CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761073Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date: April 16, 2018

From: Tiffany K. Ricks, PhD

Pharmacology/Toxicology Team Leader (acting)

Division of Hematology Oncology Toxicology (DHOT)

Office of Hematology and Oncology Products (OHOP)

To: File for 351 (k) BLA 761073 for Kanjinti (ABP 980)

Re: Approvability for Pharmacology and Toxicology

The nonclinical data submitted to BLA 761073 were reviewed by Kimberly Ringgold, PhD. The nonclinical findings are summarized in the "Executive Summary" section of the pharmacology/toxicology BLA review. Based on the determination of similarity of Kanjinti to US-Herceptin, the nonclinical sections of the labeling should be comparable to the labeling for US-Herceptin.

I concur with Dr. Ringgold's conclusion that the submitted pharmacology and toxicology data were adequate to demonstrate similarity in the safety and PK profiles of ABP 980 to EU-Herceptin in rats and cynomolgus monkeys. The applicant submitted an appropriate scientific bridge consisting of comparative analytic data of ABP 980, EU-Herceptin, and US-Herceptin to justify the relevance of data from animal studies using EU-Herceptin to determine the biosimilarity of ABP 980 to US-Herceptin. I concur that the pharmacology and toxicology data support approval of BLA 761073 for Kanjinti from the pharmacology/toxicology perspective.

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/s/

TIFFANY RICKS
04/16/2018

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	761073
Supporting document/s:	0000
Applicant's letter date:	7/28/2017
CDER stamp date:	5/28/2017
Product:	Kanjinti (ABP980)
Indication:	Treatment of HER2-overexpressing breast cancer or metastatic gastric or gastroesophageal junction adenocarcinoma
Applicant:	Amgen Thousand Oaks, CA United States
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 1)
Reviewers:	Kimberly Ringgold, PhD
Team Lead:	Tiffany Ricks, PhD (acting)
Division Director:	John Leighton, PhD, DABT (DHOT) Julia Beaver, MD (DOP1)
Project Manager:	Amy Tilley

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1 Executive Summary

1.1 Introduction

Amgen Inc. (the Applicant) has submitted a Biologics Licensing Application (BLA) 761073 for Kanjinti (ABP 980) for the treatment of patients with HER2-overexpressing breast cancer, metastatic gastric, or gastroesophageal junction adenocarcinoma. Kanjinti is a humanized recombinant IgG1 monoclonal antibody against human epidermal growth factor receptor 2 protein (HER2) that has been developed as a proposed biosimilar to the reference product, US-Herceptin® (trastuzumab). The recommended dose and indication are based on the US-Herceptin® approved label. The applicant submitted nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies in support of this BLA.

1.2 Brief Discussion of Nonclinical Findings

The anti-tumor activity of ABP 980 and EU-Herceptin® was compared in two xenograft tumor models overexpressing HER2, BT-474 (metastatic human breast cancer cells) and NCI-N87 (human gastric cancer cells). ABP 980 inhibited tumor growth in both breast cancer and gastric cancer cells in a similar manner to EU-Herceptin® as demonstrated by tumor volume and size.

The pharmacokinetics of ABP 980 and EU-Herceptin® were evaluated in cynomolgus monkeys on day 1 and week 4 (25 mg/kg) in the multiple-dose IV toxicity study. Plasma exposures in monkeys were similar after EU-Herceptin® and ABP 980 injections on day 1 and week 4. Therefore, the PK of ABP 980 was determined to be similar to EU-Herceptin®.

A comparative toxicology study was conducted in monkeys with ABP 980 and EU-Herceptin® administered at 25 mg/kg given IV twice weekly for 4 weeks. Toxicity findings were similar after EU-Herceptin® or ABP 980 injections. No toxicological findings were observed in a 14-day toxicity study performed in rats after ABP 980 or EU-Herceptin® administration. These results were expected since trastuzumab is not pharmacologically active in rats.

Tissue cross-reactivity studies were performed in human mammary neoplastic tissues overexpressing HER2 and normal human tissues and blood smears. ABP 980 staining was consistent with that of EU-Herceptin® stained tissues.

Because the applicant used a non-US-licensed comparator (EU-Herceptin®) in nonclinical studies, the applicant provided a bridge to demonstrate the similarity between EU-Herceptin® and US-Herceptin®. Results from comparative analytic data provided the necessary scientific bridge between ABP 980, EU-Herceptin®, and US-Herceptin® to justify the relevance of data from animal studies conducted using EU-Herceptin® to demonstrate biosimilarity of ABP 980 to US-Herceptin®. From the nonclinical perspective, the data from animal studies were adequate to demonstrate

similarity in the safety and PK profiles of ABP-980 and EU-Herceptin® in rats and cynomolgus monkeys. No residual uncertainties were identified by the pharmacology and toxicology discipline.

1.3 Recommendations

1.3.1 Approvability

Based on the nonclinical pharmacology and toxicology data submitted in this BLA, the application is recommended for approval from the perspective of the pharmacology and toxicology discipline.

1.3.2 Additional Non-Clinical Recommendations

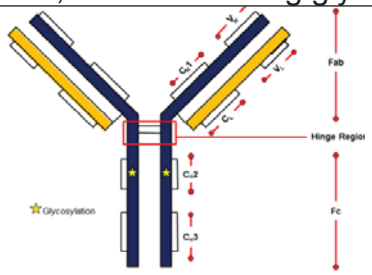
None

1.3.3 Labeling Recommendations

Changes to most nonclinical sections in the label were made based on the recent updates to the US-Herceptin® approved label where changes complied with the final rule on PLLR content and formatting (79 FR 72064) and recent practices.

2 Drug Information

2.1 Drug: KANJINTI™

Name:	Trastuzumab
Code Name:	ABP 980
Other names:	FTMB
CAS Registry #:	1446410-98-5
Chemical Name:	Anti-HER2 monoclonal antibody
Molecular Formula:	N/A
Molecular Weight:	145,171 Da for de-glycosylated molecule 148,222 Da including glycosylation
Structure	 *(excerpted from Applicant's submission)*
Pharmacologic Class:	HER2/neu receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs: IND 115424

2.3 Drug Formulation

KANJINTI is supplied in a vial as a sterile, white to pale yellow, preservative free lyophilized powder for reconstitution. Upon reconstitution, the product is intended for dilution in saline (0.9% sodium chloride) for intravenous administration. ABP 980 is formulated in 4.2 mM L-histidine, 51 mM α,α-trehalose, 0.008% (w/v) polysorbate 20 at pH 6 (b) (4)

Table 1: Composition of KANJINTI Drug Product

Component	Grade	Function	Recoverable Content per 420 mg Vial[a]	Concentration[b]
ABP 980	In house[c]	Active ingredient	420 mg	21 mg/mL
L-Histidine	USP, PhEur, JP	(b) (4)	6.1 mg	0.30 mg/mL
L-Histidine hydrochloride monohydrate	PhEur, JP		9.5 mg	0.47 mg/mL
α,α-Trehalose dihydrate	USP/NF, PhEur, JP		382 mg	19 mg/mL
Polysorbate 20	USP/NF, PhEur, JPE		1.7 mg	0.08 mg/mL

(excerpted from Applicant's submission)

2.4 Comments on Novel Excipients

NA

2.5 Comments on Impurities/Degradants of Concern

NA

2.6 Proposed Clinical Population and Dosing Regimen

KANJINTI is indicated for:

- the treatment of HER2 overexpressing breast cancer
- the treatment of HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma

The recommended dose for KANJINTI is 8 mg/kg administered intravenously (IV) as a loading dose, then 6 mg/kg given IV every 3 weeks

2.7 Regulatory Background

Original IND (115424) was submitted to the FDA on May 3, 2012.

3 Studies Submitted

Study #	Study Title	Reviewed	
		Yes	No

Pharmacology Studies			
Synthon-CP-P001.1	Evaluation of Efficacy and Safety of Synthon's FTMB in the Treatment of Orthotopic BT474 Human Breast Cancer Model	X	
Synthon-CP-P001.2	Comparison of Efficacy of FTMB and Herceptin® on N87 Xenografts in Female CD-1 Nude Mice	X	
ZNA34448.001	Anti-Tumour Efficacy Study to Assess Biosimilarity between Trastuzumab (Herceptin®) and a Trastuzumab Biosimilar	X	
Toxicology Studies			
37630 TSP	4-Week Comparative Toxicity Study by Intravenous Injection (Bolus) in Cynomolgus Monkeys	X	
118501	ABP 980: A 14-Day Intravenous Toxicology Study in the Sprague Dawley Rat		X*
37628	Tissue Cross-Reactivity Validation Study in Human Mammary Neoplastic Tissue Overexpressing HER2 Using Trastuzumab and FTMB, A Newly Developed Biosimilar Product	X	
37629	Tissue Cross Reactivity Study in Human Tissues using Trastuzumab and FTMB a Newly Developed Biosimilar Product	X	

**: Toxicokinetic evaluations were reviewed under the original IND application*

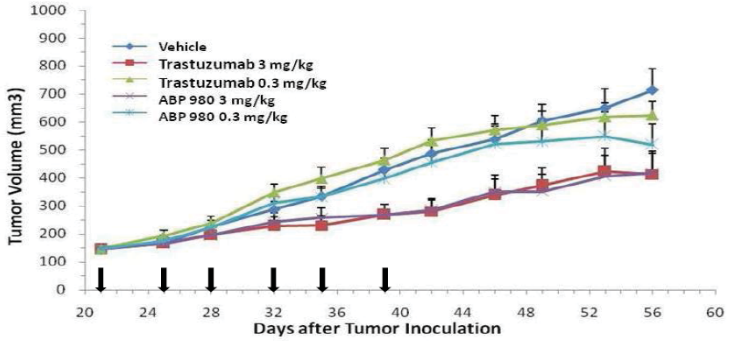
4 Pharmacology

4.1 Primary Pharmacodynamics

Study Title: Evaluation of Efficacy and Safety of Synthon's FTMB in the Treatment of Orthotopic BT474 Human Breast Cancer Model
Study No: Synthon-CP-P001.1
Conducting laboratory: (b) (4)

The Applicant evaluated the safety and efficacy of ABP 980 in a orthotopic BT474 human breast cancer mouse model (n=10 mice/group). NOD/SCID mice were injected orthotopically with BT-474 tumor cells at a concentration of 8×10^6 per mouse. Mice were implanted subcutaneous (SC) with estrogen pellets to support the growth of BT-474 cells, which are estrogen receptor positive. After 21 days, mice were treated with the vehicle control, EU-Herceptin® (0.3 & 3 mg/kg), and ABP 980 (0.3 & 3 mg/kg) on day 1 and 4 every week for 3 weeks. Tumor size was measured twice weekly. The results show that no ABP 980 or EU-Herceptin®-related mortalities or toxicities were observed. There were decreases in bodyweights in all groups at day 42.

Figure 1 Antitumor Activity of ABP 980 and Trastuzumab in NOD/SCID Mice Orthotopically Implanted with BT-474 Cells



BT-474 = metastatic human breast cancer cells; NOD/SCID = nonobese diabetic/severe combined immune deficiency; SEM = standard error of the mean.
Arrows indicate treatment days. Data represent mean ± SEM for each group.

(Excerpted from Applicant's submission)

Table 2 Tumor Size of ABP 980 and EU-Herceptin® in Orthotropic BT474 Human Breast Cancer Mouse Model

Treatment	Tumor Size (mm^3)[a]at day 42	T/C at day 42 (%)	Tumor Size (mm^3)[a]at day 56	T/C at day 56 (%)	T-C (days) at 400 mm^3	AUC (%)[b] at day 42	AUC (%)[b] at day 56
Vehicle	487±50	--	714±76	--	--	12126±1152	28938±2986
Herceptin(3mg/kg)	280±40	53	413±82	58	13	9051±1219	19961±3413
Herceptin(0.3mg/kg)	533±45	109	624±51	87	-3	13654±1272	29013±2338
FTMB(3mg/kg)	284±41	58	471±71	66	15	9332±1157	18728±2844
FTMB(0.3mg/kg)	455±59	93	519±74	73	1	11982±1469	22626±3528

Note: Mean ± SEM; b. AUC = areas under the tumor growth curve, expressed as Mean ± SEM.

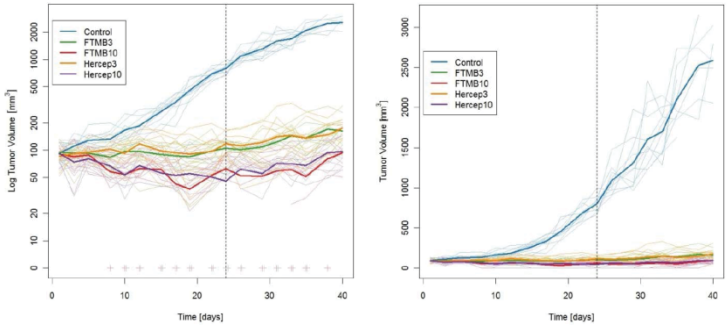
(Excerpted from Applicant's submission)

Conclusion: Treatment with ABP 980 and Herceptin® at 3 mg/kg showed comparable antitumor activity and was greater compared to vehicle controls.

Study Title: Comparison of Efficacy of FTMB and Herceptin® on N87 Xenografts in Female CD-1 Nude Mice
Study No: Synthon-CP-P001.2
Conducting laboratory: (b) (4)

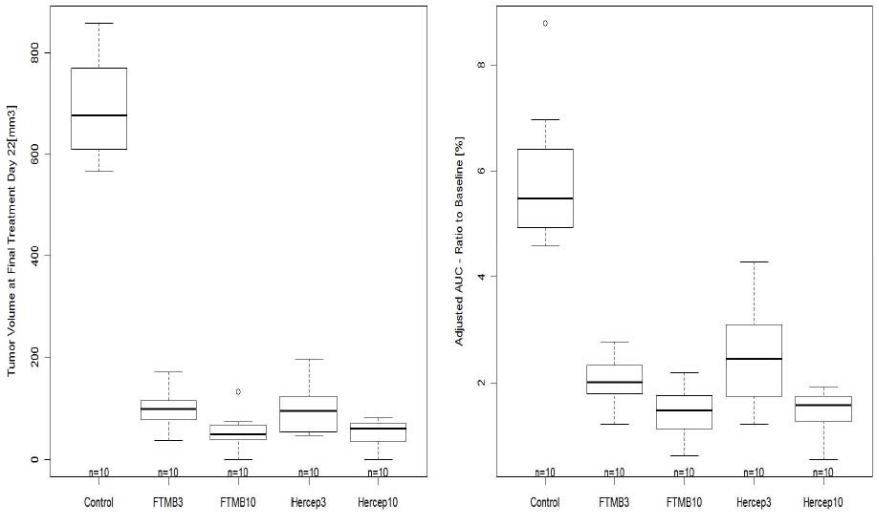
The Applicant performed efficacy comparisons of FTMB (ABP 980) with EU-Herceptin® at 3 & 10 mg/kg in a N87 human gastric carcinoma xenograft model. The applicant compared EU-Herceptin® versus controls, ABP 980 versus controls, similarity of ABP 980 vs EU-Herceptin®. Re-growth of tumor during post treatment, body weights, and safety were also evaluated. To do this, CD1 tumor-bearing mice were treated with vehicle (group1), ABP 980 at 3 mg/kg IP (group 2), ABP 980 at 10 mg/kg IP (group 3), EU-Herceptin® at 3 mg/kg IP (group 4), EU-Herceptin® at 10 mg/kg IP (group 5) twice weekly for 3 weeks. After tumor cell injection, tumor volume was determined three times per week (Monday, Wednesday, Friday) for the duration of the study.

Figure 2 Tumor volume over time during (days 1-22) and after treatment (days 23-40)



(Excerpted from Applicant's submission)

Figure 3 Box-plots of tumor volume at day 22 and AUCr



(Excerpted from Applicant's submission)

Table 3 Tumor volume ratio-to-baseline adjusted AUCr - T/C estimates with upper confidence limits

Comparison	T/C	Upper 95% confidence limit	Conclusion on tumor inhibition
Hercep3/C	40.4	58.7	Significant, but not relevant
Hercep10/C	26.9	31.6	Significant, and relevant
FTMB3/C	36.2	42.5	Significant, and relevant
FTMB10/C	25.2	32.2	Significant, and relevant

(Excerpted from Applicant's submission)

Conclusion: No ABP 980 or EU-Herceptin®-related mortalities or toxicities were observed. Statistically significant antitumor activity was similar for ABP 980 and EU-

Herceptin® versus controls at both doses. Similarity in AUCr of ABP 980 with respect to EU-Herceptin® was also demonstrated.

Study Title: Anti-Tumour Efficacy Study to Assess Biosimilarity between Trastuzumab (Herceptin®) and a Trastuzumab Biosimilar
Study No: ZNA34448.001
Conducting laboratory: (b) (4)

Methods
The applicant compared the anti-cancer efficacy of EU-trastuzumab (Herceptin®) and ABP 980 in the human BT-474 breast tumor xenograft model using immunocompromised (NOD/SCID) mice. Nine female mice per group assigned to the following groups:

Group 1	Vehicle (Placebo)	10 mL/kg
Group 2	Trastuzumab biosimilar	5 mg/kg
Group 3	Trastuzumab biosimilar	15 mg/kg
Group 4	Trastuzumab (Herceptin®)	5 mg/kg
Group 5	Trastuzumab (Herceptin®)	15 mg/kg

(Excerpted from Applicant's submission)

Mice were injected subcutaneously with 1 x 10^7 BT-474 cells in a volume of 0.1 mL sterile phosphate buffered saline (PBS) / Matrigel™ (1:1 v/v) to allow selection of optimal tumors for inclusion in the study. Animals were ranked according to tumor volumes. ABP 980, EU-Herceptin®, and vehicle (placebo) were administered twice weekly with 3 to 4 days between doses on Days 0, 4, 7, 11, 14, and 18 at a dose volume of 10 mL/kg. Tumor size was measured twice weekly.

Results:

Mortalities/Clinical signs: No mortalities or clinical signs noted in group 4 (EU-Herceptin® 5 mg/kg). Mortalities and body weight loss were observed in all other groups including vehicle controls.

Group	No. of deaths	Days of deaths	Cause of death	Prior to Death and Necropsy Findings
1	3	7, 26, & 32	Euthanized	Weight loss
2	5	29, 31, 33 (2), & 42	Euthanized	Weight loss
3	2	1 & 43	Found dead	Unremarkable
5	3	4, 7, & 19	Euthanized	Weight loss

Tumor Volume/Efficacy:

No differences in tumor volumes were noted on day 0. Tumor doubling time in the vehicle control groups was estimated at 67.1 days up to day 21 and 11.1 days from day 21 to day 42. Tumor growth was not observed in any of the ABP 980 (proposed trastuzumab biosimilar) or EU-trastuzumab (Herceptin®) treated groups after day 21.

Table 4 Growth rates, doubling times and halving times with 95% confidence intervals up to Day 21

Treatment	Lambda, growth rate (95 % CI)	Doubling time (95 % CI) (days)	Halving time (95 % CI) (days)
Group 1: Vehicle (placebo, 10 mL/kg, i.v.)	0.0103 (-0.0106, 0.0313)	67.1 (22.2, NC)	NC (65.3, NC)
Group 2: Trastuzumab biosimilar (5 mg/kg, i.v.)	-0.0366 (-0.0659, -0.0074)	NC	18.9 (10.5, 93.8)
Group 3: Trastuzumab biosimilar (15 mg/kg, i.v.)	-0.0395 (-0.0753, -0.0037)	NC	17.5 (9.2, 186.8)
Group 4: Trastuzumab (Herceptin®) (5 mg/kg, i.v.)	-0.0104 (-0.0416, 0.0209)	NC (33.2, NC)	66.8 (16.7, NC)
Group 5: Trastuzumab (Herceptin®) (15 mg/kg, i.v.)	-0.0674 (-0.0981, -0.0367)	NC	10.3 (7.1, 18.9)

Animals were allocated to the treatment groups on Day 0 and Trastuzumab biosimilar, Trastuzumab (Herceptin®) or vehicle were administered intravenously on Days 0, 4, 7, 11, 14 and 18 (total 6 doses) and tumour volume measured on these days and twice weekly thereafter. A tumour growth (random coefficient model) was fitted to the individual tumour volume (mm^3) data up to Day 21. This model estimates the tumour growth, lambda (λ_{treat}) as a slope of the fitted line on the log scale. The doubling time was then estimated as ($\log_e 2$) / λ_{treat} provided that there was positive growth. Otherwise, halving times were estimated as ($\log_e 2$) / $-\lambda_{treat}$.

NC not calculable.

(Excerpted from Applicant's Submission)

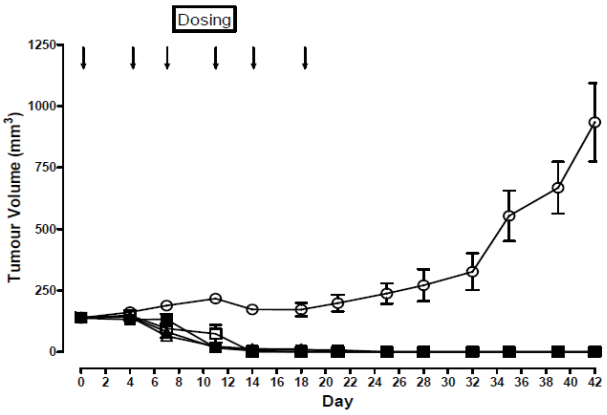
Table 5 Growth rate and doubling time with 95% confidence intervals from Day 21 to Day 42

Treatment	Lambda, growth rate (95 % CI)	Doubling time (95 % CI) (days)
Group 1: Vehicle (placebo, 10 mL/kg, i.v.)	0.0624 (0.0458, 0.0790)	11.1 (8.8, 15.1)

Animals were allocated to the treatment groups on Day 0 and Trastuzumab biosimilar, Trastuzumab (Herceptin®) or vehicle were administered intravenously on Days 0, 4, 7, 11, 14 and 18 (total 6 doses) and tumour volume measured on these days and twice weekly thereafter. A tumour growth (random coefficient model) was fitted to the individual tumour volume (mm^3) data of the vehicle group alone taking data from Day 21 to Day 42. This model estimates the tumour growth, lambda (λ_{treat}) as a slope of the fitted line on the log scale. The doubling time was then estimated as ($\log_e 2$) / λ_{treat}.

(Excerpted from Applicant's Submission)

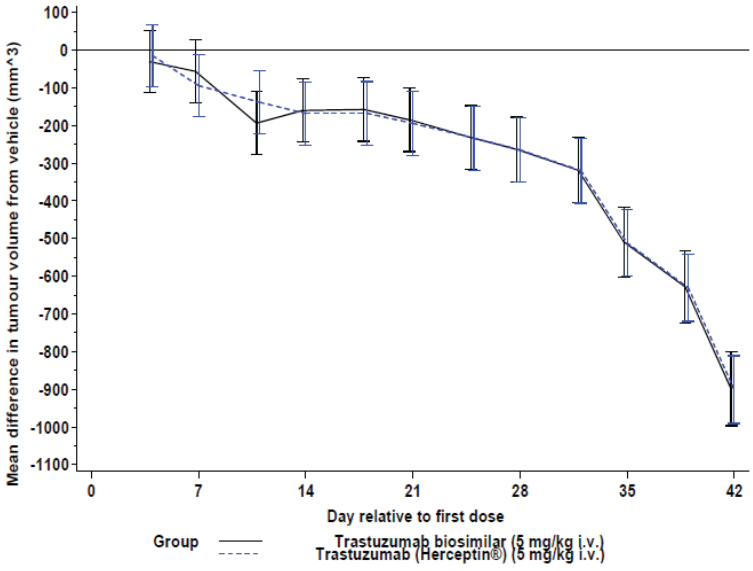
Figure 4 Effect of ABP 980 and EU-Herceptin® on Tumor Volume



Effect of Trastuzumab and Trastuzumab biosimilar on the volume of BT-474 tumour in SCID mice. Mice were injected subcutaneously in the right flank with approximately 1 x 10^7 BT-474 cells in a volume of 0.1 mL; treatment commenced when the majority of the tumours were in the range 50 to 150 mm^3 (Day 0). Trastuzumab (5 and 15 mg/kg) and Trastuzumab biosimilar (5 and 15 mg/kg) or Vehicle (10 ml/kg) were given i.v. on Days 0, 4, 7, 11, 14 and 18. Tumour volume was measured twice weekly until Day 42. Data show the mean ± sem. N=9 mice/group on Day 0.

(Excerpted from Applicant's Submission)

Figure 5 Mean difference from time-matched vehicle with 95% confidence interval (EU-trastuzumab (Herceptin®) and ABP-980 5 mg/kg)



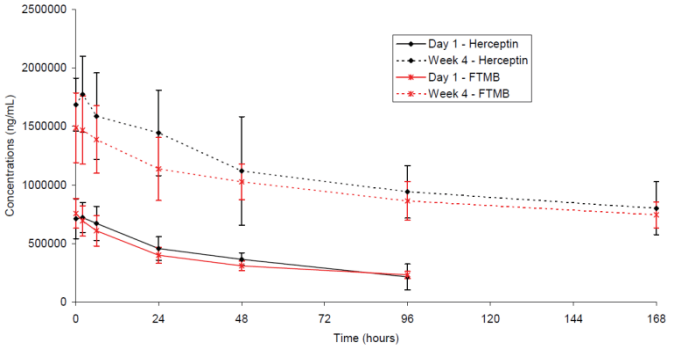
All groups measured on the same days; the biosimilar group has been shifted to the left for display purposes.

(Excerpted from Applicant's Submission)

Conclusion: Multiple deaths occurred in this study; however, the mortalities were present in the vehicle group and lacked a dose response. ABP 980 or EU-trastuzumab (Herceptin®) treated groups behaved similarly in this study. The results show that the tumors did not grow in any of the ABP 980 or EU-trastuzumab (Herceptin®) treated groups and no tumors were evident in any of these treated groups after Day 21.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Type of Study	Major Findings
Absorption	
Monkey: 4-week comparative toxicology study • Dosed twice weekly for 4 weeks • Dose levels: 25 mg/kg at 21 mg/mL • Blood samples were collected on first and last day of treatment at 5 minutes and 2, 6, 24, 48 and 96 hourspost-dose	Plasma exposure was similar after EU-Herceptin® and ABP 980 (FTMB) injections (slow bolus) on day 1 and week 4. **Figure 6 Mean EU-Herceptin® or ABP 980 Serum Concentrations at Day 1 and Week 4**  *(Excerpted from Applicant's submission)*

Day	Parameters	Units	EU-Herceptin®	ABP 980	Ratio EU-Herceptin®/ABP 980
Week 1	Tmax	h	2	0.0833	NA
	Cmax	µg/mL	814	773	1.05
	C0	µg/mL	713	760	0.94
	$AUC_{0\text{-}96h}$	µg•h/mL	37215	34501	1.08
	T1/2	h	95.8	93.3	1.03
	$AUC_{0\text{-}inf}$	µg•h/mL	75912	65895	1.15
Week 4	Tmax	h	4	1.0417	NA
	Cmax	µg/mL	1939	1722	1.13
	C0	µg/mL	1690	1501	1.13
	$AUC_{0\text{-}96h}$	µg•h/mL	117721	102685	1.15
	T1/2	h	193	178	1.12
	$AUC_{0\text{-}inf}$	µg•h/mL	399175	355745	1.08

NA: not applicable; C0: concentration at t = 0 hour, used for the AUC calculation

6 General Toxicology

6.1 Repeat-Dose Toxicity

Study title/ number: A 14-Day Intravenous Toxicology Study in the Sprague Dawley Rat

Key Study Findings

- No ABP 980 or EU-trastuzumab related effects were observed

Conducting laboratory and location: (b) (4)
GLP compliance: **Yes**

Methods

Dose and frequency of dosing:	25 mg/kg/day (1.2 mg/mL); twice weekly for 2 weeks
Route of administration:	IV (bolus)
Species/Strain:	Sprague Dawley Rat
Number/Sex/Group:	10/sex/group
Age:	7-8 weeks
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	None

Observations and Results:

Parameters	Major findings
Mortality	No drug-related mortalities
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Electrocardiography	Unremarkable
Blood pressure	Unremarkable
Ophthalmology	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Unremarkable
Histopathology Adequate battery: **Yes** Signed Pathology Report: **Yes** Peer Reviewed: **Yes**	Unremarkable

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Study title/ number: 4-Week Comparable Toxicity Study by Intravenous Injection (Bolus) in Cynomolgus Monkeys (37630 TSP)

Key Study Findings

- Findings were similar after EU-Herceptin® or ABP 980 injection
- Clinical signs include indurations, nodules or abnormal reddish color at the

injection sites
- Increased urea, triglyceride, and creatinine kinase levels

Conducting laboratory and location: (b) (4)
GLP compliance: **Yes**

Methods

Dose and frequency of dosing:	25 mg/kg/day (21 mg/mL); twice weekly for 4 weeks
Route of administration:	IV (bolus)
Species/Strain:	Cynomolgus monkeys, females only
Number/Sex/Group:	6/sex/group
Age:	26 months
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	None

Observations and Results:

Parameters	Major findings
Mortality	No drug-related mortalities
Clinical Signs	ABP 980: induration & nodules at injection sites 1 & 2; abnormal color on right hindlimb & injection site 2 EU-Herceptin®: induration & nodules at injection sites 1 & 2
Body Weights	Unremarkable
Electrocardiography	Unremarkable
Blood pressure	Unremarkable
Ophthalmology	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	ABP 980: +9.4% UREA, +0.66% TRI, +45% ALB, +1.5-fold% CK over controls EU-Herceptin®: +9% UREA, +0.69% TRI, +44% ALB, +2-fold% CK over controls
Urinalysis	Unremarkable
Gross Pathology	ABP 980 & EU-Herceptin®: enlarged popliteal lymph nodes & enlarged spleen
Organ Weights	Unremarkable
Histopathology Adequate battery: **Yes** Signed Pathology Report: **Yes** Peer Reviewed: **Yes**	

Sex	Females		
Treatment	Control	EU-Herceptin®	ABP 980
No. of animals	6	6	6
Adrenal glands mineralization -slight	- -	1 1	1 1
Mononuclear cell infiltration -minimal	- -	- -	1 1
Esophagus infiltration, mononuclear cells, slight	- -	1 1	- -
Gall bladder infiltration, mononuclear cells, slight	- -	1 1	- -
LN, inguinal Increased plasma cell -minimal -slight	- - -	- - 1	1 1 -
LN, popliteal Increased paracortex, slight	- -	1 1	- -
Sinusoidal red blood cells, minimal	- -	- -	1 1
Injection site, saph. L1 Serocellular crust, minimal	- -	- -	1 1
Acanthosis, slight	-	1	-

		Fibrosplasia/fibrosis -minimal -slight	 - -	 1 -	 - 1
		Intimal thickening, minimal	-	-	2
		Pigment, miminal	-	1	-
		Injection site L Saph L2 Serocellular crust, minimal	-	-	1
		Acathonsis, minimal	-	-	1
		Mononuclear infiltration, dermis, minimal	-	-	1
		Hemorrhage, minimal	-	-	1
		Lungs Foamy Macrophage, alveolus, minimal	-	-	1
		Rectum Protozoa, lumen, minimal	-	1	2

-: indicates reduction in parameters compared to control. +: indicates increase in parameters compared to control.

Study title: Tissue Cross-Reactivity Validation Study in Human Mammary Neoplastic Tissue Overexpressing HER2 Using Trastuzumab and FTMB, A Newly Developed Biosimilar Product (Study No. 37628vp)

The applicant tested the cross-reactivity of ABP 980 and EU-trastuzumab (Herceptin®) in human mammary neoplastic cells at a concentration of 156 µg/mL. A human IgG1 Isotype control was used. Tissue cross reactivity experiments were also performed on human duodenum, skin, breast, kidneys, salivary glands, lymph nodes, skeletal muscle and brain. Mammary neoplasms overexpressing HER2 (ILS23877 and ILS24695) were used as the positive control tissue. A human IgG1k/Biotin was used as a control. Skeletal muscle tissue was used as a negative control.

Results:
ABP 980 and EU-Herceptin® positive staining were comparable in human mammary neoplastic cells.

- Membranous staining was observed in ductal epithelial cells from the breast, the biliary tree (bile ducts in the liver), pancreas (inter-lobular ducts), and parotids; epithelial cells lining the gastrointestinal tract from the stomach to the rectum and including the gall bladder epithelium; meningeal cells from the cerebellum and cerebral cortex; malpighian squamous epithelial cells from the esophagus, tonsils, exocervix, and skin epidermis (including hair follicles); sebaceous glands and sweat glands from the skin; epithelial cells from the pulmonary airways (bronchi), renal tubules, parathyroid, prostate, uterine endometrium and fallopian tube; trophoblastic cells from the placenta, and epithelial cells located in the medulla of the thymus.

- Cytoplasmic staining was also present in liver hepatocytes, nervous plexi located in the muscular wall of the digestive tract, and ependymal epithelial cells from the spinal cord.

Study title: Tissue Cross Reactivity Study in Human Tissues using Trastuzumab and FTMB a Newly Developed Biosimilar Product (Study No. 37629)

The applicant tested the immunoreactivity of ABP 980 and EU-trastuzumab (Herceptin®) on a panel of 43 frozen human normal tissues and blood smears from 3 independent individuals. The concentrations used were 9540 µg/mL and 8800 µg/mL for ABP 980 and EU-Herceptin®, respectively. A human IgG1K Isotype control was used. Tissue cross reactivity experiments were also performed on human duodenum, skin, breast, kidneys, salivary glands, lymph nodes, skeletal muscle and brain. Human breast carcinoma over-expressing Her2/Neu were used as the positive control tissue.

Results:
ABP 980 and EU-Herceptin® positive staining were comparable in a panel of 43 frozen human normal tissues and blood smears.

- Membranous staining was observed in ductal/ ductular epithelium from the breast, the biliary tree, pancreas, parotids, hepatocellular cells, epithelium lining the gastro-intestinal tract, including the gall bladder, meningeal cells from the cerebellum and cerebral cortex, squamous epithelium from the esophagus, tonsils, exocervix, skin epidermis (including hair follicles) and adnexial glands (sweat and sebaceous), epithelium from the pulmonary airways (bronchi), renal tubules, parathyroid, prostate, uterine endometrium and fallopian tube, medulla of the thymus and trophoblastic cells from the placenta.
- Cytoplasmic staining was observed in the nervous plexi of the muscular wall in the digestive tract. Granular cytoplasmic staining of ependymal cells was also observed in the spinal cord.

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/s/

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04/10/2018

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04/11/2018