# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761106Orig1s000

# OTHER REVIEW(S)

**NOMENCLATURE REVIEW**

| | |
|---|---|
| Date: | February 27, 2019 |
| Application: | BLA 761106 |
| Product: | Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) Injection |
| Applicant: | Genentech, Inc. |
| Submission Dates: | May 1, December 21, 2018; February 14, 2019 |

## I. RECOMMENDATION

OPQ recommends the core name of *trastuzumab and hyaluronidase* for this.[1] OPQ recommends that the descriptor *human* not be included in the core name. The source and origin information for the hyaluronidase component can be more appropriately communicated within the prescribing information (PI) in section 11 DESCRIPTION for this product.

## II. BACKGROUND AND DISCUSSION

### A. Background

The purpose of this memo is to document OPQ's recommendation for the core name for Genentech's (GNE) Biologic License Application (BLA 761106) with specific regard to hyaluronidase. GNE submitted a new BLA 761106, pursuant to Section 351(a) of the Public Health Service Act, for a fixed-combination injectable solution (Injection) composed of trastuzumab and hyaluronidase for subcutaneous use. The Applicant initially proposed the core name of "trastuzumab and hyaluronidase human."

### B. Labeling of Currently Marketed Hyaluronidase Products

Some currently marketed hyaluronidase injectable products include the source within the non-proprietary name (NPN), some display it adjacent to the NPN, and some do not contain it in the NPN.

1. HYDASE (Hyaluronidase injection) bovine
2. HYLENEX recombinant (hyaluronidase human injection)
3. VITRASE (hyaluronidase injection) Ovine
4. AMPHADASE (hyaluronidase injection)
5. RITUXAN HYCELA (rituximab and hyaluronidase human)
6. HYQVIA (Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (CBER-regulated product)

OPQ previously has reached out to OND/DTOP to get a clinical perspective on the differences between the different hyaluronidase products. According to OND/DTOP, there is not a clinical need for the NPN to state the different sources (bovine vs. ovine vs. human recombinant) of hyaluronidase products. Also, certain biological products that utilize recombinant human DNA

[1] BLA 761106 will receive a suffix in the *proper name*. See PHS Act § 351(a)(1)(B)(i); 21 CFR 600.3(k); Guidance for Industry, Nonproprietary Naming of Biological Products (Jan. 2017). This memo focuses on the core name; that is, the portion of the proper name that does not include the suffix. See Naming Guidance at 1 & 12. The considerations for the suffix are addressed in another memo.

technology do not include human within the core name. Examples of these products include the following:

1. Activase (alteplase)
2. Epogen (epoetin alfa)
3. Vpriv (velaglucaerase alfa)
4. Lumizyme (alglucosidase alfa)
5. Fabrazyme (agalsidase beta)
6. Proleukin (aldesleukin)

### C. Biological Product Labeling Regulations

Unlike *albumin human*, which is required to include human in the proper name per 21 CFR 640.80, there is no regulation that requires inclusion of human in the NPN for hyaluronidase. The source and origin information for the hyaluronidase component can be appropriately communicated within the PI in section 11 DESCRIPTION. Additionally, the biological product labeling regulations (21 CFR 610.61(p)) would require the PI and carton labeling—though not the proper name—to include the source of the product if it is a factor in safe administration. For this product, FDA has not identified a safety concern that would require the application of 21 CFR 610.61(p) such that source and origin of the hyaluronidase component would need to be indicated as part of the proper name.

### D. Timeline of Communications with GNE

12/19/2018 Teleconference with GNE in which FDA explained its thinking that "human" should not be included in the core name. FDA stated that the core name should be "trastuzumab and hyaluronidase".

12/21/2018 GNE's response to Agency's Request.

02/11/2019 FDA response to GNE reiterating current thinking that "human" should not be part of the NPN for the proposed biological product that is the subject of BLA 761106.

02/13/2019 GNE accepts FDA recommendation.

## III. CONCLUSION

OPQ recommends the core name of *trastuzumab and hyaluronidase*. OPQ recommends not including the source of a biological product within the nonproprietary name (NPN) unless it is required by regulation, or it is clinically relevant for the prescriber. OPQ believes neither is the case for BLA 71106, and that the source and origin information for the hyaluronidase component can be more appropriately communicated within the PI in section 11 DESCRIPTION.

Scott Dallas

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Shen Luo

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Shadia Zaman

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Wendy Weinberg

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# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| Date of This Memorandum: | February 20, 2019 |
| Requesting Office or Division: | Division of Oncology Products 1 (DOP1) |
| Application Type and Number: | BLA 761106 |
| Product Name and Strength: | Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) Injection, 600 mg and 10,000 units/5 mL |
| Applicant/Sponsor Name: | Genentech, Inc. |
| FDA Received Date: | February 19, 2019 |
| OSE RCM #: | 2018-918-2 |
| DMEPA Safety Evaluator: | Tingting Gao, PharmD |
| DMEPA Team Leader: | Chi-Ming (Alice) Tu, PharmD |

## 1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised container label and carton labeling for Herceptin Hylecta (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

## 2 CONCLUSION

The revised container label and carton labeling for Herceptin Hylecta are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Gao, T. Memorandum of Revised Label and Labeling for Herceptin Hylecta (BLA 761106). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Feb 14. RCM No.: 2018-918-1.



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# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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|---|---|
| Date of This Memorandum: | February 14, 2019 |
| Requesting Office or Division: | Division of Oncology Products 1 (DOP1) |
| Application Type and Number: | BLA 761106 |
| Product Name and Strength: | Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) Injection, 600 mg and 10,000 units/5 mL |
| Applicant/Sponsor Name: | Genentech, Inc. |
| FDA Received Date: | January 11, 2019 |
| OSE RCM #: | 2018-918-1 |
| DMEPA Safety Evaluator: | Tingting Gao, PharmD |
| DMEPA Team Leader: | Chi-Ming (Alice) Tu, PharmD |

## 1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised container label and carton labeling for Herceptin Hylecta (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

## 2 DICUSSION

Genentech stated that they intend to use MM YYYY as the expiration date format instead of the previously recommended format (e.g., YYYY-MM) on the container labels and carton labeling.[b] Since the proposed expiration date format consists of the 2-digit numerical characters for the month (MM) and the 4-digit year (YYYY), we find this proposed expiration date format acceptable from a medication error perspective.

[a] Gao, T. Use-Related Risk Analysis and Label and Labeling Review for Herceptin Hylecta (BLA 761106). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 17. RCM No.: 2018-918 and 2018-927.
[b] Response to FDA Comments on the Proposed Container and Carton Labeling. BLA 761106. South San Francisco (CA): Genentech, Inc. 2019 Jan 11. Available at \\cdsesub1\evsprod\bla761106\0034\m1\us\resp-fda-com-carton-20190111.pdf.

The revised Herceptin Hylecta container label and carton labeling are not acceptable from a medication error perspective because the proper name lacks the FDA-designated nonproprietary name suffix, -oysk, appended to the core name, trastuzumab and hyaluronidase.

## 3 RECOMMENDATIONS FOR GENENTECH, INC.

We recommend the following be implemented prior to approval of this BLA:

1. Revise the nonproprietary name on all labels and labeling to incorporate the suffix, -oysk, appended to the core name, trastuzumab and hyaluronidase, so that the nonproprietary name appears as trastuzumab and hyaluronidase-oysk throughout the labels and labeling. This recommendation was communicated to you in the February 14, 2019 General Advice Letter.

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MEMORANDUM

NONPROPRIETARY NAME SUFFIX

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

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|---|---|
| **Date of This Review:** | February 12, 2019 |
| **Responsible OND Division:** | Division of Oncology Products 1 (DOP1) |
| **Application Type and Number:** | BLA 761106 |
| **Product Name and Strength:** | Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) Injection<br>600 mg and 10,000 Units/5 mL<br>(120 mg and 2,000 Units/mL) |
| **Product Type:** | Multiple Ingredient Product |
| **Applicant/Sponsor Name:** | Genentech, Inc. (Genentech) |
| **OSE RCM #:** | 2018-1782 |
| **DMEPA Primary Reviewer:** | Carlos M Mena-Grillasca, BS Pharm |
| **DMEPA Deputy Director:** | Danielle Harris, PharmD, BCPS |

# 1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffix for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761106.

## 1.1 Regulatory History

Genentech was notified of the Agency's intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for their product in an Advice Letter[a].

# 2 ASSESSMENT OF THE NONPROPRIETARY NAME

## trastuzumab and hyaluronidase-oysk

FDA generated a four-letter suffix, -oysk. This suffix was evaluated using the principles described in the applicable guidance[b].

We determined that the FDA-generated suffix -oysk, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

We acknowledge that the proposed product is composed of two active ingredients, 'trastuzumab' and 'hyaluronidase'. Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC), whereas hyaluronidase increases the permeability of the subcutaneuous tissue. Since the product contains two active ingredients, the core name for this product is the core names of the two components, trastuzumab and hyaluronidase[c]. We considered the placement of the suffix within the nonproprietary name (i.e., after the trastuzumab component of the core name vs. after the hyaluronidase component of the core name). We are concerned that placement of the suffix after the trastuzumab component could result in misinterpretation of the nonpropoprietary name. Since both trastuzumab and hyaluronidase are available as individual components, the nonproprietary name, trastuzumab-xxxx and hyaluronidase, could be misinterpreted as an order for the individual components versus the proposed fixed-combination product, which may lead to confusion and medication error. Thus, in this case, we determined that the suffix should be attached at the end of the core name of the product (trastuzumab and hyaluronidase) with a hyphen consistent with recommendations provided in the applicable guidance[d]. This placement would also ensure visibility of

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[a] Harris, D. General Advice Letter for BLA 761106. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US) 2018 AUG 30.

[b] See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

[c] Ongoing discussions between DOP1 and Genentech.

[d] See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

the suffix within the nonproprietary name. Thus, we determined trastuzumab and hyaluronidase-oysk will be the proper name designated in the license.

## 3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP. In email correspondence dated October 25, 2018, OPDP did not identify any concerns that would render this suffix unacceptable. DMEPA also communicated our findings to the Division of Oncology Products 1 (DOP1) via e-mail on February 12, 2019.

## 4 CONCLUSION

We find the suffix -oysk acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to trastuzumab and hyaluronidase-oysk.

### 4.1 Recommendation for Genentech, Inc.

We find the nonproprietary name, trastuzumab and hyaluronidase-oysk, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, trastuzumab and hyaluronidase-oysk will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of this suffix will be re-evaluated when you respond to the deficiencies. If we find the suffix unacceptable upon our re-evaluation, we would inform you of our finding.

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DANIELLE M HARRIS
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**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** February 13, 2019

**To:** Julia Beaver, M.D., Director
Division of Oncology Products 1 (DOP1)

Amy Tilley, Regulatory Project Manager, DOP1

William Pierce, PharmD, Associate Director for Labeling, DOP1

**From:** Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Herceptin Hylecta™ (trastuzumab and hyaluronidase human-oysk) Injection[1], for subcutaneous use

**BLA**: 761106

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In response to DOP1's consult request dated September 17, 2018, OPDP has reviewed the proposed prescribing information (PI), carton labeling and container label for the original BLA submission for Herceptin Hylecta™ (trastuzumab and hyaluronidase human-oysk) Injection, for subcutaneous use (Herceptin Hylecta).

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP1 (Amy Tilley) on February 11, 2019, and are provided below.

OPDP has reviewed the attached proposed carton labeling and container label submitted by the Sponsor to the electronic document room on January 11, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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[1] The proposed proprietary name (Herceptin Hylecta) and the proper name with suffix (trastuzumab-oysk) are conditionally accepted until such time that the application is approved.

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KEVIN WRIGHT
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# Memorandum

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| **STN:** | BLA 761106 (SD 1, May 1, 2018) |
| **Subject:** | Immunogenicity Assay Review |
| **Review/Revision Date:** | January 30, 2019 |
| **Primary Reviewer:** | Shadia Zaman, Ph.D. (DBRR I) |
| **Secondary Reviewer:** | Brian Janelsins, Ph.D. (DBRR I) |
| **RBPM:** | Andrew Shiber, Pharm.D. |
| **Applicant:** | Genentech, Inc. |
| **Product:** | trastuzumab and hyaluronidase human solution |
| **Indication:** | Treatment of patients with HER2-overexpressing breast cancer |
| **Dose Regimen and Route of Admin:** | 600 mg trastuzumab and 10,000 units hyaluronidase human every three weeks via subcutaneous injection |
| **PDUFA Goal Date:** | March 1, 2019 |
| **Proprietary Name:** | Herceptin Hylecta |

## RECOMMENDATION

Sufficient information and data were provided to support the suitability of the anti-trastuzumab immunogenicity assays to generate meaningful clinical immunogenicity data in support of the BLA.

## EXECUTIVE SUMMARY

Genentech is seeking licensure for trastuzumab and hyaluronidase human solution for subcutaneous injection (Herceptin Hylecta, referred as Herceptin SC) as a single entity biologic product under the 351(a) pathway. Herceptin SC is a new dosage form of Herceptin for intravenous injection (referred as Herceptin IV) that contains hyaluronidase human and was developed as an alternative therapy for the HER2-overexpressing breast cancer indication currently approved for Herceptin IV under BLA 103792 (approved on September 25, 1998). In support of the current BLA, Genentech performed immunogenicity analysis of patients enrolled in a Phase I/Ib study (BP22023) and a Phase III study (BO22227) that received either Herceptin SC or Herceptin IV. Separate binding antibody assays were used to detect the presence of anti-drug antibodies (ADAs) against trastuzumab and hyaluronidase. Each binding antibody assay used a 3-tier approach to (i) screen samples for ADAs, (ii) confirm the specificity of ADA responses, and (iii) titer confirmed ADA responses. The neutralizing capability of confirmed ADA responses to trastuzumab and hyaluronidase was assessed using separate neutralizing antibody (NAb) assays. This review includes the assessment of the anti-trastuzumab immunogenicity assays. During the course of the review, there were issues identified with respect to the drug tolerance of the binding antibody and NAb assays. Based on the analysis of ADA/NAb impact on PK, efficacy, and safety, and the observed serum levels of Herceptin SC and IV, the clinical pharmacology and clinical teams stated they did not have concerns from their perspectives regarding the potential for ADAs (low levels) and NAbs being undetected in clinical samples due to drug interference. Considering the product and indication and the totality of data and information provided, the immunogenicity assays are acceptable to analyze the clinical samples in support of the BLA.

## REVIEW

***Note:*** *Reviewer Comments are indicated in italic font. The tables are copied directly from the submission.*

## 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

***Reviewer comment:*** *This section includes the review of the validation of the binding antibody and NAb assays specific for trastuzumab. In addition to information and data provided in the original BLA submission (SD1), information and data provided in IR responses received on 10/5/18 (SD16), 10/12/18 (SD18), 1/16/19 (SD35), and 1/28/19 (SD40) were reviewed. The immunogenicity assays (binding and neutralizing) for hyaluronidase were reviewed by DBRRIII (Shen Luo) and will be described in a separate CMC review for the hyaluronidase component of Herceptin SC.*

**Anti-Trastuzumab Binding Antibody Assay**

**Study No. (b) (4) 8220-9702: Bioanalytical Method Validation and Long-Term Freezer Stability Report for Analysis of Anti-RO0452317 Antibodies in Human Serum from (b) (4) Study 8220-970 Amended Version of the Amended Report Dated April 18, 2011**

The binding antibody assay was developed by Hoffmann-La Roche as a bridging assay using Meso Scale Discovery (MSD) technology. The method was transferred to (b) (4) and validated prior to analysis of BO22227 clinical samples. The final study report was finalized by (b) (4) on October 4th, 2012.

**Screening Assay**

Controls and test samples are incubated with biotin and ruthenium-labeled Herceptin. Anti-Herceptin antibodies form a bridge between biotin-labeled Herceptin and ruthenium-labeled Herceptin. The labeled complex is captured on streptavidin-coated multi-assay MSD plates. Read buffer is added to the plates and voltage is applied to generate a light signal (ECL) that is measured by the MSD SECTOR Imager 6000. The light signal response is directly proportional to the level of ADAs in the test sample. If the assay response is above the screening cut-point, then the test sample is classified as potentially positive and is analyzed in the confirmatory assay.

**Confirmatory Assay**

The confirmatory assay is run in the same manner as the screening assay with the exception of a pre-incubation step performed using test samples and controls with and without 10 µg/mL Herceptin. Percent (%) signal inhibition [100*[1-(signal with drug/signal without drug]) is calculated for all samples and controls. Test samples with percent % inhibition at or greater than the confirmatory assay cut-point are classified as confirmed positive for ADAs.

**Titer Assay**

Antibody titer is determined for confirmed positive samples. The titer assay follows the same procedure as the screening assay, except samples are diluted serially prior to running of the assay. Samples are diluted two-fold starting at 1/2 to 1/512 using normal human serum pool. If based on the assay response of the screening or confirmatory assay that a dilution of >1/512 may be required for a sample signal to drop below the screening cut-point, an initial dilution greater than 1/2 may be performed and will be taken into account in reporting the titer. Each serial dilution of a sample, including the neat sample, and controls are then diluted 1/5 (minimum required dilution, MRD) prior to incubation with labeled drug. This 1/5 dilution is not considered in the determination of the titer result.

***Reviewer comment:*** *An IR was sent on 1/10/19 to inform Genentech that all dilutions, including the MRD of 1/5, should be considered in determination of the titer result. In the IR response received on 1/16/19 (Question 1B), Genentech stated that because the practice of not considering the MRD was applied consistently across all controls and samples for studies BO22227 and BP22023, inclusion or exclusion of the final dilution would not impact the assessment of immunogenicity. Therefore, Genentech did not update the titer values with consideration of the MRD. As a result, the titer values reported in the BLA are inaccurate with respect to magnitude (i.e., reported 5x less than the true titer values); however, as noted by Genentech, this does not impact the immunogenicity assessment.*

**Minimum Required Dilution (MRD)**
The MRD for all samples and controls for the screening, confirmatory, and titer assays is 1/5 with assay buffer (provided in IR response 10/5/18, Question 1G).

**Positive and Negative Controls**
The positive control (PC) antibody is a rabbit polyclonal IgG antibody against Herceptin (pAb<RO0452317>Rb-IgG (IS), Lot # Wbr_101, expiration date 04/2013). A low positive control (LPC, 11 ng/mL) and a high positive control (HPC, 400 ng/mL) were prepared in pooled normal human serum, which was used as the negative control (NC).

**Establishment of the LPC and HPC Concentrations**
The LPC was established by serial dilution of the PC antibody (300 ng/mL) to the dilution that provided a consistent positive reading above the CP. The LPC signal of 199.1 was calculated using the standard deviation (SD) of the sera blanks used to establish the CP such that the lower limit of one-sided 99% prediction interval corresponded to the CP: LPC signal = CP + 2.33*SD of blanks. The average LPC concentration from three runs was calculated to be 11 ng/mL. The concentration of the HPC was determined as the PC antibody concentration that produced an assay response such that the ratio of HPC assay response to the LPC assay response was 30 (>15 and <50). The average HPC from three runs was 400 ng/mL.

***Reviewer comment:*** *It is unclear why a HPC to LPC ratio of 30 was chosen to set the HPC concentration; however, this is acceptable because the LPC appears to be suitable and the assay is not impacted by high levels of ADAs above the HPC level (see prozone effect discussion below).*

**System Suitability**
System suitability criteria include (i) all LPC replicates must be above the CP, (ii) at least 7 out of 8 NC replicates must be below the CP, (iii) the ratio of HPC to LPC must be between 15 and 50, and (iv) the %CV of LPC and HPC replicates must be ≤ 20.0%. Assay acceptance criteria are noted in the validation report (pages 22 – 23). NC, LPC, and HPC data were analyzed from the 14 validation runs. The mean NC response was 81.9 (n=112, 29.1% CV). All NC responses, with the exception of one mean NC value, were below the plate CP. The mean LPC response from the 14 runs was 294.8 (n=68, 17.8% CV), and the mean HPC response from the 14 runs was 8039.7 (n=68, 17.1% CV). All LPC and HPC signals were above the CP. The mean ratio of HPC to LPC was 27.

***Reviewer comment:*** *System suitability and assay acceptance criteria (described in pages 22 – 23 of the validation report) appear reasonable and were met during the validation and clinical sample analysis runs.*

**Screening Cut Point**

The screening CP (SCP) was calculated based on data from 40 commercially sourced, healthy human serum samples. Outliers were identified using boxplot analysis and removed from analysis. The data distribution after removal of outliers was non-normal as assessed by the Anderson-Darling test (P-value <0.005); therefore, the 95$^{th}$ percentile (non-parametric method) was used to calculate the CP of 164. Homogeneity of the variance for CP runs was demonstrated using Levene's test, which supports using a floating cut-point approach. Additionally, the NC and sample mean values generally correlated from plate to plate (r=0.75, Tables 1 and 2), which supports normalizing with the NC. The NC assay readings from the plates used for screening CP determination were used to calculate the global NC value. This determination was based on six validation runs performed by two analysts over two days (Table 2 in IR response received on 10/12/18), which gave a global NC mean of 98.0. The normalization factor (NF) was calculated as the CP (164.0) – global NC mean (98.0), which gave a value of 66.0. The plate-specific SCP for the assay is calculated as the NC mean per a given plate plus the established NF (66.0).

***Reviewer comment:*** *The approach used to determine the SCP is acceptable; however, it is unclear whether the validated SCP (based on the analysis of commercial normal serum) is acceptable to analyze the BP22023 (healthy and HER2-breast cancer subjects) and BO22227 (HER-2 breast cancer subjects) clinical samples. An IR was sent to Genentech to clarify whether study-specific SCPs based on the analysis of pre-dose clinical samples were used to analyze the clinical samples or whether the validated SCP was used. In the IR response received on 10/12/18 (Question 1), Genentech clarified that the validated SCP and CCP were used to analyze the BP22023 and BO22227 clinical samples. To support the suitability of the validated SCP and CCP, Genentech provided the false positive rates generated during the analysis of the pre-dose BP22023 and BO22227 clinical samples (see below).The data show that the SCP determined during assay validation provides an acceptable false positive rate, and as a result, is suitable to analyze the BP22023 and BO22227 clinical samples. Although the false positive rate is higher than expected, there is no concern of not detecting samples with low levels of ADAs.*

| | BP22023 | BO22227 | Expected |
|---|---|---|---|
| Total pre-dose samples | 66 | 681 | |
| Total screen positive samples | 9 | 134 | |
| **% screen positive** | **13.6%** | **19.7%** | |
| Total Confirm Negative Samples | 9 | 100 | |
| **% confirm negative (false positive)** | **13.6%** | **14.7%** | **5%** |

**Confirmatory Cut Point**

The confirmatory CP (CCP) was determined from analysis of 40 commercially sourced, healthy human serum samples in the presence and absence of 10 µg/mL Herceptin. The CCP was determined based on a 99.9% prediction interval (0.1% false positive rate) and was calculated as mean (% Inhibition) + 3.09 x SD (% Inhibition). Outliers were identified and excluded using boxplot analysis, and the resultant dataset was determined to be normally distributed using the Anderson-Darling test (P-value = 0.623). Based on the results, the CCP was calculated at 29.3% inhibition. Therefore, samples with % inhibition greater than 29.3% will be reported as confirmed positive.

***Reviewer comment:*** *The CCP was changed from 30.9% to 29.3% in version 2 of the report. An IR was sent on 1/10/19 to specify if the clinical samples from studies BP22023 and BO22227 were analyzed*

*with the updated CCP. In the IR response received on 1/28/19, the sponsor stated that analysis of clinical samples from study BP22023 was completed on 1/5/10 and the error in the CCP calculation was discovered on 1/4/13, prior to the analysis of the BO22227 clinical samples. Because a limited number of samples was collected for study BP22023 and the immunogenicity data are not as meaningful as the immunogenicity data generated from study BO22227, it was determined not to re-analyze BP22023 study samples with the current CCP. This is acceptable because the bulk of immunogenicity data that was generated to support the BLA was derived from the analysis of BO22227 clinical samples.*

*In addition, Genentech was informed that a CCP calculated based on a 0.1% false positive rate is not appropriate because it may underestimate the number of patient samples with low levels of ADAs. In the IR response (received on 1/28/19, Question 1A), Genentech recalculated the CCP based on a 1% false positive rate. The details of this CCP re-calculation and an assessment of the response are described below.*

### In-Study Screening and Confirmatory Cut Point

To address the Agency's concerns, in-study SCP and CCP were determined based on 5% and 1% false positive rates, respectively. For the in-study SCP, the mean responses of 581 baseline samples from study BO22227 were pooled into a single dataset. Outliers were determined using the limits: Q1-3 x IQR and Q3 + 3 x IQR, which resulted in the exclusion of 50 out of the 581 samples. The remaining 531 baseline samples were used to determine the SCP at a 5% false positive rate (Table 1, IR received on 1/28/19, Question 1A). For determination of the in-study CCP, the % inhibition from 66 baseline samples from study BO22227 that confirmed negative using the validation 0.1% CCP were pooled into a single dataset to determine the most conservative in-study 1% CCP. The dataset was evaluated for outliers as described above and no outliers were identified. The SCP and CCP based on the evaluation of the validation and clinical study BO22227 samples are shown in Table 1 (IR received on 1/28/19, Question 1A). The in-study SCP and CCP were shown to be less conservative with respect to the validated SCP and CCP.

**Table 1: Summary of mean signal and % inhibition observed during validation and using baseline samples from study BO22227**

| | Validation | | BO22227 In-study | |
|---|---|---|---|---|
| | Screen Assay (signal) | Confirmatory Assay (% inhibition) | Screen Assay (signal) | Confirmatory Assay (% inhibition) |
| N | 40 individual healthy donors | | 581 | 100 |
| Mean | 88.4 | 3.3 | 81.4 | 11.5 |
| SD | 37.6 | 8.4 | 48.6 | 24.1 |
| Cut Point 95th percentile | 164.0 | | 161.7[1] | |
| Mean NC signal | 98.0 | | 84.7 | |
| Normalization[2] Factor (95th percentile) | 66.0[3] | | 76.7[2] | |
| Confirmatory Cut Point | | 29.3 (0.1%) | | 42.1 (1%) |

[1] Cut Point = Mean + (1.645*SD)
[2] Normalization factor = Cut point - Mean NC signal
[3] The in-study confirmatory cut point was calculated from 66 samples that screened positive and confirmed negative using the validation 0.1% confirmatory cut point.

The clinical sample re-analysis results from using the in-study SCP and CCP are shown in Table 2 (IR received on 1/28/19, Question 1A). The data from the re-analysis shows that less samples were screened and confirmed positive for ADAs in comparison to the samples analyzed with the validated CPs.

**Table 2: Assessment of Validation and In-study Screen and Confirmatory Cut points for Study BO22227**

| | Validation Cut Points: 5% screen/ 0.1% confirmatory | In-study Cut Points: 5% screen/ 1% confirmatory | Expected |
|---|---|---|---|
| Total baseline Samples screened | 581 | 581 | |
| Total Screen Positive samples | 100 | 93 | |
| % screen positive (False Positive) | 17.2% (100/581) | 16.0% (93/581) | 5% |
| Total Confirm Negative | 66 | 73 | |
| Total Confirm Positive | 6.0% (35/581) | 3.4% (20/581) | 0.1% Validation 1% In-study |

***Reviewer comment:*** *Based on the results of this re-analysis, Genentech concluded that using the CCP determined during assay validation with 0.1% false positive rate resulted in a conservative calculation of ADA incidence. However, Genentech did not re-analyze the validation data to determine a CCP*

*based on a 1.0% false positive rate, which would have resulted in an acceptable CCP. Considering the option of Genentech to use the less conservative in-study SCP and CCPs based on 5% and 1% false positive rates, respectively, Genentech's approach for clinical sample analysis using the validated SCP and CCP is acceptable. As a result, Genentech did not update the BLA with the newly generated immunogenicity data. This is acceptable.*

**Titer Assay Cut Point**

The SCP is used as the CP for the titer assay (IR response received on 10/5/18, Question 1C). Titers are used to categorize an ADA response in patients that are ADA positive at baseline and post-baseline as either treatment-enhanced or treatment unaffected. The sponsor stated that a treatment-enhanced ADA response is when a patient has one or more post-baseline titers which are at least 4-fold greater than the baseline titer. A treatment-unaffected ADA response is when a patient's post-baseline titers are not at least 4-fold greater than the baseline titer. ADA responses characterized as treatment-enhanced are considered to be treatment-emergent; and therefore, contribute to the determination of incidence of post-baseline ADAs (IR response received on 1/16/19 Question 1B).

**Precision for the Screening Assay**

Precision was determined from 6 runs of the HPC and LPC tested in triplicate per run and performed by 2 analysts. Inter-assay precision was determined by the %CV of the mean signal for the LPC and HPC across the six runs. The inter-assay %CV for the LPC and HPC achieved the targeted performance criterion of %CV $\leq$ 20% (i.e., 8.0% and 12.5%, respectively). Intra-assay precision was determined by the %CV of the mean signal for each of the 6 assay runs. The intra-assay %CV for the LPC and HPC achieved the target performance criterion of %CV $\leq$ 20% (i.e., ranges of 2.2% to 5.1% and 3.5% to 13.1%, respectively).

**Precision for the Confirmatory Assay**

Precision was determined from 6 assay runs of the HPC and LPC, each performed in triplicate per run by two analysts. The inter-assay precision for the LPC and HPC achieved the targeted performance criterion of %CV $\leq$20 (i.e., 2.0% and 0.7%, respectively). The intra-assay precision for the LPC and HPC achieved the targeted performance criterion of %CV $\leq$20 (i.e., ranges of 0.5% to 3.2% and 0.1% to 0.2%, respectively). The data were provided in IR response received on 10/5/18 (Question 1E).

**Precision for the Titer Assay**

Precision for titer was determined from 6 assay runs preformed in triplicate by two analysts (total of 18 runs). The positive control (400 ng/mL) was serially diluted to a dilution factor of 512. Both linear and 4-parameter regressions were performed by plotting assay response mean values (y axis) against dilution (x axis). Titer inter- and intra-assay precision (inter and intra) were outside 25% CV of mean titer response using linear and 4-parameter regressions (Table 6).

An additional approach of calculating the titer was used in this study (i.e., without curve fitting). The titer was the highest dilution factor for a detectable antibody level. The titer values were within two-fold dilution (64 and 128). The approach will be adapted for sample analysis (Table 6).

**Assay Sensitivity**

Assay sensitivity was determined using data (without curve fitting) generated from the 18 titer assay runs (see above). The sensitivity of the method was determined as the mean of the concentration at the CP for the 18 runs (i.e., 5.7 ng/mL, %CV 20.9%).

***Reviewer comment:*** *The determination of assay sensitivity is acceptable. Alternative approaches to determine the assay sensitivity using linear regression and 4-parameter fit generated similar values (6.7 ng/mL and 3.7 ng/ml, respectively) to the value determined without fitting the data. However, these alternative approaches generated sensitivity values with high %CV values (i.e., 43.7% and 33.3%, respectively).*

**Matrix Effect/Method Selectivity**

Ten individual and pooled human serum samples were unspiked or spiked with the PC antibody at the LPC and HPC levels and evaluated in the screening assay. All unspiked samples were below the CP, and all spiked samples were above the CP and achieved the targeted performance criteria (Table 7).

***Reviewer comment:*** *The results show that no matrix effect was observed with the tested samples, i.e., analysis of normal human serum samples does not impact the ability of the assay to detect ADA responses at the LPC and HPC levels. An IR was sent on 9/28/18 to provide analysis of matrix effect/selectivity of human serum samples from the diseased population (BO22227). In the IR response received on 10/5/18, Genentech provided matrix effect/selectivity data from evaluation of 10 commercially sourced sera samples from breast cancer individuals plus a normal human serum control (NC matrix) (Table 26C, IR response received on 10/5/19, Question 1F). Untreated HER2-positive early breast cancer patients were difficult to obtain commercially; therefore, were not used. All 10 breast cancer individual samples and the NC matrix pool were evaluated without the PC antibody and also in the presence of the PC antibody at the LPC level and an intermediate level (100 ng/mL). All 10 of the breast cancer individual samples and the pooled sample tested without the PC antibody screened and confirmed negative in the assay. Nine out of 10 (90%) of the breast cancer individual samples and the pooled sample each containing either 11 ng/mL or 100 ng/mL of the PC antibody screened and confirmed positive. This demonstrates that breast cancer serum does not significantly impact the ability of the assay to detect ADAs at low levels. Considering the additional data provided, the matrix effect/selectivity of the assay was appropriately tested and demonstrated.*

**Cross-reactivity of HER2 ECD**

Cross-reactivity for HER2 ECD, which is the extracellular domain of the transmembrane protein that can be shed into the circulation, was tested. Cross-reactivity was assessed using recombinant shed antigen (HER2 ECD) in both the screening and confirmatory assays. The results show that in the absence of Herceptin a positive signal was produced with HER2 ECD concentration of 500 ng/mL and above. Herceptin inhibited HER2 ECD cross-reactivity in a dose-dependent fashion. At 10 - 50 µg/mL of Herceptin, samples with HER2 ECD concentrations as high as 1000 ng/mL were negative. With Herceptin concentrations less than 10 µg/mL, HER2 ECD may cross react in the assay at concentrations between 500 – 1000 ng/mL.

***Reviewer comment:*** *Mean $C_{trough}$ values for Herceptin IV and Herceptin SC at the time of immunogenicity sampling were typically above 50 µg/mL. For example, at Cycle 8 onboard levels of Herceptin IV and Herceptin SC were 57.8 µg/mL and 78.7 µg/mL, respectively (clinical study BO22227). This indicates that the onboard levels of Herceptin would inhibit the cross-reactivity effect of*

*circulating HER2 ECD in the clinical samples (median concentration in baseline serum samples is 11 ng/mL).*

**Drug Tolerance**

The PC antibody at concentrations of 11, 200, 400, and 4000 ng/mL in normal human serum was incubated with Herceptin at concentrations of 0, 100, 200, 100, 10000, 20000, and 50000 ng/mL (Table 8, copied below). ADAs as low as 200 ng/mL was detected in the presence of Herceptin as high as 50 µg/mL (higher concentrations of Herceptin were not tested). However, the ADA sample with a very low level of ADAs (11 ng/mL) was not detected in the presence of Herceptin at concentrations of 100 ng/mL and higher.

**Table 8**

**Free-Drug Tolerance of Anti-Herceptin Antibody in Human Serum**

Assay Run #CB-0590-8220-970-Val-023

| Herceptin (ng/mL) | 0 | 100 | 200 | 1000 | 10000 | 20000 | 50000 |
|---|---|---|---|---|---|---|---|
| Anti-Herceptin Positive Controls (ng/mL) | Mean Signal | | | | | | |
| 4000 | 103211.0 | 90220.0 | 91064.5 | 46640.0 | 7450.5 | 4010.5 | 1537.5 |
| 400 | 7580.0 | 4274.0 | 2541.0 | 1692.5 | 816.5 | 619.5 | 248.5 |
| 200 | 3584.5 | 1438.5 | 1170.5 | 916.5 | 432.5 | 276.5 | 158.0 |
| 11 | 288.0 | **140.5** | **134.0** | **122.5** | **95.0** | **94.5** | **90.0** |

Cut Point =147.3
**Bold** = signal below cut point

***Reviewer comment:*** *The highest concentration of Herceptin tested in the drug tolerance assessment was 50 µg/mL. Therefore, it is unclear whether this assay is suitable to detect ADAs in the presence of onboard level of drug (noted above). An IR was sent to Genentech on 9/28/18 to submit additional information and data that would address this concern.*

*In response to the IR (received on 10/5/18, Question 1D), Genentech provided additional data (Table 25B of the IR response received on 10/5/18, Question 1D) using the confirmatory ADA assay to show that the ADA positive control at 100 ng/mL was detectable in the presence of 50 µg/mL Herceptin. However, the data was inconclusive for the detection of 100 ng/mL ADA in the presence of 60 µg/mL and 80 µg/mL Herceptin. 400 ng/mL of ADA was detectable in the presence of 60 µg/mL Herceptin. However, the data was inconclusive for the detection of 400 ng/mL ADA in the presence of 80 µg/mL Herceptin. These additional data do not adequately address the concern of whether ADAs at an appropriate level will be detectable during the in-study phase analysis.*

**Table 25B**
**Drug Tolerance of Antibody to Herceptin in Human Serum, Confirmatory (Repeat)**

Assay Run #CB-0590-8220-970-Val-049, Val-050, Val-051 and Val-052

| Set | Set 1 | | | | | Set 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Herceptin (µg/mL) | 0 | 50 | 60 | 80 | 100 | 0 | 50 | 60 | 80 | 100 |
| Anti-Herceptin Positive Controls (ng/mL) | Val-050 | Val-049 | | | | Val-052 | Val-051 | | | |
| | Mean Signal RLU | | | | | Mean Signal RLU | | | | |
| 400 | 5017.5 | 91.0 | 71.5 | 71.5 | 55.0 | 5722.5 | 96.0 | 74.5 | 67.0 | 60.0 |
| 400 (+) Drug | 127.0 | 48.5 | 45.5 | 47.0 | 46.5 | 143.5 | 53.5 | 47.0 | 49.0 | 43.5 |
| 400 % inhibition | 97.5 | 46.7 | 36.4 | 34.3 | **15.5** | 97.5 | 44.3 | 36.9 | **26.9** | **27.5** |
| 100 | 3621.5 | 71.5 | 63.0 | 66.5 | 53.5 | 3971.5 | 77.5 | 66.5 | 60.0 | 54.5 |
| 100 (+) Drug | 97.5 | 42.0 | 45.0 | 44.0 | 41.0 | 112.0 | 48.5 | 42.0 | 47.0 | 41.0 |
| 100 % inhibition | 97.3 | 41.3 | **28.6** | 33.8 | **23.4** | 97.2 | 37.4 | 36.8 | **21.7** | **24.8** |
| 11 | 352.0 | 41.0 | 37.0 | 40.5 | 36.0 | 486.0 | 42.5 | 38.5 | 38.5 | 40.0 |
| 11 (+) Drug | 40.5 | 37.0 | 35.0 | 38.5 | 36.5 | 45.0 | 35.0 | 41.0 | 35.5 | 36.5 |
| 11 % inhibition | 88.5 | **9.8** | **5.4** | **4.9** | **-1.4** | 90.7 | **17.6** | **-6.5** | **7.8** | **8.8** |
| 0 | 45.0 | 36.5 | 36.5 | 41.0 | 35.0 | 51.5 | 36.0 | 36.5 | 37.0 | 39.0 |
| 0 (+) Drug | 32.0 | 38.0 | 34.5 | 36.0 | 37.0 | 35.0 | 33.0 | 39.0 | 34.0 | 38.0 |
| 0 % inhibition | 28.9 | **-4.1** | **5.5** | **12.2** | **-5.7** | 32.0 | **8.3** | **-6.8** | **8.1** | **2.6** |
| Cut Point | 29.3 | | | | | | | | | |

**Bold** = signal below cut point
Confirmatory Cutpoint = 29.3%

*In Appendix A of the IR response, the sponsor provided additional data on the percentage of patients from clinical study BO22227 that tested ADA negative and ADA positive based on whether onboard levels of Herceptin SC and IV were < 50 µg/mL or ≥50 µg/mL (see table below). Out of the post-baseline ADA positive samples, 9 out of 36 had Herceptin levels ≥50 µg/mL, indicating that the assay can detect ADAs in levels of drug beyond the established drug tolerance limit. Although most of the ADA positive samples were detected in samples with Herceptin SC levels < 50 µg/mL at Cycle 2 (n=14), this phenomenon was inversed as more samples had Herceptin SC levels ≥50 µg/mL at Cycles 5, 13, and 18. For example, the % of ADA positive samples was 0.34% (n=1) in samples that had Herceptin SC levels ≥50 at Cycle 2 and increased to 1.0% (n=3) at Cycle 5 and 0.67% (n=2) at Cycles 13 and 18, while only one ADA positive sample was detected in samples with Herceptin SC levels < 50 µg/mL after Cycle 2.*

Trastuzumab Concentration by Antibody Presence

| Result Status | Trastuzumab SC (N=297) N | <50 ug/mL | =>50 ug/mL | Missing | Trastuzumab IV (N=298) N | <50 ug/mL | =>50 ug/mL | Missing |
|---|---|---|---|---|---|---|---|---|
| BASELINE | | | | | | | | |
| N | 290 (98%) | 290 (98%) | 0 | 0 | 291 (98%) | 291 (98%) | 0 | 0 |
| Negative | 275 (93%) | 275 (93%) | 0 | 0 | 273 (92%) | 273 (92%) | 0 | 0 |
| Positive | 15 (5.1%) | 15 (5.1%) | 0 | 0 | 18 (6.0%) | 18 (6.0%) | 0 | 0 |
| CYCLE 2 | | | | | | | | |
| N | 288 (97%) | 257 (87%) | 29 (9.8%) | 2 (0.67%) | 280 (94%) | 247 (83%) | 30 (10%) | 3 (1.0%) |
| Negative | 273 (92%) | 243 (82%) | 28 (9.4%) | 2 (0.67%) | 270 (91%) | 237 (80%) | 30 (10%) | 3 (1.0%) |
| Positive | 15 (5.1%) | 14 (4.7%) | 1 (0.34%) | 0 | 10 (3.4%) | 10 (3.4%) | 0 | 0 |
| CYCLE 5 | | | | | | | | |
| N | 285 (96%) | 91 (31%) | 194 (65%) | 0 | 281 (94%) | 197 (66%) | 82 (28%) | 2 (0.67%) |
| Negative | 282 (95%) | 91 (31%) | 191 (64%) | 0 | 280 (94%) | 196 (66%) | 82 (28%) | 2 (0.67%) |
| Positive | 3 (1.0%) | 0 | 3 (1.0%) | 0 | 1 (0.34%) | 1 (0.34%) | 0 | 0 |
| CYCLE 13 | | | | | | | | |
| N | 262 (88%) | 44 (15%) | 217 (73%) | 1 (0.34%) | 265 (89%) | 111 (37%) | 151 (51%) | 3 (1.0%) |
| Negative | 260 (88%) | 44 (15%) | 215 (72%) | 1 (0.34%) | 264 (89%) | 111 (37%) | 150 (50%) | 3 (1.0%) |
| Positive | 2 (0.67%) | 0 | 2 (0.67%) | 0 | 1 (0.34%) | 0 | 1 (0.34%) | 0 |
| CYCLE 18 | | | | | | | | |
| N | 244 (82%) | 38 (13%) | 205 (69%) | 1 (0.34%) | 246 (83%) | 100 (34%) | 143 (48%) | 3 (1.0%) |
| Negative | 241 (81%) | 37 (12%) | 203 (68%) | 1 (0.34%) | 245 (82%) | 99 (33%) | 143 (48%) | 3 (1.0%) |
| Positive | 3 (1.0%) | 1 (0.34%) | 2 (0.67%) | 0 | 1 (0.34%) | 1 (0.34%) | 0 | 0 |

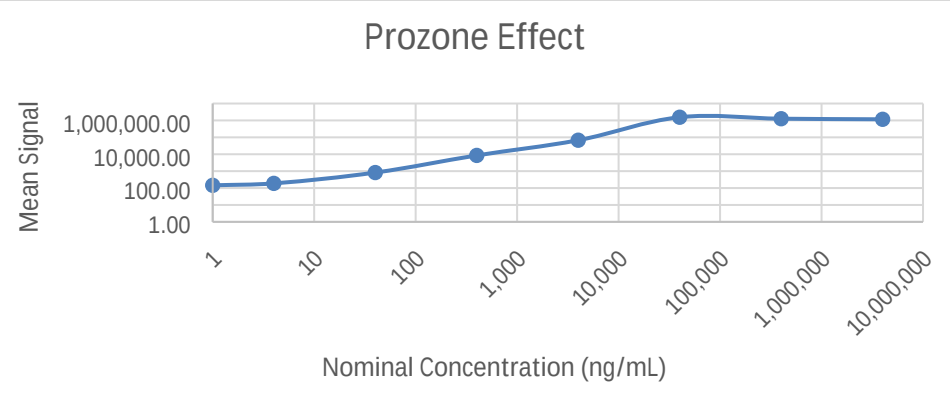
NOTE: 1: All CYCLE concentrations are PRE-DOSE concentrations.
2: Included in the '<50 ug/mL' category are samples with Below Limit of Quantification (BLQ) concentrations.
3: BASELINE and FU MONTH concentrations are included in '<50 ug/mL' category. Since, the concentration level will be very low at these times.
4: Follow-up database lock 09Jul2012.

Source: Biostatistics(vadhavks) pgm(/immuno/her2/bo22227/final2012/programs/t_abconc_ques27)
Database (OPEN) Datasets ( abconc pkconc )
: Generated 14SEP12 16:50 Page 1 of 2

*These data were presented to the clinical and clinical pharmacology reviewers at an internal meeting (11/6/2018) that was held to address the drug tolerance issue with the assay. From this meeting, it was discussed that there might be samples with low levels of ADAs that are not captured by the assay; however, because the onboard levels of Herceptin SC and Herceptin IV at the time of immunogenicity sampling are not statistically different, any bias in detecting ADAs would be comparable for patients treated with Herceptin SC or Herceptin IV. As discussed in the clinical and clinical pharmacology BLA reviews, anti-trastuzumab ADAs did not impact PK, safety, and efficacy. As a result, the clinical and clinical pharmacology teams stated they did not have concerns regarding a potential for not detecting lower levels of ADAs in the clinical samples.*

**Prozone (Hook) Effect**

Prozone effect was examined by serial dilution of the PC antibody from a starting concentration of 4,000,000 ng/mL (Table 9). There was a positive correlation between increasing concentrations of the PC antibody and mean assay signal. No apparent prozone effect was observed at ADA levels up to at least 4,000,000 ng/mL (see below for figure prepared by reviewer).




***Reviewer comment:*** *ADAs at high levels up to 4,000,000 ng/mL did not result in a prozone effect, whereby the response was reported as negative or significantly reduced. The data also suggest that the assay response is saturated around 50,000 – 100,000 ng/mL ADA.*

**Analyte Stability Evaluation**

The stability evaluations were run using NC, LPC and HPC stability samples that were exposed to varying conditions (see below). Freshly prepared non-frozen control samples were included. The targeted performance criteria for all stability evaluation experiments were that stability was acceptable if the means of all LPC and HPC stability samples were within 80 to 120% of response for freshly prepared LPC and HPC stability samples. NC stability samples should test negative relative to the assay CP.

The analyte stability results show:

- Bench top stability of analyte stored at room temperature was shown for 4 and 20 hours (mean PC responses ranged between 82.9 – 95.7%).
- Refrigerator stability of analyte stored at 2 – 8 °C was shown for up to 3 days (mean PC responses ranged between 89.4 – 96.3%).
- Short-term stability of NC, LPC, and HPC stored at -15 to -30°C and -60 to -80°C for 28 days was demonstrated (mean PC responses ranged between 88.7 – 104.0%).
- Freeze/thaw stability and long-term stability results are described below.

Freeze/Thaw (F/T) Stability

Stability samples were subjected to 1F/T, 2 F/T, 4 F/T, and 6 F/T cycles. The F/T samples were compared to freshly prepared PC signals. LPC and HPC control samples for up to 6 F/T cycles had percent mean signal that ranged between 76.2% and 107.1%. NC stability samples were negative relative to assay CP.

***Reviewer comment:*** *One HPC sample had % signal relative to freshly prepared sample below the acceptance criterion of 80 to 120%, i.e., 76.2% for the 2 F/T test; however, 4 F/T and 6 F/T resulted in % relative assay signal that met the acceptance criterion. Therefore, F/T of up to 6 cycles is acceptable.*

Long-Term Storage Stability

Long-term stability of NC, LPC, and HPC stored at -15 to -30°C and -60 to -80°C for 3, 6, 9, and 12 months (± 5 days) relative to freshly prepared samples was evaluated. All NC stability samples were

negative relative to the assay CPs. The mean signal responses for LPC and HPC stability samples stored at -60 to -80°C ranged between 91.6 and 118.1%. For the HPC stability samples stored at -15 to -30°C, the 6-month and 12-month samples had relative mean signal of 126.9 and 134.6%, which were outside the acceptance criteria of 80 to 120%. Therefore, these results demonstrated 9 months stability at -15 to -30°C and 12 months stability at -60 to -80°C.

***Reviewer comment:*** *All testing conditions demonstrated adequate stability of the analyte. We do note that for long-term stability at -15 to -30°C, the HPC stability sample at 6 and 12 months of storage showed higher relative mean signals (126.9% and 134.6%, respectively) compared to the acceptance criterion of 80 to 120%; however, a higher signal indicates that ADA detection will not be missed and is acceptable. PCs and clinical samples were stored at -70°C prior to assay analysis.*

**Neutralizing Antibody Assay**
**Cell-Based Assay to Detect Neutralizing Anti-Trastuzumab Antibodies in Human Matrix (BA.MET.HH2.016.AVR_0)**
The Nab assay was developed and qualified at Roche Penzberg, then transferred and validated at Roche Nutley (Appendix 1), and finally transferred and partially validated at Genentech (Appendix 2). The assay transfer experiments at Genentech were performed from July 3, 2013 to August 26, 2013. The study report was finalized on February 5, 2014. The latest version of BA.MET.HH2.016 is presented in Appendix 3. Clinical samples from study BO22227 were tested for neutralizing antibody activity from September 18, 2013 to January 16, 2014, and the study report was finalized on August 26, 2014 (BO22227_NAb_BAR_0, Section 5.3.1.4).

**Appendix 1 (Roche, Nutley): Validation Report for Analysis of Anti-RO0452317 Neutralizing Antibodies in Human Serum – Amended Version of Original Report Dated December 20, 2011**

**Screening Assay**
The NAb assay is a cell-based assay using BT-474 breast cancer cells, which express Her2/Her2 and Her2/Her3 receptor dimers. BT-474 cells are treated with Herceptin in the presence of confirmed ADA positive samples and incubated for 5 days. WST-1 cell proliferation reagent is added, which produces an assay response that is proportional to the number the viable cells. The optical density (OD) values obtained were used as a measure of cell proliferation. Levels of proliferation (%P) were calculated relative to the mean values of a maximum and a minimum proliferation control. Binding of Herceptin to Her2/Her2 or Her2/Her3 receptor dimers inhibits proliferation of the BT-474 breast cancer cells resulting in a decrease in cell counts and assay response. In the presence of NAbs to Herceptin, the inhibitory effect of Herceptin is blocked, leading to increase in cell counts and assay response. A plate-specific SCP was set at the mean %P of the NC plus the NF (17.5%). Samples that produced a %P less than the SCP are reported as NAb negative; however, samples that produced a %P greater than or equal to the SCP are further analyzed in the confirmatory assay.

**Confirmatory Assay (also referred as Matrix Interference Assay)**
Samples that screen positive are tested in a confirmatory assay using an alternative stimulus. In this assay, BT-474 cells are incubated with an alternative stimulus, Her2/neu (an antibody against Her2), that binds Her2/Her2 or Her2/Her3 receptor dimers. The cells are then treated with WST-1 cell proliferation reagent that produces an assay response proportional to the number of viable cells. Similar to Herceptin, the alternative stimulus inhibits proliferation of BT-474 cells. However, NAbs specific to Herceptin do

not bind to the alternative stimulus. Therefore, if NAbs against Herceptin are present, there will not be an increase in proliferation in the presence of the alternative stimulus. If a patient sample contains factors that inhibit the response of the alternative stimulus, it would result in an increase in proliferation. The result would be assessed as NAb negative, not specific to trastuzumab. Samples that produced a %P in the confirmatory assay greater than the CCP (56%) are reported as NAb negative, while samples that produced a %P less or equal to the CCP are reported as NAb positive.

**Titer Assay**
If required, samples that are confirmed NAb positive are assayed at different dilutions to determine the anti-Herceptin NAb titer.

***Reviewer comment:*** *The method includes a titer assay; however, validation data were not provided to support the suitability of the titer assay. It is unclear under what conditions would NAb positive samples be evaluated in the titer assay. Because NAb titer data from clinical sample analysis were not reported in the BLA, this is acceptable.*

**Assay Controls**
The NC was established by pooling equal volumes of ten individual lots of normal human serum. The NC was stored at -20°C. The PC is an affinity purified rabbit polyclonal anti-RO0452317 antibody, which was aliquoted and stored at approximately -70°C. The PC was prepared at low (LPC,2.0 µg/mL) and high (HPC, 10 µg/mL) concentrations. Additional controls include blank and minimum (OD min) and maximum (OD max) proliferation controls. Although the proliferation controls were not sufficiently described, it is reasonable to conclude that the minimum proliferation control consists of BT-474 cells treated with WST-1 and Herceptin (screening assay) or the alternative stimulus (confirmatory assay), while the maximum proliferation control consist of BT-474 cells treated with WST-1.

***Reviewer comment:*** *Insufficient justification was provided for setting the LPC and HPC. It is recommended that the LPC is set to allow an appropriate rejection rate (e.g., 1% failure of the runs). Therefore, an IR was sent on 1/10/19 to provide justification for the selection of the LPC. In the IR response received on 1/16/19 (Question 2E), the sponsor stated that during analysis of BO22227 clinical samples for NAbs, the assay failure rate was 13.3% (2/15) because the LPC at 2 µg/mL failed to consistently screen positive. Genentech noted that the LPC concentration was not statistically determined but was set to provide a response 3 times higher than the assay sensitivity. Genentech should determine whether the LPC is set at an appropriate concentration for future use of the assay. No comment is needed at this time.*

**Analytical Run Acceptance Criteria (System Suitability)**
Each assay is run with NC, LPC, HPC, blank, OD min, and OD max controls (Section 5.3 of the method protocol). An analytical run is considered acceptable if (i) Ratio of Mean ODMax/Mean ODMin ≥ 1.6 and (ii) %P of NC < CP < %P of LPC < %P of HPC.

The plate acceptance criteria for the NC, LPC, HPC, and the Max/Min ratio during validation and sample analysis are show below (IR response received on 1/28/19, Question 2G):

- The mean OD of the NC must be greater than the mean OD of the Min and less than the mean OD of the Max

- The ratio of the Max mean OD/Min mean OD must be ≤ 1.6
- For the screen assay, the %P of the LPC and HPC must be greater than the screening plate specific cut point
- For the confirmatory assay, the %P must be less than the fixed confirmatory cut point
- The %P of the NC must be less than the plate specific cut point
- The value % P is calculated using the following formula: ((mean OD control/sample - mean OD Min)/(mean OD max – mean OD min))x100

***Reviewer comment:*** *The system suitability and assay acceptance criteria appear appropriate and were met during validation and clinical sample analysis runs. Because of the method variability of the assay (discussed below), it was recommended that a system suitability or assay acceptance criterion be included to control for the precision (%CV) of replicates for each control. Genentech acknowledged the Agency's comment.*

**Screening Cut Point and Normalization Factor Determination**

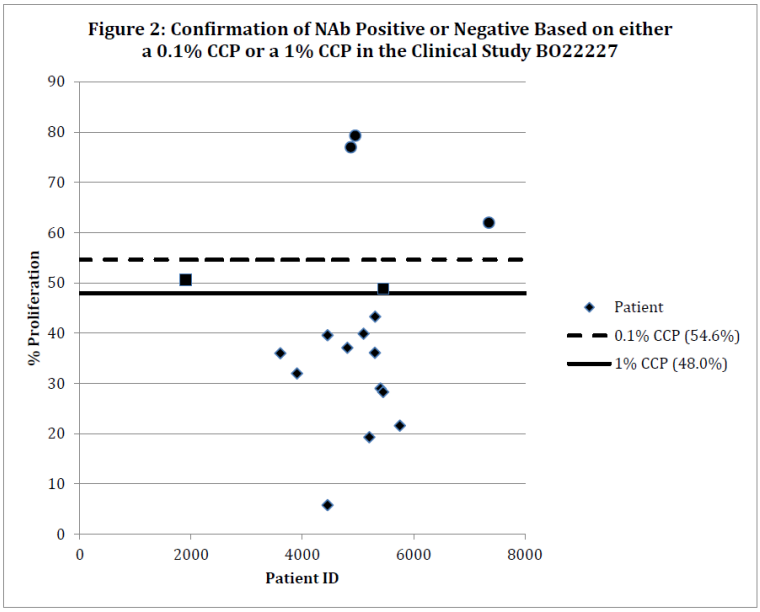
The SCP was determined from evaluation of 52 commercially-sourced, individual, normal human serum samples (IR response, 1/16/19, Question 2B) that were assayed in triplicate on three separate runs resulting in 156 mean optical density (OD) values (Table 2, NAb Validation Report, page 17). The mean OD values are converted using the minimum and maximum cell proliferation OD values to generate % P values for each sample (%P = ($MeanOD_{sample}$-$MeanOD_{Min}$) / ($MeanOD_{Max}$-$MeanOD_{Min}$) * 100). The %P values from the samples were compared to the %P mean of the plate NCs to obtain a NF (CP - %P of the NC for each plate). Initially, the distribution of the %P values was evaluated using box plot analysis and outliers were identified as being higher than the 75$^{th}$ percentile plus 1.5 x IQR or lower than the 25$^{th}$ percentile minus 1.5 x IQR (IR response received on 1/28/19, Question 2C). One outlier was identified and removed. The resulting data were evaluated for normality using Shapiro-Wilk test, which indicated the data were non-normal (p=0.0096). The upper limit of one-sided 95% prediction confidence interval (CI) was used to non-parametrically calculate the plate specific floating SCP based on a 5% false positive rate. The CP value was calculated to be 56% P. The mean NC value was calculated as 38.5% P, which resulted in a NF of 17.5%. The plate specific floating SCP is calculated as NF + %P of the mean NC for a given plate.

**Confirmatory Cut Point**

The CCP was determined from analysis of the same serum samples that were assessed in the screening assay but were treated with the alternative stimulus instead of Herceptin. These samples were assayed in triplicate on three separate days resulting in 156 mean %P values (Table 11). The data distribution was evaluated for outliers using boxplot analysis. Outliers were identified as higher than the 75$^{th}$ percentile plus 1.5 x IQR or lower than the 25$^{th}$ percentile minus 1.5 x IQR. Six outliers were identified and removed. The resulting data were tested for normality using Shapiro-Wilk test, which indicated that the data are normally distributed. A parametric method (mean + 3.09 x SD) was used to determine the CCP based on a 0.1% false positive rate, which was calculated as 54.6% P.

***Reviewer comment:*** *Genentech had set the CCP at a false positive rate of 0.1%. An IR was sent regarding the suitability of their CCP. In the IR response received on 1/28/19, Question 2A, Genentech provided the following explanation on the suitability of their CCP. The sponsor's justification is acceptable.*

The CCP of the NAb assay was defined to overestimate the percentage of confirmed NAb positive samples (including potential false positive NAbs) because of the known nature of cell-based NAb assays to be susceptible to matrix effects. Therefore, the one-sided 99.9% prediction interval, based on distribution of the blank samples spiked with the alternative stimulus from validation, was used to calculate the CCP of 54.6%. Using the same dataset, the one-sided 99% prediction interval CCP (1% false positive rate) would be 48%. Changing the one-sided prediction interval from 99.9% to 99% would result in detection of fewer confirmed NAb positive samples. This is different from the typical ADA screening/confirmatory assays due to the format of the CCP. In this assay, an increased assay response above the CCP is assessed as confirmed NAb-negative. The sponsor provided Figure 2 in the IR response to illustrate this point. Because in this assay a %P response at or above the CCP would indicate the presence of NAbs, the 0.1% false positive rate CCP (dotted line) is more conservative than the 1% false positive rate CCP (solid line).




**Suitability of Validation Cut Point for Clinical Study Samples**

***Reviewer comment:*** *An IR was sent to Genentech on 1/10/19 (Question 2B) to provide data to support the suitability of the validated SCP and CCP to analyze the clinical samples from study BO22227. Genentech's response is summarized below.*

During qualification, Genentech initially calculated the SCP and CCP from 42 commercially sourced healthy human serum samples (24 female and 18 male). The samples were analyzed in triplicate in 4 runs. The normalized %P values for the serum samples are presented in Table 2 (IR response 1/16/19, Question 2B). The global CP was calculated as 66% P. To demonstrate the suitability of this CP for analysis of diseased serum samples, the CP from commercially sourced serum samples from 20 female breast cancer subjects was determined. These samples were analyzed in 3 replicates in plate 1 and 6 replicates in plate 2 and the results are presented in Table 3 (IR response 1/16/19, Question 2B). The CP from plate 1 was 58% and from plate 2 was 67%, which are similar to the CP based on the analysis of normal human serum samples (66%). The %P values were generally comparable between the two datasets. In addition, all the breast cancer serum samples tested negative using the plate-specific SCP calculated from the commercially-sourced healthy human serum samples. Furthermore, Genentech

calculated the false positive rate for the analysis of pre-dose study BO22227 samples using the SCP and CCP determined during assay validation. These results are shown in Table 4 of the IR response 1/16/19, Question 2B).

**Table 4: Cut Point Assessment Using Baseline Samples from Study BO22227**

| | BO22227 | Expected |
|---|---|---|
| Confirmed ADA positive baseline samples | 33 | |
| Screen NAb positive baseline samples | 8 | |
| **% baseline screen positive** | **24% (8/33)** | **5%** |
| Confirm NAb Negative baseline Samples | 1 | |
| Confirm NAb Positive baseline Samples | 7 | |
| **% Screen False Positive (Screen Positive/Confirm Negative)** | **3% (1/33)** | |
| **% baseline Confirm Positive** | **21% (7/33)** | **1%** |

***Reviewer comment:*** *The table shows that the validated SCP and CCP are set conservatively, resulting in a greater percentage of screened positive and confirmed positive NAbs than expected based on CP calculation. Based on the additional data provided, the validated SCP and CCP appear appropriate to analyze the clinical BO22227 samples.*

## Assay Sensitivity

Assay sensitivity was determined using the PC antibody diluted in two-fold serial dilutions using the NC as a matrix. The samples were run in 6 independent assays on three different plates. The point at which the concentration versus OD curve intersected with the plate CP had an average antibody concentration of 580 ng/mL (Table 5).

**Table 5**

**Sensitivity for Anti-RO0452317 in Human Serum**

**Observed % Proliferation of Anti-RO0452317 Spiked at Varying Concentrations**

| Run Number 5 | Curve Number | Anti-RO0452317 (µg/mL) | | | | | | | Antibody Concentration at CP (µg/mL) |
|---|---|---|---|---|---|---|---|---|---|
| | | 10.0 | 5.0 | 2.5 | 1.0 | 0.5 | 0.25 | 0 | |
| Plate Number | | % Proliferation | | | | | | | |
| 1 | 1 | 93.4 | 100.7 | 79.8 | 59.6 | 51.5 | 46.8 | 39.6 | 0.8 |
| CP = 57.2 % | 2 | 95.2 | 92.1 | 74.0 | 52.3 | 44.1 | 36.5 | 39.8 | 1.3 |
| 2 | 3 | 102.0 | 91.7 | 72.6 | 45.0 | 43.4 | 32.2 | 10.8 | 0.3 |
| CP = 32.8% | 4 | 92.3 | 83.8 | 80.2 | 48.0 | 35.7 | 38.6 | 19.8 | 0.3 |
| 3 | 5 | 82.7 | 72.1 | 67.1 | 38.3 | 39.5 | 34.6 | 14.8 | 0.3 |
| CP = 32.9 % | 6 | 81.2 | 71.8 | 60.9 | 39.2 | 30.6 | 29.3 | 16.1 | 0.5 |
| | | | | | | | | | |
| Mean | | 91 | 85 | 72 | 47 | 40.8 | 36.3 | 23.5 | 0.58 |
| % CV | | 8.7 | 13.7 | 10.3 | 17.2 | 17.8 | 16.7 | 54.9 | 68.9 |
| | | | | | | | | | |
| Assay Sensitivity = Mean Antibody Concentration at CP = 0.58 µg/mL ± 0.4 | | | | | | | | | |
| CP = Plate specific cut point (% Proliferation) | | | | | | | | | |

***Reviewer comment:*** *There was significant variability in the determination of the assay sensitivity (69% CV), which was not observed during the analysis of the %P mean values for each PC concentration. It appears that this is a result of a higher background for Plate 1 (assay runs 1 and 2) in comparison to that of Plate 2 (assay runs 3 and 4) and Plate 3 (assay runs 5 and 6). As noted below, there is some variability in the assay for the NC signal. Regardless, considering the worst-case sensitivity reported for*

*the 6 assay runs (i.e., 1300 ng/mL in assay run 1), the sensitivity value is still acceptable for a cell-based NAb assay. Therefore, the determination of assay sensitivity is acceptable.*

**Intra-Assay and Inter-Assay Precision for Screening Assay**
The precision of the OD mean values from cell proliferation controls and Max/Min ratio was determined from plate controls that were run in triplicate and consisted of 21 assays performed on 7 different days. The inter-assay %CV for ODMin was 25.3%, for ODMax was 23.7%, and for Max/Min ratio was 11.9% (Table 3).

Inter-assay precision (OD and %P mean values) and intra-assay precision (OD mean values) of NC, LPC, and HPC from all available validation runs (Table 4 and Table 6, respectively). Inter-assay precision of the OD mean values for NC, LPC, and HPC were 29.3%, 29.3%, and 22.0%, respectively. Inter-assay precision of the %P mean values for NC, LPC, and HPC were 69%, 37%, and 29%, respectively. Intra-assay precision of OD mean values for NC ranged 2.1 to 9.2%, for LPC ranged 0.2 to 16.5%, and for HPC ranged 1.1 to 7.8%.

***Reviewer comment:*** *Intra-assay precision for NC, LPC, and HPC was acceptable, while the inter-assay precision was high for NC. An IR was sent to Genentech on 1/10/19 to provide an explanation for the observed variability with the NC. In the IR response (received 1/28/19, Question 2G), Genentech stated that high inter-assay variability was expected with cell-based NAb assays, which may include, characteristics of the cell lines, seed densities, cell passage, and many other parameters. The significant observed variability (%CV) of the NC %P mean values was a combination of the observed variability from the mean ODs of the NC, Min and Max controls across assay runs. Given the nature of the NAb assay and the adequate precision of the PCs, the precision of the assay is acceptable.*

**Intra-Assay and Inter-Assay Precision for Confirmatory Assay**
Inter- and intra-assay precision for the confirmatory NAb assay was determined from 15 assay runs performed over 5 days (IR response received on 1/28/19, Question 2F). Inter-assay precision for OD mean values for NC, LPC, and HPC were 19.1%, 18.5%, and 18.9%, respectively. Inter-assay precision of the %P mean values for NC, LPC, and HPC were 30.0%, 35.8%, and 25.7%, respectively. Intra-assay precision for OD mean values for NC, LPC, and HPC were 2 to 9%, 1 to 10%, and 1 to 6%, respectively.

**Matrix Effect**
Matrix effect was assessed by spiking 10 different lots of human serum with the PC antibody at LPC (2 µg/mL) and HPC (10.0 µg/mL) concentrations. The %P for all the HPC spiked samples was above the CP. %P for 9 out 10 LPC spiked samples was above the CP.

***Reviewer comment:*** *The results indicate no major matrix effect. Although diseased samples were not evaluated for matrix interference; data provided from commercial breast cancer patient samples resulted in similar background levels in comparison to the commercial normal human serum samples that were used to validate the assay (see CP discussion above).*

**Drug Tolerance**
Drug tolerance was determined by incubating human serum with the PC antibody at LPC and HPC concentrations and adding Herceptin at concentrations of 0.15, 0.5, 1, 10, 30, and 70 µg/mL. The highest

concentration of Herceptin that allowed for the detection of the HPC (10 µg/mL) was 1 µg/mL, and the highest concentration of Herceptin that allowed for the detection of the LPC (2 µg/mL) was 0.5 µg/mL.

**Table 9**

**Drug Tolerance Test**

**Observed % Proliferation of Anti-RO0452317 Spiked in Human Serum in the Presence of RO0452137**

| Run Number 7 | RO0452317 (µg/mL) | | | | | |
|---|---|---|---|---|---|---|
| Anti-RO0452317 Antibody | 70 | 30 | 10 | 1 | 0.5 | 0.15 |
| | % Proliferation | | | | | |
| 10.0 µg/mL | -29.0 | -27.1 | -23.0 | **65.0** | **94.7** | **100.2** |
| | | | | | | |
| 2.0 µg/mL | -20.3 | -27.2 | -22.3 | 0.7 | **61.4** | **113.4** |
| | | | | | | |
| Plate Specific CP = 39.4% | | | | | | |
| Observed %Proliferation ≥ Plate Specific CP is indicated in bold | | | | | | |

***Reviewer comment:*** *Given that onboard levels of Herceptin at the time of immunogenicity sample was 78.7 µg/mL on Cycle 8 pre-dose and 90.4 µg/mL Cycle 13 pre-dose, the assay does not appear to be sensitive at detecting NAb activity during the in-study phase. An IR was sent to Genentech on 1/10/19 to provide additional validation data and information (i.e., Herceptin levels in clinical samples that were evaluated by the NAb assay) to demonstrate the suitability of their NAb assay for detection of NAbs in the clinical BO22227 study samples. In the IR response received on 1/16/19 (Question 2D), Genentech acknowledged that Herceptin concentration during the in-study phase was higher than the drug tolerance level of the NAb assay but stated that the assay was capable of detecting some NAb positive samples during the in-study phase. Genentech provided PK data that shows NAb positive and NAb negative samples detected during the in-study phase had comparable mean levels of Herceptin. Because of the lack of drug tolerance to onboard levels of drug in the in-study phase demonstrated during validation, it is likely that samples with Nab present may have been undetected. Beyond the in-study phase, NAb positive samples were detected up to the follow-up 12-month time point. Genentech stated that Herceptin concentrations in clinical samples collected during the follow-up phase (treatment-free) were below the drug tolerance for the NAb assay; however, these data were not provided in the IR response to support Genentech's claim. Discussion with the clinical and clinical pharmacology teams they did not have concerns from their perspectives regarding a potential of not detecting samples with NAbs present.*

**Effect of Cell Passage Number**

The validation experiments were performed on cells ranging from passage number 2 to 16; therefore, assay performance is validated in this range of cell passages.

**Positional Effects**

Positional effect of samples on the assay plate was evaluated in one run using the LPC. The LPC was positioned in rows B – G and columns 4 – 9. The results in Table 8 showed that the OD values varied from 0.909 – 1.137 irrespective of the location of the LPC, and %P for each plate location was above the plate specific CP.

***Reviewer comment:*** *The assessment of positional effects is acceptable. The location of controls and samples does not show a bias in OD value readings.*

**Stability**

The stability of the LPC (2 µg/mL) and HPC (10 µg/mL) in NC serum was tested in 3 replicates. The studies are described in Section 4 of the validation report and results are shown in Tables 12 to 14 and Tables 16 to 18.

- Benchtop (room temperature) stability (Table 12): Samples were tested for 4 and 36 hours storage at room temperature and the results showed that they were stable for up to 4 hours.
- Freese/Thaw (F/T) stability: Samples were tested for 0, 1, and 5 F/T and the results showed that the PC antibody was stable in human serum for one F/T cycle (Table 13). Additional studies were performed to test 1, 6, 7, 8, 9, and 10 F/T cycles and the results showed that samples were stable for up to 10 F/Ts (Table 17).
- Freezer Stability (Table 14): Samples were tested after storage at -20°C and -70°C for 11, 470, and 678 days and the results demonstrated that the samples were stable under the indicated conditions.

***Reviewer comment:*** *For assessment of F/T stability, there is a discrepancy between the first study and the second study. The first study (Table 13) showed a linear relationship between PC concentration and %P, as expected, and the validated condition was 1 F/T. The second study (Table 17) does not show a linear relationship between PC concentration and %P; however, the validated condition was 10 F/T. It is not clear what was different between the 2 studies.*

*An IR was sent to Genentech on 1/10/19 to provide (i) an explanation for the discrepancy in LPC results between the two studies, (ii) the LPC and HPC results prior to F/T cycling from the second study, and (iii) the NC results from the first and second studies. In the IR response (received on 1/28/19, Question 2H), Genentech attributed the discrepancy to method variability of assay. They stated that the NAb assay is a qualitative assay, where samples are classified as Positive or Negative. Even with the high variability at the LPC level (values ranging 67.2% to 113.0% in the second study, Table 17), the assay results in all cases were classified as Positive, which demonstrated the stability of the positive control antibody for at least 10 F/T cycles at the LPC level. The NC had %P of 4.5% (6 replicates) in the first F/T study (Table 13) and 19.8% in the second F/T study (Table 17), which indicates that the NCs were below the plate-specific SCP as expected.*

**Appendix 2 Method Transfer to Genentech**

The method was partially validated at Genentech to support the suitability of the method to analyze the BO22227 clinical samples. The partial validation included an evaluation of inter-assay and intra-assay precision (data were provided in IR response received on 1/16/19, Question 2I). The precision assessment was determined from 4 assay runs, each consisting of two plates (total 8 plates). For the screening assay, Plate 1 from run 7 did not pass the assay acceptance criteria for the min/max ratio; therefore, the sponsor provided precision results with or without plate 1/run7 included.

<u>Screening Assay</u>

Inter-assay precision (%CV) for OD mean values for NC, LPC, and HPC, were 11%, 8%, and 10% respectively. Inter-assay precision (%CV) for %P mean values for NC, LPC, and HPC, were 40%, 46%,

and 35% respectively. If plate1/run7 is excluded, inter-assay precision (%CV) for OD mean values for NC, LPC, and HPC, were 10%, 7%, and 7% respectively. Inter-assay precision (%CV) for %P mean values for NC, LPC, and HPC, were 28%, 19%, and 13% respectively. Intra-assay precision (%CV) for OD mean values for NC, LPC, and HPC, were 4.4 – 28.6%, 1.7 – 7.5%, and 1.6 – 37.7% respectively. If plate1/run7 is excluded, inter-assay precision (%CV) for OD mean values for NC, LPC, and HPC, were 4.4 – 8.2%, 1.7 – 7.5%, and 1.6 – 10.3% respectively.

Confirmatory Assay

Inter-assay precision (%CV) for OD mean values for NC, LPC, and HPC, were 16%, 13%, and 8% respectively. Inter-assay precision (%CV) for %P mean values for NC, LPC, and HPC, were 14%, 22%, and 29% respectively. Intra-assay precision (%CV) for OD mean values for NC, LPC, and HPC, were 2.3 – 30.8%, 0.1 – 22.4%, and 1.6 – 8.0% respectively.

***Reviewer comment:*** *The precision data suggest that the method performs adequately at the Genentech site and is suitable for clinical sample analysis.*

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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SHADIA ZAMAN
02/01/2019 09:24:04 PM

BRIAN M JANELSINS
02/01/2019 10:13:12 PM

# CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

| | |
|---|---|
| **COA ID** | C2018173 |
| **BLA #** | 761106 |
| **Referenced IND for NDA/BLA** | 109168 |
| **Established Name/Trade Name** | Herceptin subcutaneous (trastuzumab and human hyaluronidase – rHuPH20) |
| **Applicant** | Genentech |
| **Indication** | Treatment of HER2-overexpressing breast cancer |
| **Meeting Type/Deliverable** | Review |
| **Applicant Letter Date/SDN #** | May 1, 2018 |
| **Date of Consult Request** | June 8, 2018 |
| **Review Completion Date** | January 29, 2019 |
| **Review Division** | Division of Oncology Products 1 |
| **Clinical Reviewer/Clinical Team Leader(CTL)** | Danielle Krol/ Jennifer Gao / Laleh Amiri Kordestani |
| **Review Division PM** | Amy Tilly |
| **COA Reviewer** | Yasmin Choudhry |
| **COA TL** | Selena Daniels |
| **COA Associate Director** | Elektra Papadopoulos |
| **Instrument 1** | Patients' Experiences and Preferences towards either IV or SC Herceptin – Pre-Study and Post Study Interview |
| **Instrument 2** | Health Care Professional Questionnaire |
| **COA Type 1 and Endpoint Concepts** | Patient-reported outcome (PRO)-interview administered; patient preference of treatment route of administration |
| **COA Type 2 and Endpoint Concepts** | Clinician-reported outcome (ClinRO); HCP satisfaction |
| **Intended Population** | Adult subjects with HER2-positive early breast cancer undergoing neoadjuvant treatment |
| **Internal Meeting** | N/A |
| **Applicant Meeting/WRO** | N/A |

***Please check all that apply:*** ☐Rare Disease/Orphan Designation
☐Pediatric

# A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Oncology Products 1 (DOP1) regarding BLA 761106 for trastuzumab (Herceptin) and hyaluronidase human solution injection for subcutaneous (SC) use. Herceptin is currently marketed in a formulation of a powder for concentrate for solution for infusion (via intravenous (IV) access) for the treatment of HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. The Applicant has developed a SC formulation of Herceptin. The proposed indication for Herceptin SC is treatment of HER2-overexpressing breast cancer.

The Applicant implemented the following instruments in their international, randomized, multicenter, open-label, two-cohort, two-arm, crossover phase 2 trial (Study MO22982; PrefHER) in adult patients with HER2-positive[1] early breast cancer undergoing neoadjuvant treatment:

**Table 1.** Study endpoints in PrefHER study

| **Instrument name (COA Type)** | **Concept(s)** | **Endpoint** | **Copy of Instrument** |
|---|---|---|---|
| Patients' Experiences and Preferences towards either IV or SC Herceptin –Pre-and Post Study Interview Guide (PINT1, PINT2)-PIN2 Items 53; 54a and b (PRO-interview administered) | Preference of method of treatment administration (SC vs IV) | Primary | See Appendix A |
| Health Care Professional Questionnaire (HCPQ) | Satisfaction with treatment administration; Perceived time savings | Secondary | See Appendix B |

**ClinRO=** Clinician-reported outcome; **PRO=** Patient-reported outcome

The Applicant seeks labeling claims related to the instruments used in the PrefHER study (Table 1). For the proposed claim language, see section D (1.4) of this COA review.

The Division seeks COA Staff input on:
(1) the adequacy of the methods used to conduct the patient preference telephone interviews, including the instrument (interview guide) to support labeling claims; and
(2) the wording of the Applicant's proposed targeted labeling claims

[1] HER2-positive defined as 3+ overexpression by immunohistochemistry [IHC] or HER2-positive by in situ hybridization [ISH]

This review concludes the following:

1. The methods used to conduct the telephone interviews appear to be consistent with best practices of survey research (e.g., the Applicant sought expert opinion and patient input for item generation of the interview guide, translated the interview guide using forward and backward translation, pilot-tested the interview guide). While interviewer bias is a common limitation of telephone interviews/surveys, the extent of such a bias is unknown and cannot be fully eliminated. In an effort to mitigate this limitation, the Applicant proactively recorded the telephone interviews for quality control purposes.
2. Based on review of the PrefHER study materials (e.g., methodology of patient interviews, translation process, standard operating procedures, training manual for interviewers), the patient preference telephone interviews appear to be conducted in a standard manner. Further, the instrument (interview guide) appears to be fit-for-purpose to assess patient preference for the method of treatment administration (SC vs. IV).
3. With regard to wording of the labeling claims, we recommend using wording that is consistent to previously patient preference data (e.g., provide a balanced description of both methods of treatment administration, specify that the data is from patients outside the U.S.). The data from the telephone interviews does not adequately support labeling claims related to symptomatic adverse events as the PrefHER study did not include any patient-reported assessments of symptomatic adverse events (e.g., pain/discomfort associated with injection or intravenous site).

# B. BACKGROUND

Material reviewed:

- Genentech's Submission (SDN 1) dated May 1,2018
- DOP 1 consult request dated June 8, 2018

Investigational Product

Trastuzumab (Herceptin) is a humanized monoclonal antibody that selectively targets the extracellular domain of Human epidermal growth factor receptor-2 (HER2). The SC administration of Herceptin is enabled by the use of recombinant human hyaluronidase (rHuPH20) which acts as a permeation enhancer in the Herceptin SC formulation. Hyaluronidase transiently depolymerizes hyaluronan, a component of the SC tissue extracellular matrix, while leaving important structural macromolecules, such as collagen and elastin unaffected.

# C. CLINICAL OUTCOME ASSESSMENT REVIEW

# 1 CONTEXT OF USE

## 1.1 Clinical Trial Population

The clinical trial population was adult subjects with primary invasive adenocarcinoma of the breast that was histologically confirmed and HER2-positive (defined as 3+ overexpression by

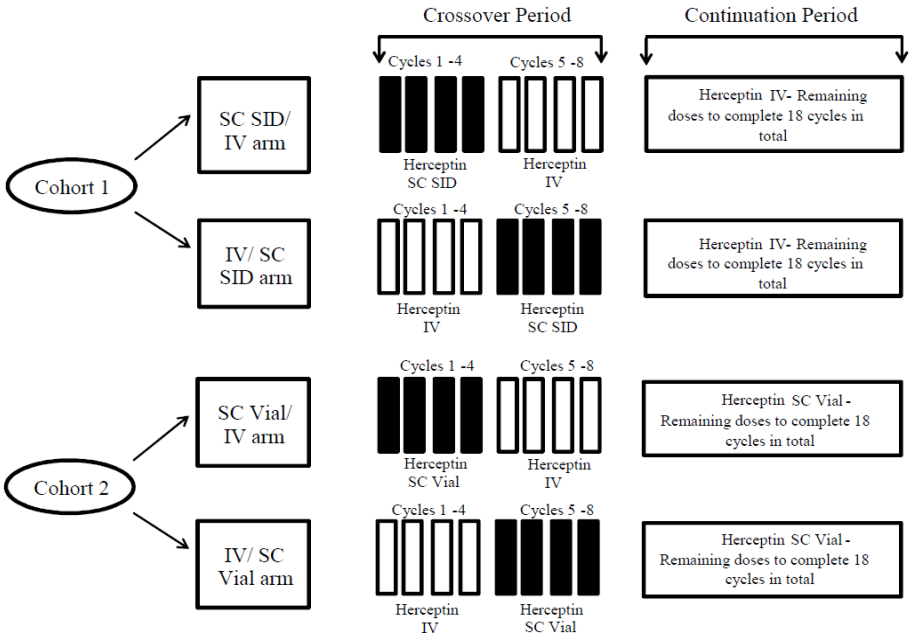
immunohistochemistry or HER2-positive by in situ hybridization with no evidence of residual, locally recurrent or metastatic disease after completion of surgery and chemotherapy. Refer to the Clinical review for a complete list of the inclusion and exclusion criteria for the Study PrefHER.

## 1.2 Clinical Trial Design

**Study MO22982 (PrefHER)]:** N=488
Study PrefHER is an international, randomized, multicenter, open-label, two cohort, two-arm, crossover phase 2 trial conducted in a population of HER2-positive EBC patients undergoing adjuvant treatment. The trial was designed to investigate patient preference for method of treatment administration of Herceptin IV or Herceptin SC (via single use injection device [SID] or handheld syringe [Vial]) and to compare health care professional (HCP) satisfaction and perceived time-savings with the two methods of administration (IV vs. SC) in the adjuvant treatment setting.

Patients (n=488) were randomized following surgery and the completion of neoadjuvant chemotherapy (possibly including neoadjuvant Herceptin) in a 1:1 ratio to one of two sequences of Herceptin treatment in Cohorts 1 and 2. The study schema is shown in Figure 1.

**Figure 1.** PrefHER Study Design



Abbreviations: IV=intravenous; SC=subcutaneous; SID=single-use injection device
Notes:
Treatment in Cohort 1 continuation period was Herceptin IV; treatment in Cohort 2 continuation period was Herceptin SC Vial.
Prior to randomization, patients were interviewed via the telephone to assess the factors influencing preference (first patient interview [PINT1]). At the end of the eighth cycle subsequent to randomization, a second patient interview (PINT2) was performed. This interview concluded with a single binary assessment of preference.
Herceptin SC dose (for both SC SID and SC Vial) was 600 mg 3-weekly.
Herceptin IV dose was 6 mg/kg 3-weekly. A loading dose of 8 mg/kg was required only if Cycle 1 of study treatment was the initial IV dose of Herceptin, otherwise dose was 6 mg/kg 3-weekly.
Patients in Cohort 1 (SID) who had at least 2 treatment cycles remaining of their full 18-cycle treatment course were offered the opportunity to self-administer SC Herceptin using the SID under the supervision of a trained HCP.
Enrollment into each cohort did not occur in parallel. The addition of Cohort 2 occurred after a protocol amendment and was optional for each site. It was only implemented if feasible at that site.

Herceptin was administered every 3 weeks on Day 1 of each cycle. For patients who had already started adjuvant Herceptin (as monotherapy following completion of chemotherapy or in combination with adjuvant chemotherapy followed by Herceptin monotherapy), the first dose of trial Herceptin was given 3 weeks after the last dose of Herceptin received prior to randomization in this trial.

***Reviewer's comment(s):*** *SID development was discontinued so the Applicant's proposed labeling claims are restricted to cohort 2.*

*Initially, the following concerns were raised on the adequacy of the PrefHER study design to assess patient preference:*

1. *Patients were not all treatment naïve (de novo). Seventy-nine percent of patients (n=183/231) were not naïve (non de novo) to Herceptin treatment.*

2. *Susceptibility to recall error. Patients were to compare the method of administration of the last four cycles to the first four cycles.*

3. *Susceptibility to bias. There was a preference by patients for Herceptin SC regardless of whether they had received Herceptin IV before enrollment.*

4. *Potential lack of standardization of assessment. Interview guides for sites could be adapted for each site/country.*

*However, based on discussions with Clinical and Biostatistics, it was not deemed critical for the patients to be treatment naïve. Further, the randomization scheme was stratified by whether or not the patient had received Herceptin prior to trial entry. The issue of recall error was acknowledged by Clinical; however, the recall with this cross-over study design was consistent to previous preference studies. The susceptibility to bias of preference for SC was expected; however, there were also patients with this preference distributed across both treatment arms.*

*Regarding the lack of standardization of assessment, an information request was submitted to further evaluate the operation procedures. For more details, refer to Section C.5.*

*The schedule of assessments is shown in Table 2.*

**Table 2.** Schedule of Assessments

| Assessment Schedule | Screen-ing | Base-line | Crossover trial week (cycle) | | | | | | | | Continuation of trastuzumab 3-weekly up to 18 cycles [j] | | | | Safety Follow-up visit[n] | Follow-up visits[i] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trial week (trial cycle #) | Day -28 to -1 | Day -7 to 1 | 1 (1) | 4 (2) | 7 (3) | 10 (4) | 13 (5) | 16 (6) | 19 (7) | 22 (8) | 25 (9) | 37 (13) | 52 (18) | | | Until 3 years after last patient entered [o] |
| Patient pretrial interview PINT1 (C1) Cohort 1, PINT1 (C2) Cohort 2 [k] | x | | | | | | | | | | | | | | | |
| Patient post-trial interview PINT2 (C1), Cohort 1, PINT2 (C2) Cohort 2[l] | | | | | | | | | | x | | | | | | |
| HCP Questionnaire[m] | | | | | | | | | | x | | | | | | |
| Self-administration satisfaction questionnaire (only in selected patients)[p] | | | | | | | | | | | x | | | | | |

[k] Semi-structured telephone interview with the patient could be performed as soon as written consent was obtained and prior to randomization.

[l] Semi-structured telephone interview with the patient after the eighth cycle and before the ninth cycle of the trial. If patients withdrew from the trial or progressed after only completing the first telephone interview (PINT1), all efforts were made for patients receiving Herceptin by both routes of administration, at any time point, to complete the second telephone interview (PINT2) as part of the final assessment.

[m] HCP questionnaire was completed by the Investigator and a trial nurse at the site when every 5 patients from their site had received the first 8 cycles of trial treatment. For those sites that recruited fewer than 5 patients, the Investigator and a trial nurse each completed an HCPQ only at the end of crossover period (i.e. when all patients at their site had received the first 8 cycles of trial treatment).

[p] After the 1st self-administered cycle and at their final trial visit, (at least 1 day after the Herceptin SC injection), patients in Cohort 1 who had successfully completed self-administration of the trial drug were asked to assess their satisfaction with the administration of Herceptin SC using the SID by completing the 5-item SID Satisfaction Questionnaire. If patients self-administered more than once, a maximum of 2 questionnaires were completed by the patient over the course of the trial.

***Reviewer's comment(s):***
*The PrefHER study results are summarized as follows:*

- *In the overall population, 86% of patients (199/231) preferred Herceptin SC administration*
  - *SC Vial/IV arm: 83% of patients (n=99/118) preferred SC administration*
  - *IV /SC Vial arm: 88% of patients (n=100/113) preferred SC administration*

- *Overall, 57% of patients (n= 132/231) reported reduced time of administration as their first main reason for preference for SC. The second main reason for preference for SC was reduced pain (12%; n=28/231).*

- *The first main reason for preference for IV was fewer reactions. The second main reason for preference for IV was psychological factors.*
  - *6% of patients (n=15/231) reported fewer reactions as first main reason for preference for IV.*
  - *2% of patients (n=6/131) reported psychological factors as first main reason for preference for IV.*

## 1.3 Endpoint Hierarchy and Definition

The study endpoints for the PrefHER study are summarized in Table 3.

**Table 3.** PrefHER Endpoint Hierarchy

| Concept | Endpoint/Objective | Assessment |
|---|---|---|
| **Primary Endpoint** | | |
| Patient preference for SC versus IV route of administration; reasons for preference | Proportion of patients indicating an overall preference for either the SC or the IV route of administration after the completion of Cycle 8 | Patients' Experiences and Preferences towards either IV or SC Herceptin –Post Study Interview Guide (PINT2)-Items 53, 54 a and b |
| **Secondary Endpoints** | | |
| HCP satisfaction with treatment administration | Proportion of HCPs reporting satisfaction with SC or IV administration | HCP Questionnaire (HCPQ) |
| HCP perceived time savings | Minutes of preparation time | HCPQ |
| Patient chair time | Recorded patients' time in infusion chairs and active HCP time | Stop/Start time |

## 1.4 Labeling or promotional claim(s) based on the COA

The Applicant seeks the following labeling claims:

*"The PrefHER Study (NCT01401166) was conducted* (b) (4) *with HER2-positive EBC undergoing neoadjuvant or adjuvant treatment* (b) (4)

(b) (4)

(b) (4)

***Reviewer's comment(s):***
*Based on review of the PrefHER study materials (e.g., methodology of patient interviews, translation process, standard operating procedures, training manual for interviewers), the patient preference telephone interviews appear to be conducted in a standard manner. Further, the instrument (interview guide) appears to be fit-for-purpose to assess patient preference for the method of treatment administration (SC vs. IV). For more details, see Section C.5.*

*With regard to wording of the labeling claims, we recommend the Division to use wording that is consistent to previously patient preference data (e.g., provide a balanced description of both methods of treatment administration, specify that the data is from patients outside the U.S.).*

*We recommend removing* (b) (4)

*Based on discussion with Clinical, the concepts of HCP satisfaction, perceived HCP time savings, and reduction of patient chair time does not describe clinical benefit in patients (i.e., a positive effect in how a patients feels, functions, or survives). Therefore, the subject of this review was limited to the patient preference telephone interviews.*

# 2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The PPQ PINT2 conceptual framework is shown in Table 4.

**Table 4.** Patients' Experiences and Preferences towards either IV or SC Herceptin Post-Study Interview (PINT2) Guide conceptual framework

| Items | General Concept |
|---|---|
| **PINT2 Item 53:** *All things considered which method of administration did you prefer? IV, SC, Neither* | *Patient preference for method of treatment administration* |
| **PINT2 Items 54a/54b:** *How strong is this preference? Very, fairly, not very What are the 2 main reasons for your preference?* | |

# 3 CLINICAL OUTCOME ASSESSMENT(S)

**Patients' Experiences and Preferences towards either IV or SC Herceptin –Pre- and Post Study Interview Guide**

Pre-study Interview (PINT1) Guide
The PINT1 interview guide (Appendix A) includes 37 items which assess the following concepts:

- patients' prior exposure to different types of drug administration (including treatment for non-cancer related disease),
- distance/ease/cost of travelling to and from the cancer center/doctors' office,
- needle phobia,
- recent experiences whilst having chemotherapy including acceptability of environment,
- relationship with staff, and
- any adverse events during chemotherapy treatment including problems with IV site

***Reviewer's comment(s):*** *The PINT1 was not used as a key objective in the PrefHER study. The PINT1 was administered at baseline in this study.*

Post-study Interview (PINT2) Guide
The PINT2 (Appendix B) includes 61 items which assess the following concepts:

- site of administration,
- type of IV administration,
- experiences during study with both methods of administration (e.g. time taken, perceived confidence/competency of staff, injection site reactions (infection, bruising), and
- treatment symptoms (pain, bruising, irritation, anxiety).

For the overall preference item (PINT2 item 53), the recall period was a comparison to a previous time (i.e., patients had to compare the method of administration of the last four cycles to the first four cycles).

# 4 SCORING ALGORITHM

The items in the PINT1 and PINT2 interview guides consisted of categorical and verbal rating scale response options. The results from the PINT2 interview guide were described by item distribution by categories of response for each item.

# 5 CONTENT VALIDITY

The steps utilized in developing the patient interview guides are summarized as follows per the Applicant:

1. Experienced clinicians, chemotherapy nurses and psychologists generated a list of aspects (in English) that might influence patient preferences. Questions about these relevant topics were then developed and re-discussed and refined.
2. The draft patient interview questionnaires were tested with patient volunteers, all of whom had received treatment for breast cancer. Following the feedback of these volunteers, a final version of the patient interview questionnaire was prepared to improve clarity and to remove any ambiguities.
3. When all stakeholders involved in the preparation and review of the questionnaires (including clinicians, chemotherapy nurses and psychologists) were confident that the patient interview questionnaire had both face and content validity, the questionnaires were translated and back translated for field testing in the different countries involved in PrefHER. Any remaining irregularities or confusions caused by translating words and concepts into different languages were corrected and the final versions were then approved.
4. Patients were interviewed twice in their respective national language via the telephone by a trained interviewer independent from the treating hospital. The interviewers were experienced in healthcare setting interviews and received study-specific training and supervision throughout the study. Interviewers were female, bi-lingual and conducted both patient interview questionnaires with individual patients.

***Reviewer's comment(s):*** *Because further clarification was needed with regard to standardization of interviews and the study results, FDA generated an information request (IR) on October 3, 2018. The Applicant's Response (including Appendix A [Summary of the Patient Interview Process in MO22982 (PrefHER Study)], Appendix B [Standard Operating Procedures - PrefHER Study], and Appendix C [PrefHER Investigator Meeting] were reviewed and are summarized (by topic) below:*

- *Standardization of telephone interviews*
    - *It appears that the final version of the PPQ was pilot-tested (including test runs) and the interview guides were translated into the following languages: French,*

*German, Swedish, Spanish, Polish, Russian, Italian, Turkish and Danish using forward and backward translation process.*

- *Patients were interviewed via the telephone to assess the factors influencing preference at two time points:*
  - *Prior randomization (first patient interview (PINT1))-15 min*
  - *At the end of the eighth cycle (PINT2)-25-30 min*
- *Each interview was recorded. However, the Applicant notes that the recordings were subsequently destroyed.*
- *Each interviewer captured the responses from women electronically onto a bespoke website.*
- *All interviewers were bilingual females who completed face-to-face training*
  - *breast cancer treatment;*
  - *the device;*
  - *how to respond to difficult and unexpected questions; and*
  - *standard interview procedures, including completion of the online form*
- *Timing of the PINT2 with regard to Cycle 8 was median 6 days*

- *Country differences*
  - *There were no select countries that overly influenced the results. Out of total sample, most patients came from France, Germany, and Spain*

- *Responses to PINT2 Q53 (Overall Preference) were consistent to how patients responded to questions related to preference factors*
  - *Preference strength*
  - *Degree of bother with treatment administration*
  - *Least painful method*
  - *Method that caused least anxiety*
  - *Most convenient method*

*From the Applicant's response, it appears that the telephone interviews appear to be administered in a standard manner. There is no significant variability in preference across countries; and the responses to items related to preference factors appears to be consistent to final response to overall preference of route of administration.*

# 6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Applicant did not evaluate the psychometric properties (reliability, construct validity, and

ability to detect change) of the PINT1 and PINT2 interview guides in the PrefHER study or provide supporting literature.

# 7 INTERPRETATION OF SCORES

The Applicant did not provide documentation of score interpretation of the PINT1 and PINT2 interview guides for review.

# 8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The final version of the PINT1 and PINT2 interview guides were translated into the following languages: French, German, Swedish, Spanish, Polish, Russian, Italian, Turkish and Danish using forward and backward translation process.

***Reviewer's comment(s):*** *The process of translation appears reasonable.*

# 9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable.

# 10 REVIEW USER MANUAL

A training manual for the telephone interviews was developed and provided in response to the FDA IR. See Reviewer's comments under Section C.5.

# D. APPENDICES

**Appendix A:** Patients' Experiences and Preferences towards Either IV or SC (vial) Herceptin in Breast Cancer: Pre-study Interview (PINT1) Guide

**Appendix B:** Patients' Experiences and Preferences towards Either IV or SC (vial) Herceptin in Breast Cancer: Post-study Interview (PINT2) Guide

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ELEKTRA J PAPADOPOULOS
01/30/2019 03:18:30 PM

# Clinical Inspection Summary

| | |
|---|---|
| **Date** | January 2, 2019 |
| **From** | Lauren Iacono-Connors, Ph.D., Reviewer<br>Susan Thompson, M.D., Team Leader<br>Kassa Ayalew, M.D., M.P.H., Branch Chief<br>Division of Clinical Compliance Evaluation |
| **To** | Amy Tilley, Regulatory Project Manager<br>Jennifer Gao, Clinical Reviewer<br>Division of Oncology Products 1 |
| **BLA #** | 761106 |
| **Applicant** | Genentech, Inc. |
| **Drug** | Trastuzumab and hyaluronidase human solution for subcutaneous injection |
| **NME** | Yes |
| **Therapeutic Classification** | Human epidermal growth factor receptor 2 (HER2) inhibitor |
| **Proposed Indication** | Treatment of HER2-overexpressing breast cancer |
| **Consultation Request Date** | June 20, 2018 (Submission date: May 1, 2018) |
| **Summary Goal Date** | January 15, 2019 |
| **Action Goal Date** | March 1, 2019 |
| **PDUFA Date** | March 1, 2019 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study BO22227 was submitted to the Agency in support of BLA 761106. Three clinical sites, Dr. Robert Hegg, M.D. (Site 163927), Dr. Bozena Kukielka-Budny, M.D. (Site 163863), and Dr. Renata Sienkiewicz-Kozlowska, M.D. (Site 163861), were selected for audit.

There were no significant inspectional findings for clinical investigators Dr. Robert Hegg, Dr. Bozena Kukielka-Budny and Dr. Renata Sienkiewicz-Kozlowska. The data from Study BO22227 submitted to the Agency in support of BLA 761106, appear reliable.

## II. BACKGROUND

Genentech, Inc., seeks approval to market trastuzumab and hyaluronidase human solution for subcutaneous injection (SC) for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer. The key clinical study supporting this application is Study BO22227, a randomized, open-label, multi-center Phase III trial in the neoadjuvant-adjuvant setting. The following overview of the Study BO22227 is intended as background context for interpreting the inspectional findings.

As of the data cutoff date, January 24, 2017, 596 subjects (299 Herceptin IV, 297 Herceptin SC) were randomized to treatment at 81 study centers in 24 countries.

This study was conducted outside of the U.S. The study was not conducted under IND.

Study BO22227, is entitled, "A Phase III, randomized, open-label study to compare pharmacokinetics, efficacy, and safety of subcutaneous (SC) trastuzumab with intravenous (IV) trastuzumab administered in women with human epidermal growth factor 2 (HER2)-positive early breast cancer (EBC)"

Study Period: Date of first subject randomized: October 19, 2009
Last subject study visit: January 24, 2017
Data cut-off date for analysis: January 24, 2017

Primary efficacy endpoint: Pathological complete response (pCR), defined as the absence of invasive neoplastic cells of the primary tumor in the breast after surgery.

Objectives of Inspections:

a. Verify select efficacy endpoint variables as determined by the clinical investigator
   - pCR
b. Verify OS
c. Identification, documentation, and reporting of adverse events (AEs)
d. General compliance with the investigational plan.

# III. RESULTS (by site):

| Name of CI, Site #, Address | Protocol # and # of Subjects | Inspection Date | Final Classification |
|---|---|---|---|
| **CI: Dr. Robert Hegg, M.D. (Site 163927)**<br>Hospital Perola Byington, Av. Brigadeiro Luis Antonio 683, 01317-000, Sao Paulo 01317-000<br>Brazil | Protocol: BO22227<br><br>Subjects: 31 | September 17-20, 2018 | NAI |
| **CI: Dr. Bozena Kukielka-Budny, M.D., Ph.D. (Site 163863)**<br>COZL Oddzial Onkologii Klinicznej z pododdzialem Chemioterapii Dziennej, UL. Jaczewskiego 7, 20-090, Lublin, NA 20-090<br>Poland | Protocol: BO22227<br><br>Subjects: 19 | October 15-19, 2018 | NAI |

| Name of CI, Site #, Address | Protocol # and # of Subjects | Inspection Date | Final Classification |
|---|---|---|---|
| **CI: Dr. Renata Sienkiewicz-Kozlowska, M.D. (Site 163861)** Onkologii – Instytut im. Marii Sklodowskiej-Curie Klinika Nowotworów Piersi i Chirurgii, UL. Roentgena 5, 02-781, Warszawa, NA 02-781 Poland | Protocol: BO22227<br><br>Subjects: 19 | October 22-26, 2018 | NAI |
| *CI: Dr. Daniil Stroyakovskii, M.D. (Site 164804) Moscow city oncology hospital #62 of Moscow Healthcare Department, Russian Federation Moscow, NA 143423 Russia* | *Protocol: BO22227*<br><br>*Subjects: 39* | *Cancelled by ORA due to failure of Russian Embassy to issue VISA* | *N/A* |

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

**1. Dr. Robert Hegg, M.D. (Site 163927)**

The site screened 40 subjects and randomized 31 subjects. A record review was done for all 31 subjects. At the time of this inspection, 12 subjects had completed all study visits including the post-treatment follow up phase, and 19 subjects had discontinued from the study. Out of the 19 subjects that discontinued, three voluntarily withdrew consent, and 15 had disease recurrence. The three subjects who withdrew consent completed the neoadjuvant phase. Records reviewed during the inspection included informed consent documents, inclusion/exclusion criteria compliance, monitoring logs, delegation of authority logs, screening and enrollment logs, ethics committee correspondence and approvals, sponsor and monitor correspondence, investigator agreements, AE reports, IP accountability, and general source documentation. The source documents consisted of records such as data collection worksheets, Informed Consent Documents (ICDs), medical progress notes, laboratory assessments, radiology records, and chemotherapy treatment records. Source documentation was specifically reviewed to verify efficacy assessments and safety/AEs entered into eCRFs and that reported in data listings submitted in the application, as well as overall protocol compliance.

The inspection revealed no significant deficiencies. The primary efficacy endpoint data were verifiable with the source records maintained at the site. With a few minor exceptions, AEs were reported adequately. Briefly, the data line listing for adverse

events submitted to the application lists influenza (Grade 1; non-serious) AE for Subject (b) (6) but not Subject (b) (6). Source documentation revealed that Subject (b) (6) had influenza between (b) (6); however, there was no documentation for influenza occurrence for Subject (b) (6).

Alopecia is listed as an adverse event for Subject (b) (6), Subject (b) (6) and Subject (b) (6) in their respective source documents, however it is does not appear in data line listing for adverse events submitted to the application. Alopecia was also not documented in eCRFs for these subjects.

*OSI Reviewer Notes: According to the FDA field investigator, the eCRFs for Subject (b) (6) and Subject (b) (6) were reviewed and compared to source documentation and data listings submitted to the application by sponsor representatives. It was concluded that this inconsistency in AE reporting appears to have been a transcription error; Subject (b) (6) did not have an AE of influenza and Subject (b) (6) did have an AE of influenza on the dates noted. Both subjects were randomized to receive IV trastuzumab, the active control.*

*Subjects (b) (6) were all randomized to receive IV trastuzumab; the active control. Source documents for each of these subjects includes alopecia, Grade 2/non-serious, and all were determined to be related to the study treatment.*

*There is no evidence to suggest that subjects were placed at undue risk, or that the AE reporting discrepancies had any impact on overall study outcomes.*

The inspection revealed no significant deficiencies. The primary efficacy endpoint data were verifiable with the source records maintained at the site. With a few minor exceptions, as discussed above, AEs were reported adequately.

**2. Dr. Bozena Kukielka-Budny, M.D., Ph.D. (Site 163863)**

The site screened 26 subjects and randomized 19 subjects. A record review was done for 11 subjects. At the time of this inspection, 15 subjects had completed the treatment phase of the study. The inspection covered review of primary efficacy endpoint data and safety data in subject source records including pCR assessments, survival time, laboratory results, test article accountability, adverse and serious adverse events, clinical monitoring, and protocol deviations. Review of study records also included informed consent documents, monitoring logs, delegation logs, enrollment logs, ethics committee correspondence and approvals, sponsor and monitor correspondence, investigator agreements, financial disclosure forms and AE reports. Source documentation was specifically reviewed to verify efficacy and safety assessments.

Review of Subject (b) (6) source documents, specifically, the 'Histopathology Examination [report]' of specimen(s) collected on (b) (6), suggests that Subject (b) (6) achieved a pCR. However, the data listings submitted to the application indicate that Subject (b) (6) did not have a pCR, per protocol. Subject (b) (6) was randomized to IV trastuzumab; the active control.

Subjects (b) (6)

*OSI Reviewer Notes: Dr. Kukielka-Budny reviewed the source documents related to histopathology interpretation for Subject (b) (6) and concurs that Subject (b) (6) achieved pCR. The pCR status for Subject (b) (6) should have no impact on overall study outcome. DOP1 may wish to pursue clarification with the sponsor regarding the determination of the primary efficacy endpoint for Subject (b) (6).*

The inspection revealed no significant deficiencies. The efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

**3. Dr. Renata Sienkiewicz-Kozlowska, M.D. (Site 163861)**

The site screened 30 subjects and randomized 19 subjects. A record review was done for 19 subjects. At the time of this inspection, 17 subjects had completed the treatment phase of the study. The inspection covered review of primary efficacy endpoint data and safety data in subject source records including pCR assessments, survival time, laboratory results, test article accountability, adverse and serious adverse events, clinical monitoring, and protocol deviations. Review of study records also included informed consent documents, monitoring logs, delegation logs, enrollment logs, ethics committee correspondence and approvals, sponsor and monitor correspondence, investigator agreements, financial disclosure forms, and AE reports. Source documentation was specifically reviewed to verify efficacy and safety assessments for 15 subjects.

One SAE, for Subject (b) (6), was reported after four business days instead of one business day after the site become aware of the SAE, as required by the Protocol. Briefly, the subject was hospitalized for a scheduled procedure (anterior wall prolapse surgery; vaginal prolapse); the start date was (b) (6) and the end date was (b) (6). During a follow-up study visit on (b) (6), Subject (b) (6) shared the hospitalization discharge summary regarding her recent surgery with sub-investigator Dr. Dubianski. The sub-investigator did not prepare and submit the SAE report until (b) (6), four days after becoming aware of the event. A clinical monitor identified the unreported SAE during a site monitoring visit conducted between (b) (6). The SAE was reported to the Sponsor on (b) (6). Dr. Dubianski also submitted a follow-up SAE report in (b) (6) concluding that the SAE was a pre-existing condition and not related to study treatment. The data listings submitted to the application include the SAE noted above.

The inspection revealed no significant deficiencies. The efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

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Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Susan Thompson, M.D.
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OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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LAUREN C IACONO-CONNORS
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USE-RELATED RISK ANSLYSIS AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

| | |
|---|---|
| Date of This Review: | December 17, 2018 |
| Requesting Office or Division: | Division of Oncology Products 1 (DOP1) |
| Application Type and Number: | BLA 761106 |
| Product Name and Strength: | Herceptin Hylecta[a] (trastuzumab and hyaluronidase human-xxxx[b]) Injection, 600 mg and 10,000 Units/5 mL |
| Product Type: | Multiple Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | Genentech, Inc. |
| FDA Received Date: | May 1, 2018 and August 2, 2018 |
| OSE RCM #: | 2018-918 and 2018-927 |
| DMEPA Safety Evaluator: | Tingting Gao, PharmD |
| DMEPA Team Leader (Acting): | Sevan Kolejian, PharmD, MBA |
| DMEPA Deputy Director: | Danielle Harris, PharmD, BCPS |

[a] The proposed proprietary name, Herceptin Hylecta, is only conditionally accepted for this product until the application is approved.

[b] Since the proper name for Herceptin Hylecta has not yet been determined, the nonproprietary name, trastuzumab and hyaluronidase human-xxxx, is used in this review to refer to this product.

# 1 REASON FOR REVIEW

As part of this BLA, this review evaluates the proposed Herceptin Hylecta use-related risk analysis (URRA), prescribing information (PI), container labels, and carton labeling to identify areas of vulnerability that could lead to medication errors in response to a consult request from DOP1.

## 1.1 PRODUCT BACKGROUND

The proposed product, Herceptin Hylecta is a co-formulation of currently approved Herceptin (trastuzumab) and recombinant human hyaluronidase.

- Herceptin is approved for the treatment of HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.
- Recombinant human hyaluronidase is a transiently active, locally acting permeation enhancing enzyme that facilitate Herceptin delivery into the systemic circulation.

Herceptin is available as 150 mg/vial single dose and 420 mg/vial multi-dose vials and the dose is based on the patient's body weight and indication (see Appendix A).

The proposed product, Herceptin Hylecta, is a single strength (600 mg and 10,000 Units/5mL) product with a fixed dose (600 mg/10,000 units administered subcutaneously over approximately 2-5 minutes every three weeks) for subcutaneous injection indicated for treatment of HER2-overexpressing breast cancer (see Appendix A).

## 1.2 REGULATORY HISTORY

In a Pre-BLA meeting package, Genentech asked for Agency's feedback on whether their proposed risk mitigation measures are sufficient to distinguish between the approved marketed Herceptin intravenous formulation and the proposed Herceptin Hylecta subcutaneous formulation.[c] Specifically, Genentech proposed measures included differentiating unique features (e.g., color scheme, vial size, dosage form, separate US prescribing information) to be clearly visible on both the primary and secondary packaging to differentiate the proposed Herceptin subcutaneous formulation from the currently marketed Herceptin intravenous formulation. The Agency provided preliminary recommendations and recommended Genentech to submit a comprehensive risk analysis in their BLA submission, and that the acceptability will be a review issue.[d]

[c] Type B Pre-Meeting Package Pre-BLA Meeting: Herceptin (Trastuzumab) solution for subcutaneous injection 600 mg/5 mL vial. Lake Zurich (IL): Genentech, Inc. 2017 AUG 31. Available from: \\cdsesub1\evsprod\ind109168\0002\m1\us\meeting-bg-materials.pdf

[d] Venugopal, R. Type B Pre-BLA Memorandum of Meeting Minutes for Herceptin® (trastuzumab) solution for subcutaneous injection. Silver Spring (MD): FDA, CDER, OND, DOP1 (US); 2017 October 31. PIND 109168.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Table 1. Materials Considered for this Label and Labeling Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B |
| Use-Related Risk Analysis | C |
| ISMP Newsletters | D |
| FDA Adverse Event Reporting System (FAERS)* | E – N/A |
| Information Request | F |
| Labels and Labeling | G |

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

### 3.1 USE-RELATED RISK ANALYSIS (URRA)

We reviewed the use-related risk analysis (URRA) for the proposed Herceptin Hylecta product and we agree that the use tasks identified and evaluated are comprehensive and appropriate for the use of the proposed product. We also reviewed the submitted URRA to ensure that all potential risks involved in using the proposed product, including known use issues with currently marketed products, have been considered and adequately mitigated.

We assessed potential risks involving confusion between Herceptin intravenous formulation and Herceptin subcutaneous formulation and reviewed the Applicant's presented risk mitigation measures to differentiate the proposed Herceptin subcutaneous formulation from the currently marketed Herceptin intravenous formulation. To understand the residual risk related to potential confusion between the two formulations, we met with the DOP1 Medical Officer and discussed the clinical significance of the overdose and underdose errors that may occur because of formulation confusion.

We note that Genentech provided additional clarifications in response to FDA Information Request dated September 7, 2018 (see Appendix F).[e] We have summarized the potential outcomes of the confusion between Herceptin intravenous formulation and Herceptin subcutaneous formulation in Table 2 below.

[e] Tilley, A. TIME SENSITIVE re BLA 761106 Hyaluronidase Human and Trastuzumab - Clinical IR. Silver Spring (MD): FDA, CDER, OND, OHOP, DOP1 (US); 2018 September 7. BLA 761106.

| Table 2. Potential outcomes of the confusion between Herceptin intravenous formulation and Herceptin subcutaneous formulation provided by Genentech[f] | | | |
|---|---|---|---|
| Intended formulation | Formulation administered | Error type | Potential patient outcome |
| Subcutaneous | Intravenous | Overdose<br>"minimal-moderately increased dose"[g] | A high dose of Herceptin IV, up to three times the standard dose, was tested in Study H0452g, a Phase I study in which 5 patients received 500 mg per week for up to 8 doses in the treatment phase of the study (Genentech, Inc. 1997). The dose of 500mg is approximately 8 mg/kg. Adverse reactions seen in this group were abdominal pain, asthenia, fever, pain, nausea, vomiting, anemia and cough. All of the adverse events seen at high doses are consistent with the known safety profile of Herceptin IV and no increase in event severity was observed.<br>Leyland-Jones et al. reported using an accelerated Herceptin loading dose regimen in a Phase I/II trial in which females with HER2-positive MBC (n=72) were administered 6 mg/kg of trastuzumab (approximately 400mg) on Day 1, 8, and 15 of the first q3w treatment cycle, and then on Day 1 of each subsequent q3w cycle. The regimen was well tolerated and had a good efficacy profile. The most common adverse reactions were fatigue, nausea, chills, headache, diarrhea, vomiting, cough and pyrexia. Dyspnea was the most commonly reported Grade 3 or above adverse reaction (Leyland-Jones et al. 2010). |
| Intravenous | Subcutaneous | Underdose[h] | "efficacy would be 'minimally reduced'" is based on the theoretical dose reduction that would occur if a patient is administered a single IV dose subcutaneously.<br>Patient may experience injection site reaction |

In summary, if the subcutaneous formulation is inadvertently given intravenously, overdose and minimal systemic toxicity or immunological system response may occur. On the other hand, if

[f] Response to FDA Request for Information BLA 761106 Trastuzumab and hyaluronidase human. South San Francisco (CA): Genentech, Inc., 2018 Sept 19. Available from: \\cdsesub1\evsprod\bla761106\0011\m1\us\ir-response-20180621.pdf.

[g] For example, if a 68 kg patient receives an erroneous administration of the subcutaneous formulation (600 mg dose), this would be 8.82 mg/kg on a body weight adjusted dose and is approximately a 10% increase from the Herceptin IV loading dose of 8 mg/kg. Therefore, depending on the patient's weight, delivering a dose of the subcutaneous formulation intravenously could theoretically result in a slightly increased dose, which was determined to be minimal-moderately increased. See \\cdsesub1\evsprod\bla761106\0011\m1\us\ir-response-20180621.pdf.

[h] For example, using the q3w dosing schedule of 6 mg/kg of Herceptin IV, the dose for a 68 kg patient would be 408 mg, while the dose of the subcutaneous (SC) formulation would be 600 mg. Therefore, depending on the patient's weight, delivering a dose of the IV formulation subcutaneously could theoretically result in a lower dose. See \\cdsesub1\evsprod\bla761106\0011\m1\us\ir-response-20180621.pdf.

the intravenous formulation is inadvertently given subcutaneously, underdose with minimal reduction in efficacy may occur.

Based on this risk analysis, Genentech proposes to differentiate the two formulations through label (e.g., color differentiation), labeling (e.g., instructions in PI to instruct healthcare providers to check the product label to ensure the correct formulation is selected), and packaging (e.g., vial size and dosage form) to mitigate the risk of wrong formulation errors (see Appendix C). Furthermore, Genentech concluded that no additional human factors validation data is needed and referenced a Human Factors Study that was conducted for Rituxan intravenous formulation and Rituxan Hycela subcutaneous formulation that indicate that 30 US healthcare professionals (HCP) (including Nurses and Pharmacists) were able to successfully distinguish between dosage forms and dosage strengths of Rituxan products based on the cartons and vials presentations.[i] We find this to be a relevant comparator product and agree that the data referenced by Genentech is useful for the evaluation of this proposed product.

Based on the aforementioned reasons above, we agree that no additional human factors validation data is necessary and that the two formulations may be differentiated through label and labeling strategies.

### 3.2 PRESCRIBING INFORMATION (PI)

We reviewed the proposed Herceptin Hylecta PI and determined that it may be improved to ensure safe use of the product.

### 3.3 CONTAINER LABEL AND CARTON LABELING

We reviewed the proposed Herceptin Hylecta container label and carton labeling and determined that it may be improved to ensure safe use of the product.

## 4 CONCLUSION & RECOMMENDATIONS

Based on the use-related risk analysis (URRA), we agree with Genentech's justification that a human factors (HF) validation study does not need to be submitted for Herceptin Hylecta. The proposed Herceptin Hylecta PI, container label, and carton labeling may be improved to ensure safe use of the product. We provide specific recommendations in Section 4.1 and 4.2 below.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    1. Dosage and Administration Section
        a. Consider creating a new section titled "2.4 Administration" and relocate instructions regarding to administration site from "2.3 Important Dosing Considerations" to this new section. This will minimize the potential that important administration instructions are overlooked.

[i] Human Factors Summary Report - Vial, 600mg/5mL, Herceptin SC. South San Francisco (CA): Genentech, Inc. 2018 MAY 1. Available from: \\cdsesub1\evsprod\bla761106\0001\m1\us\herceptinsc-hf.pdf

b. Consider revising the sentence "New injections should be given at least 2.5 cm from the old site and never into areas where…" to "New injections should be given at least 2.5 cm from the previous site on healthy skin and never into areas where…" for clarity.
c. Consider adding instructions to encourage users to use the peel-off sticker for the syringe to minimize the risk of wrong route of administration errors.
d. There are no instructions to explain how long the solution of HERCEPTIN HYLECTA may be stored in the syringe if not administered immediately. Consider asking Genentech to add this important information.

## 4.2 RECOMMENDATIONS FOR GENENTECH

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)
   1. On August 30, 2018, you were notified of the Agency's intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for your product in an Advice Letter.
      Once you receive our notification of the four-letter distinguishing suffix that will be designated for your product, revise your labels and labeling accordingly and resubmit those materials to the application.

B. Container Label
   1. The drug barcode is often used as an additional verification before drug administration in the hospital setting. Consider reorienting the linear barcode to a vertical position to improve the scanability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.[j]
   2. Include the route of administration, "For subcutaneous use only" on the peel-off panel to minimize the risk of wrong route of administration errors.
   3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends

[j] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

that a hyphen or a space be used to separate the portions of the expiration date.[k]

C. Carton Labeling

1. See comment B.3.
2. Since the usual dosage is a fixed dose (600 mg/10,000 units subcutaneously over 2 to 5 minutes every 3 weeks), consider revising (b) (4) to "Usual dosage: 600 mg/10,000 units subcutaneously over 2 to 5 minutes every 3 weeks. See prescribing information." if space permits.

[k] Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. September 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Herceptin Hylecta received on August 2, 2018 from Genentech, and Herceptin.

| Table 2. Relevant Product Information for Herceptin and Herceptin Hylecta | | |
|---|---|---|
| Product Name | Herceptin[I] | Herceptin Hylecta |
| Initial Approval Date | September 25, 1998 | N/A |
| Active Ingredient | trastuzumab | trastuzumab and hyaluronidase human |
| Indication | The treatment of HER2-overexpressing breast cancer.<br>The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. | treatment of HER2 overexpressing breast cancer |
| Route of Administration | intravenous | subcutaneous |
| Dosage Form | For Injection | Injection |
| Strength | 150 mg/vial, 420 mg/vial | 600 mg and 10,000 units /5 mL |
| Dose and Frequency | Adjuvant Treatment of HER2 Overexpressing Breast Cancer<br>Administer at either:<br>• Initial dose of 4 mg/kg over 90 minutes intravenous infusion, then 2 mg/kg over 30 minute intravenous infusion weekly for the first 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Herceptin, administer 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy. | 600 mg and 10,000 units subcutaneously over approximately 2-5 minutes every three weeks |

[I] Herceptin. Drugs@FDA. U.S. Food and Drug Administration; October 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103792s5347lbl.pdf.

| Table 2. Relevant Product Information for Herceptin and Herceptin Hylecta | | |
|---|---|---|
| Product Name | Herceptin[l] | Herceptin Hylecta |
| | • Initial dose of 8 mg/kg over 90 minutes intravenous infusion, then 6 mg/kg over 30-90 minutes intravenous infusion every three weeks for 52 weeks.<br>• Metastatic HER2 Overexpressing Breast Cancer<br>• Initial dose of 4 mg/kg as a 90 minute intravenous infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute intravenous infusions.<br>Metastatic HER2 Overexpressing Gastric Cancer<br>Initial dose of 8 mg/kg over 90 minutes intravenous infusion, followed by 6 mg/kg over 30 to 90 minutes intravenous infusion every 3 weeks. | |
| How Supplied | One carton containing 150 mg Single dose vial<br>One carton containing 420 mg multi-dose vial and Bacteriostatic Water for Injection | Single dose vial |
| Storage | 2°C to 8°C (36°F to 46°F) | 2°C to 8°C (36°F to 46°F) |
| Container Closure | Single-dose vial - (b) (4) stopper and aluminum seal with flip-off cap<br>Multi-dose vial - (b) (4) stopper and aluminum seal with flip-off cap | (b) (4) colorless USP/Ph. Eur./JP (b) (4) glass vial, sealed with a (b) (4) rubber stopper (b) (4) that is crimped with an aluminum seal and fitted with a plastic light blue flip-off cap |

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 2, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, hyaluronidase. Our search identified 3 previous reviews[m,n,o], and we considered our previous recommendations to see if they are applicable for this current review.

[m] Garrison, N. Label and Labeling Review for Rituxan Hycela (BLA 761064). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUNE 20. RCM No.: 2016-1980-2 and 2017-59-2.

[n] Garrison, N. Label and Labeling Review for Rituxan Hycela (BLA 761064). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUNE 15. RCM No.: 2016-1980-1 and 2017-59-1.

[o] Garrison, N. Label and Labeling Review for Rituxan Hycela (BLA 761064). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MARCH 13. RCM No.: 2016-1980 and 2017-59.

APPENDIX C. Use-Related Risk Analysis

Using the principles of human factors and Failure Mode and Effects Analysis[p], along with postmarket medication error data, we reviewed the following documents submitted by Genentech, Inc.

- The core risk management plan for trastuzumab/Herceptin[q]
- Human Factors Summary Report - Vial, 600mg/5mL, Herceptin SC[r]
- Use related risk assessment FMEA - Vial, Herceptin SC[s]
- Use related risk management plan & Hazard Analysis - Vial, Herceptin SC[t]

Genentech provided the commercial packaging detail for Herceptin (trastuzumab) and Herceptin Hylecta. We prepared Table 3 to summarize the differences identified.

Table 3. Packaging Information for Herceptin and Herceptin Hylecta

| | Herceptin (trastuzumab) | | Herceptin Hylecta (trastuzumab and hyaluronidase human) |
|---|---|---|---|
| Route of administration | Intravenous | Intravenous | Subcutaneous |
| Strength | 420 mg/vial | 150 mg/vial | 600 mg and 10,000 units/5 mL |
| Dosage Form | For Injection (lyophilized powder) | For Injection (lyophilized powder) | Solution |
| Strength bar color | 420 mg per vial | 150 mg per vial | 600 mg and 10,000 Units/5 mL (120 mg and 2,000 Units/mL) |
| Vial Size | 50 mL | 15 mL | 6 mL |
| Vial Flip Cap Color | Green | Red | Blue |

[p] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[q] The core risk management plan for trastuzumab/Herceptin. South San Francisco (CA): Genentech, Inc. 2018 MAY 1. Available at \\cdsesub1\evsprod\bla761106\0001\m1\us\risk-mgmt-non-rems.pdf.

[r] Human Factors Summary Report - Vial, 600mg/5mL, Herceptin SC. South San Francisco (CA): Genentech, Inc. 2018 MAY 1. Available at \\cdsesub1\evsprod\bla761106\0001\m1\us\herceptinsc-hf.pdf

[s] Use related risk assessment FMEA - Vial, Herceptin SC. South San Francisco (CA): Genentech, Inc. 2018 MAY 1. Available at \\cdsesub1\evsprod\bla761106\0001\m1\us\userelated-risk-fmea-vial-hersc.pdf

[t] Use related risk management plan & Hazard Analysis - Vial, Herceptin SC. South San Francisco (CA): Genentech, Inc. 2018 MAY 1. Available at \\cdsesub1\evsprod\bla761106\0001\m1\us\rsk-mgmt-pln-hzrd-aly-hersc.pdf

## APPENDIX D. ISMP NEWSLETTERS

### D.1 Methods

On August 3, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

| ISMP Newsletters Search Strategy | |
|---|---|
| ISMP Newsletter(s) | Acute Care and Community/Ambulatory Care |
| Search Strategy and Terms | Match Any of the Words: trastuzumab hyaluronidase |

### D.2 Results

The search retrieved one relevant article that recommended the syringe to include a prominent warning that states, "FOR SUBCUTANEOUS USE ONLY" for Rituxan Hycela.[u]

[u] Institute for Safe Medication Practices. Don't confuse the IV and subcutaneous forms of riTUXimab. ISMP Med Saf Alert Acute Care. 2017 OCT 5;22(20):1-3.

## APPENDIX F. INFORMATION REQUEST

We reviewed the September 7, 2018 FDA Information Request[v] and Genentech's response to the Information Request received on September 19, 2018 for this review[w].

[v] Tilley, A. TIME SENSITIVE re BLA 761106 Hyaluronidase Human and Trastuzumab - Clinical IR. Silver Spring (MD): FDA, CDER, OND, OHOP, DOP1 (US); 2018 September 7. BLA 761106.

[w] Response to FDA Request for Information BLA 761106 Trastuzumab and hyaluronidase human. South San Francisco (CA): Genentech, Inc., 2018 Sept 19. Available from: \\cdsesub1\evsprod\bla761106\0011\m1\us\ir-response-20180621.pdf.

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

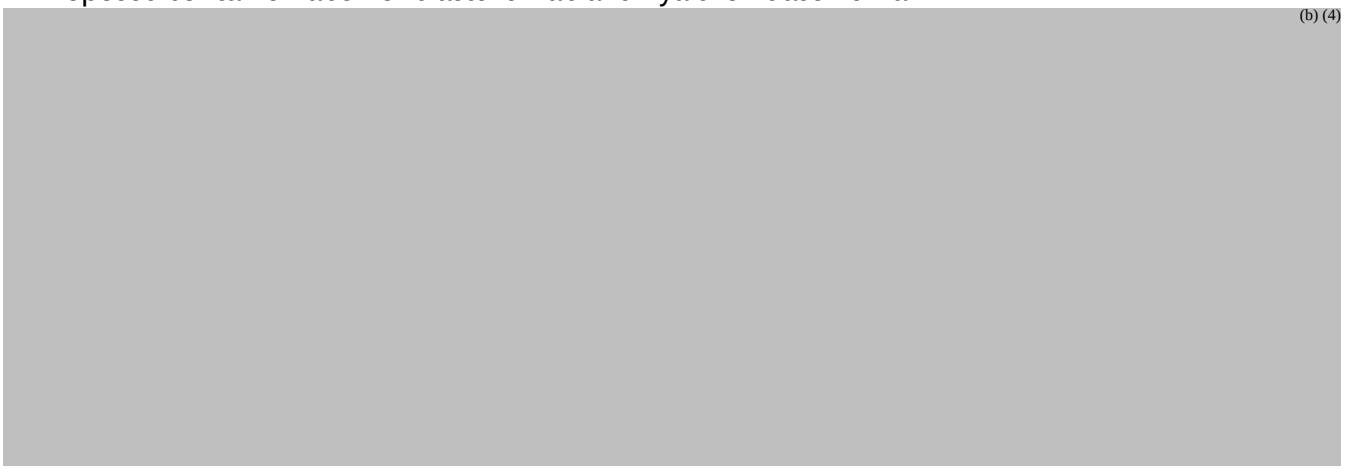
Using the principles of human factors and Failure Mode and Effects Analysis,[x] along with postmarket medication error data, we reviewed the following Herceptin Hylecta labels and labeling submitted by Genentech.

- Container label received on May 1, 2018
- Carton labeling received on May 1, 2018
- Prescribing Information (Image not shown) received on August 2, 2018
- Currently marketed container labels and carton labeling for Herceptin (trastuzumab) – submitted on November 17, 2017 (Annual Report)

### G.2 Label and Labeling Images

Proposed container label for trastuzumab and hyaluronidase human

(b) (4)



4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

[x] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/
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TINGTING N GAO
12/17/2018

SEVAN H KOLEJIAN
12/17/2018

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12/18/2018