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APPLICATION NUMBER:

761091Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	761091
Supporting document/s:	1
Applicant's letter date:	May 30, 2017
CDER stamp date:	May 30, 2017
Product:	CT-P6 (proposed biosimilar to trastuzumab)
Indication:	HER2-overexpressing breast cancer HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
Applicant:	Celltrion
Review Division:	Division of Hematology Oncology Toxicology
	(for Division of Oncology Products 1)
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1 Executive Summary

1.1 Introduction

Celltrion is requesting market approval for CT-P6, a proposed biosimilar product to US-licensed trastuzumab for all indications currently included in the Herceptin label. Herceptin (trastuzumab) was approved in the US in 1998 (BLA 103792) and the current label includes indications of HER2-overexpressing breast cancer, and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Trastuzumab is a recombinant humanized monoclonal IgG1 antibody that binds to the extracellular domain of the HER2 protein, preventing activation of its intracellular tyrosine kinase. CT-P6 has the identical amino acid sequence to the US-licensed Herceptin drug substance, trastuzumab. In vitro pharmacology studies comparing HER2 binding affinity of CT-P6 and US-licensed Herceptin have been conducted and show that CT-P6 is similar to trastuzumab in these studies. In addition, repeat-dose toxicity and toxicokinetic (TK) assessment did not reveal toxic responses with either product; there were no apparent differences in systemic exposures. See below a summary of nonclinical findings.

1.2 Brief Discussion of Nonclinical Findings

Based on summary information presented in Module 2 of the BLA, CT-P6 and US-licensed Herceptin had similar profiles on HER2 binding affinity, FcγRIIIa/RIIIb/RIIa/RIIb/RI binding affinity, FcRn binding affinity, C1q binding affinity, cell-based binding affinity, antibody-dependent cellular cytotoxicity (ADCC), and anti-proliferation activity. However, for a conclusion on physicochemical similarity of CT-P6 and the reference product (which includes similarity in functional assays), see the review by the quality team.

A 4-week study with weekly administration of CT-P6 and US-licensed Herceptin were conducted in monkeys to compare the toxicity profiles and the toxicokinetic (TK) profiles of CT-P6 and US-licensed Herceptin. Monkey has been identified as a pharmacologically relevant species. CT-P6 or US-licensed Herceptin was administered to Cynomolgus monkeys at doses of 0 (Control), 14 and 42 mg/kg/week on Days 1, 8, 15 and 22. No apparent toxic response was observed in monkeys treated with CT-P6 or US licensed Herceptin at doses up to 42 mg/kg, which was consistent with published data for US-licensed Herceptin. TK evaluation showed that animals were continuously exposed to CT-P6 or US-licensed Herceptin for the duration of the study. Following repeated administration of CT-P6 and US licensed Herceptin at 14 and 42 mg/kg, similar systemic exposures were observed for both products. Accumulation of CT-P6 drug product and US-licensed Herceptin in serum was observed with repeated dosing over the 4-week dosing period. No immunogenic (anti-drug antibodies) responses to CT-P6 or US-licensed Herceptin were detected in samples taken from treated animals.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective CT-P6 may be approved for the proposed indication.

1.3.2 Additional Non Clinical Recommendations

Additional nonclinical studies are not needed at this time.

1.3.3 Labeling

The nonclinical sections of the label will be comparable to the label of the reference product trastuzumab.

2 Drug Information

2.1 Drug

CAS Registry Number: 180288-69-1
Trade name: Herzuma
Code Name: CT-P6
Chemical Name: a humanized monoclonal IgG1 antibody against HER2
Molecular Formula/Molecular Weight:
Amino Acid Sequence of CT-P6 (copied from the Applicant's submission)

Heavy Chain

1	EVQLVESGGG LVQPGGSLRL S**C**AASGFNIK DTYIHWVRQA PGKGLEWVAR
51	IYPTNGYTRY ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYY**C**SRWG
101	GDGFYAMDYW GQGTLVTVSS *ASTKGPSVFP LAPSSKSTSG GTAALG**C**LVK*
151	*DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT*
201	*YI**C**NVNHKPS NTKVDKKVEP KS**C**DKTHT**C**P P**C**PAPELLGG PSVFLFPPKP*
251	*KDTLMISRTP EVT**C**VVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQY**N**[1]*
301	*STYRVVSVLT VLHQDWLNGK EYK**C**KVSNKA LPAPIEKTIS KAKGQPREPQ*
351	*VYTLPPSREE MTKNQVSLT**C** LVKGFYPSDI AVEWESNGQP ENNYKTTPPV*
401	*LDSDGSFFLY SKLTVDKSRW QQGNVFS**C**SV MHEALHNHYT QKSLSLSPGK*[2]

Light Chain

1	DIQMTQSPSS LSASVGDRVT ITC**R**ASQDVN TAVAWYQQKP GKAPKLLIYS
51	ASFLYSGVPS RFSGSRSGTD FTLTISSLQP EDFATYY**C**QQ HYTTPPTFGQ
101	GTKVEIKRTV *AAPSVFIFPP SDEQLKSGTA SVV**C**LLNNFY PREAKVQWKV*
151	*DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYA**C**EVTHQG*
201	*LSSPVTKSFN RGE**C***

[1]Glycosylation site is Asn300 of the heavy chain.
[2] C-terminal lysine is nearly 100 % cleaved from the heavy chain.
Note: The amino acid sequences were defined according to both the patented protein and gene structure. The sequences have been confirmed for CT-P6 and Herceptin® by CELLTRION using MS/MS analysis. The letters shown denote the one-letter code for 20 common amino acids. Variable regions for both heavy and light chains are indicated in normal font; italicized letters designate the constant regions for both chains. Cysteine residues are in bold font; all cysteine residues are involved in disulfide bonds.

Heavy chain-$C_{2192}H_{3387}N_{583}O_{671}S_{16}$
Light chain-$C_{1032}H_{1603}N_{277}O_{335}S_{6}$

Molecular weight: 145,165 g/mol (~145 kDa)
Structure or Biochemical Description: a humanized monoclonal IgG1 antibody
Pharmacologic Class: HER2/neu receptor antagonist
Relevant INDs, NDAs, BLAs and DMFs: IND 119650, BLA 103792 (Herceptin)

2.2 Drug Formulation: lyophilized powder containing 440 mg of CT-P6 drug substance

Composition of the CT-P6 Drug Product

Ingredient	Quantity/Vial	Function
CT-P6	440 mg	Active ingredient
α,α-Trehalose, Dihydrate	(b) (4) mg	(b) (4)
L-Histidine HCl	mg	
L-Histidine	mg	
Polysorbate 20	mg	

The CT-P6 440mg drug product formulation differs from that of US-licensed Herceptin with respect to the quantity of trehalose. See the detail comparison in the table below (copied from the Applicant's submission)
Formulations for CT-P6 Drug Product and US-licensed Herceptin

Ingredient	Nominal Quantity per Vial	
	CT-P6 Drug Product	US-licensed Herceptin® Drug Product
Active substance	440 mg CT-P6	440 mg Herceptin®
(b) (4)	(b) (4) mg α,α-Trehalose, dihydrate	(b) (4) mg α,α-Trehalose, dihydrate
	(b) (4) mg L-Histidine HCl	(b) (4) mg L-Histidine HCl
	(b) (4) mg L-Histidine	(b) (4) mg L-Histidine
	(b) (4) mg Polysorbate 20	(b) (4) mg Polysorbate 20

2.4 Comments on Novel Excipients: **N/A**

2.5 Comments on Impurities/Degradants of Concern:
There are no outstanding issues.

Studies for qualification of a potential impurity (a (b) (4) analog) were conducted and reviewed:

- A general toxicology study (results presented within this review); and
- A GLP-compliant bacterial reverse mutation (Ames) assay in test strains TA98, TA100, TA1535, TA1537 and WP2uvrA at concentrations up to 5000 µg/plate in the presence and absence of metabolic activation system: negative mutagenic results (data reviewed but not presented).

2.6 Proposed Clinical Population and Dosing Regimen

Same as for the reference product, Herceptin.

APPEARS THIS WAY ON ORIGINAL

3 Studies Submitted

Studies Reviewed

	Title	Study no.
1	CT-P6: Comparative Toxicity Study by Weekly Intravenous (Bolus) Administration to Cynomolgus Monkeys for 4 Weeks	ZIP0014
2	Single Dose Intravenous Administration Toxicity Study of (b) (4) in Sprague-Dawley Rats *(impurity qualification)*	GT13-00497
3	Bacterial Reverse Mutation test of (b) (4) *(impurity qualification)*	GT13-00498

Studies submitted, but not reviewed

Pharmacokinetics

	Title	Study no.
1	Validation Report for the Determination of CT-P6 in Cynomolgus Monkey Serum by Quantitative ELISA	2290/0038a
2	Validation Report for the Determination of Trastuzumab in Cynomolgus Monkey Serum by Quantitative ELISA	2290/0038b
3	Immunoassay Validation Report for the Detection of Anti-CT-P6 Antibodies in Cynomolgus Monkey Serum by an Electrochemiluminescent Assay (ECLA)	2290/0038c
4	Immunoassay Validation Report for the Detection of Anti-Trastuzumab Antibodies in Cynomolgus Monkey Serum by an Electrochemiluminescent Assay (ECLA)	2290/0038d

4 Pharmacology

The pharmacology study results were summarized in the non-clinical overview section (Module 2 Section 2.4) and detailed in the Quality section (Module 3, Section 3.2.R) of the BLA. Data in support of the physicochemical similarity assessment have been reviewed by the quality team.

Based on summary information presented in Module 2, CT-P6 and US-licensed Herceptin have similar profiles on HER2 binding affinity, FcγRIIIa/RIIIb/RIIa/RIIb/RI binding affinity, FcRn binding affinity, C1q binding affinity, cell-based binding affinity, antibody-dependent cellular cytotoxicity (ADCC), and anti-proliferation activity. For a conclusion on physicochemical (analytical and functional) similarity between CT-P6 and the reference product, see the review by the quality team.

6 General Toxicology

Study title: CT-P6: Comparative Toxicity Study by Weekly Intravenous (Bolus) Administration to Cynomolgus Monkeys for 4 Weeks

Key Study Findings

- Weekly administration of CT-P6 or US-licensed Herceptin for 4 weeks resulted in no apparent adverse effects in monkeys
- There were no differences in systemic exposure to CT-P6 and US-licensed Herceptin at 14 mg/kg and 42 mg/kg.

Study no.:	ZIP0014
Study report location:	Module 4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 11, 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CT-P6 Batch # 13A3C003 Purity: 100%

Methods

Doses:	14, 42 mg/kg
Frequency of dosing:	Weekly x 4 (on Days 1, 8, 15 and 22)
Route of administration:	intravenous (bolus) injections
Dose volume:	2 mL/kg
Formulation/Vehicle:	sterile water for injection
Species/Strain:	Cynomolgus monkey (Macaca fascicularis).
Number/Sex/Group:	3/sex/group
Age:	29 to 32 months
Weight:	Male: 1.99 kg to 2.76 kg; Female: 2.27 kg to 2.79 kg
Satellite groups:	None
Unique study design:	none
Deviation from study protocol:	none

The following table shows the details on experimental design (copied from the submission)

Group	Treatment	Dose (mg/kg/occasion)	Number of animals Male	Number of animals Female	Animal numbers Male	Animal numbers Female
1	Control	0	3	3	651, 653, 655	652, 654, 656
2	CT-P6	14	3	3	657, 659, 661	658, 660, 662
3	CT-P6	42	3	3	663, 665, 667	664, 666, 668
4	US Herceptin®	14	3	3	669, 671, 673	670, 672, 674
5	US Herceptin®	42	3	3	675, 677, 679	676, 678, 680

Observations and times:

Clinical signs: At least twice daily for evidence of ill-health or reaction to treatment. Detailed observations were recorded on dosing days at the following times in relation to dose administration: During and immediately after dosing, 1 to 2 hours after dosing, and as late as possible in the working day. Weekly for detailed physical examination

Body weights: in the week before treatment (Week -1), on the day that treatment commenced, weekly throughout the treatment period and before necropsy.

Food consumption: not performed

Ophthalmoscopy: once pretreatment and Week 4

EKG and blood pressure: once pretreatment, and in week1 and 4 at 1.5 and 4 hours after dosing

Clinical chemistry: once pretreatment, on Day 3, and once in week 4

Hematology: once pretreatment, on Day 3, and once in week 4

Coagulation: once pretreatment, on Day 3, and once in week 4

Urinalysis: once pretreatment, and once in week 4

Gross pathology: all animals at necropsy,

Organs weigh: all animals at necropsy, on study day 28

Histopathology: all animals at necropsy, on study day 28

Adequate Battery: yes (x), no ( )
Peer review: yes (x), no ( )

Toxicokinetics: Blood samples were collected from all animals. The sampling schedule was as follows

Occasion	Time of sampling (hours after dosing)	Animals
Day 1 and 22	Predose, 0.5, 1, 2, 6, 12, 24, 72, 120 and 168	All animals

Other assessments:
Anti-drug antibody): Pretreatment and termination
Injection site observations: on each day of treatment (prior to dosing), the day after each dose and daily thereafter
Respiration rate: once pretreatment, and once in weeks 1 and 4 at 1.5 and 4 hours after dosing
Body temperature: once pretreatment, and once in weeks 2 and 4 at 1.5 hours after dosing
Immunophenotyping of peripheral blood leucocytes: once pretreatment, and once in weeks 1 and 4 at 24 and 72 hours after dosing

Results
Mortality: none
Clinical Signs: unremarkable
Body Weights: unremarkable
Ophthalmoscopy: unremarkable
ECG: unremarkable
Clinical Chemistry: unremarkable
Hematology: unremarkable
Coagulation: unremarkable
Urinalysis: unremarkable
Gross Pathology: unremarkable
Organ Weights: unremarkable
Histopathology: unremarkable
Toxicokinetics: See table below

Summary of Toxicokinetic Parameters in monkeys

Dose level Study day	(mg/kg/dose)	Gender	C_{max} (µg/mL)	Dose normalized C_{max}	AUC_{0-168h} (µg.h/mL)	Dose Normalized AUC_{0-168h}
CT-P6						
1	14	M	344	25	27900	1992
		F	342	24	29000	2071
	42	M	1167	28	96000	2286
		F	1093	26	93800	2233
22	14	M	557	51	60500	4321
		F	619	64	62200	4443
	42	M	1896	45	213000	5071
		F	1922	51	200000	4762
Herceptin						
1	14	M	358	26	28500	2036
		F	426	30	37400	2671
	42	M	1140	27	100000	2381
		F	1194	28	98500	2345
22	14	M	587	42	59100	4221
		F	811	58	80200	5729
	42	M	2218	53	207000	4929
		F	1952	47	193000	4595

Conclusions on TK:

- The systemic exposure to CT-P6 and Herceptin (trastuzumab) in monkeys was generally similar at both 14 mg/kg and 42 mg/kg dose levels;
- On day 1 and Day 42, C_{max} and AUC increased approximately proportionately with increasing dose over the dose range 14 to 42 mg/kg;
- No apparent gender differences in plasma exposures;
- C_{max} and AUC were higher (≈ 2x) on day 22 comparing to the values on day 1, indicating some accumulation with repeat dosing.

Other assessments:

Anti-drug antibody: All animals were confirmed as being negative for the presence of anti-CT-P6 or anti-US Herceptin antibodies.
Injection site observations: unremarkable
Respiration rate: unremarkable
Body temperature: unremarkable
Immunophenotyping of peripheral blood leucocytes: unremarkable

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Qualification of a potential impurity, a (b) (4) analog.

Study title: Single Dose Intravenous Administration Toxicity Study of (b) (4) in Sprague-Dawley Rats

Study no.: GT13-00497
Conducting laboratory and location: (b) (4)

Date of study initiation:	September 12, 2013
GLP compliance:	no
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4) Lot # MD060891309 Purity: 98%

Key Study Findings

- No adverse effect was observed in animals at dose up to 1000 mg/kg.

Methods

Doses:	250, 500, 1000 mg/kg* * No clinical symptoms appeared at 250 mg/kg in the preliminary tests, therefore; the maximal dose of 1000 mg/kg was selected as the HD (ICH M3, referred by the Applicant)
Frequency of dosing:	Single dose
Route of administration:	intravenous (bolus) injections
Dose volume:	5 mL/kg
Formulation/Vehicle:	sterile water for injection
Species/Strain:	Sprague-Dawley(SD) rats
Number/Sex/Group:	5/sex/group
Age:	8 weeks at the initiation of the administration
Weight:	Male: 201.06 – 215.66 g Female: 175.93 – 185.89 g
Satellite groups:	None
Unique study design:	none
Deviation from study protocol:	none

The following table shows the details of the experimental design (copied from the submission)

Group	Sex	Number of animals	Animal No.	Injection volume (㎖/kg)	Dose (mg/kg)
G1	Male	5	G1-1~G1-5	5	0
	Female	5	G1-21~G1-25		
G2	Male	5	G2-6~G2-10	5	250
	Female	5	G2-26~G1-30		
G3	Male	5	G3-11~G3-15	5	500
	Female	5	G3-31~G3-35		
G4	Male	5	G4-16~G4-20	5	1,000
	Female	5	G4-36~G4-40		

G1: Vehicle control group, G2~G4: Test group

Observations and times:

Clinical signs: continuously during the first half-hour, after that one hour intervals until six hours after injection, starting 2nd day, once every day up to 14 days
Body weights: on the days of acquisition and grouping, prior to administration, and on 1, 7 and 14 days after the administration
Food consumption: not performed
Ophthalmoscopy: not performed
EKG/ blood pressure: not performed
Clinical chemistry: not performed
Hematology: not performed
Coagulation: not performed
Urinalysis: not performed
Gross pathology: all animals On Day 14 after the administration
Organs weigh: not performed
Histopathology: not performed
Toxicokinetics: not performed

Results

Mortality: none
Clinical Signs: unremarkable
Body Weights: unremarkable
Gross Pathology: unremarkable

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/s/

WEI CHEN
02/20/2018

HALEH SABER
02/20/2018