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A Bioequivalence Study for Hercules, a Biosimilar Trastuzumab Candidate in Development

Introduction: Trastuzumab, marketed as Herceptin®, is a humanized monoclonal antibody which binds HER2-oncoprotein and is effective against breast cancer over expressing HER2. We here report the results of a Phase 1 study designed to investigate bioequivalence between Hercules and Herceptin®. The assessment of bio similarity included not only pharmacokinetic (PK) but also pharmacodynamic (PD) equivalence.

Subjects and Methods: A single centre, single dose, randomized, double-blind, crossover study was conducted in 22 healthy males; 19 completed both 3-month periods separated by 2-8 week wash-out. On each period the volunteers received an 8mg/kg trastuzumab intravenous infusion over 90 minutes (Hercules or Herceptin®). The main objective was PK bioequivalence (serum ELISA assay using anti-idiotypic antibody). For PD comparaison, e*x-vivo* serum antiproliferative activity on a breast cancer cell line (SKBR3) over expressing HER2 was assessed, as well as numerous *ex-vivo* and *in-vitro* immunomodulation markers. ANOVA was applied to PK and PD results. Safety included local and systemic tolerance, laboratory tests, echocardiography and immunogenicity.

Results: Time concentration curves and PK parameters were very close:

Parameter	Units	Hercules GeoMean (GeoCV%)	Herceptin® GeoMean (GeoCV%)	Point Estimate (90% CI)
C_{max} normalized[a]	µg/mL	165 (15.7)	178 (15.6)	0.922 (0.876; 0.970)
$AUC_{0-\infty}$ normalized[a]	µg.h/mL	45486 (22.7)	48350 (28.5)	0.937 (0.887; 0.989)
T_{max} (median [range])	h	1.5 (1.4-9.0)	1.5 (1.3-9.0)	-
$T_{1/2}$ (day)	Day	6.94 (22.6)	7.02 (26.3)	0.988 (0.943; 1.035)
CL[b]	L/day	0.296 (22.7)	0.278 (28.5)	1.068 (1.011; 1.127)

[a] Normalized to 8.0 mg/kg dose; [b] Clearance normalized to 70 kg body weight; GeoCV% = Geometric Coefficient of Variation

Antiproliferative activity time curves were super imposable between both drugs, and concentration-effect relationships were similar (with 95%CI of ±4%). Immunomodulation markers were essentially comparable. Satisfactory and similar safety profiles were observed without elicitation of immunogenicity or changes in cardiac left ventricular ejection fraction.

Conclusion: These results confirm pharmacokinetic bioequivalence for Hercules vs. Herceptin®, but also demonstrate comparable antiproliferative activity, immunomodulation and safety profiles in healthy volunteers, providing strong support for bio similarity.