32 h, respectively, after single SC doses of 1 mg to 160 mg of JNJ-42721458.

Conclusion
The predicted human pharmacokinetics of JNJ-42721458 based on the single species approach was used to design and select the doses for the first-in-human study. In the FIH study of JNJ-42721458, the observed CL/F was higher and Vz/F was larger compared to the values predicted from the two allometric scaling approaches, resulting in considerably lower-than-predicted drug exposure in healthy human subjects.