ONLINE RESOURCES

A randomised trial comparing the pharmacokinetics and safety of the biosimilar CT-P6 with reference trastuzumab

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Journal: *Cancer and Chemotherapy Pharmacology*

Online Resource Table A1: Inclusion criteria

Inclusion criteria
Healthy male subject between 18 and 55 years of age, both inclusive. ('Healthy' was defined as no clinically relevant abnormalities identified by a detailed medical history, physical examination including blood pressure, heart rate measurement, respiratory rate and body temperature, 12-lead electrocardiogram, and clinical laboratory tests)
Body mass index between 18.0 and 29.9 kg m^{-2} and a body weight between 55 and 99.9 kg, both inclusive
Able to understand and comply with protocol requirements, instructions, and restrictions
Voluntarily agreed to participate in this study and provided written informed consent prior to any of the screening procedures being performed
Men of childbearing potential were obliged to agree to use a highly effective method of contraception for 7 months after the dose of assigned treatment. A man was considered to be of childbearing potential if, in the opinion of the investigator, he was biologically capable of having children and was sexually active

Online Resource Table A2: Exclusion criteria

Exclusion criteria
Female
Medical condition of disease including one or more of the following: • History and/or presence of clinically significant atopic allergy (e.g. asthma [including childhood], urticaria, angio-edema, eczematous dermatitis), hypersensitivity or known or suspected clinically relevant drug hypersensitivity to any components of the test and reference investigational medicinal product formulations or similar drugs • History of and/or current cardiovascular, gastrointestinal (with the exception of appendectomy and/or cholecystectomy), renal, hepatic, haematological (including pancytopenia, aplastic anaemia, or blood dyscrasia), metabolic (including known diabetes mellitus), neurological or pulmonary disease including current medical or psychiatric condition or laboratory abnormality considered as clinically significant by the investigator • Other concomitant active malignancy or history of malignancy except treated basal or squamous cell carcinoma of the skin • Infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus, or had a positive result to the screening test for those infections • Any recent infection requiring a course of systemic anti-infectives that were completed ≤14 days before randomisation (with the exception of uncomplicated urinary tract infection) • History of congestive heart failure, New York Heart Association class ≥II, or serious cardiac arrhythmia requiring treatment • A left ventricular ejection fraction value outside the normal range (defined as ≥55% at baseline), as measured by echocardiogram within 3 weeks prior to randomisation
Previous exposure to a monoclonal antibody or current use of other biologics
Underwent surgical intervention or an operation within 4 weeks before administration of the investigational medicinal product, or planned to have a surgical procedure during the study
Used prescription or non-prescription drugs and dietary supplements within 7 days or five half-lives (whichever is longer) prior to the first dose of investigational medicinal product. Herbal supplements had to be discontinued 28 days prior to the first dose of investigational medicinal product

Received treatment with an investigational drug or participated in another study within 30 days or five half-lives (whichever is longer) preceding the first dose of investigational medicinal product
Plans to father a child or donate sperm within a 7-month period following investigational medicinal product administration
Shows reasonable evidence (in the opinion of the investigator) of drug abuse, including alcohol, as indicated by a positive urinary drug test result at screening and/or baseline (day –1)
Moderate or heavy smoker, i.e. consumes more than 10 cigarettes or equivalent per day and/or is unable to refrain from smoking during in-house stays
Donated or lost ≥450 ml of blood within 8 weeks prior to the administration of investigational medicinal product
Subject is not likely to complete the study for whatever reason, in the opinion of the investigator
Subject is vulnerable (e.g. employees of the study centre or any other individuals involved with the conduct of the study, or immediate family members of such individuals; persons kept in prison; or other persons institutionalised by law enforcement)

Online Resource Table A3. Primary PK data in Japanese sub-population (PK population)

PK parameter	Geometric LS means[a]		% Ratio[a] (CT-P6/ reference trastuzumab)	90% CI[a]
	CT-P6 (n = 12)	Reference trastuzumab (n = 12)		
AUC_{inf} (h µg ml^{-1})	18667.43	17606.20	106.03	95.47, 117.75
AUC_{last} (h µg ml^{-1})	17422.37	16272.02	107.07	95.58, 119.94
C_{max} (µg ml^{-1})	118.83	122.67	96.88	87.06, 107.79

[a]The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric LS means (CT-P6/Reference trastuzumab) and corresponding 90% CIs

Note: An analysis of covariance was performed with the natural log-transformed PK data as the dependent variable, race (Japanese and all subjects) as a fixed effect

AUC_{inf} area under the serum concentration–time curve from time 0 to infinity, *AUC_{last}* area under the serum concentration–time curve from time 0 to the last quantifiable concentration, *CI* confidence interval, *C_{max}* observed maximum measured serum concentration, *LS* least squares, *PK* pharmacokinetic