CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761106Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 109168

MEETING MINUTES

Genentech, Inc.
Attention: Allison Guy, M.Sc., RAC
Regulatory Program Management
c/o Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Guy:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Herceptin® (trastuzumab) solution for subcutaneous injection.

We also refer to the meeting between representatives of your firm and the FDA on October 17, 2017. The purpose of the meeting was to discuss the development program for the Herceptin SC formulation containing rHuPH20 and to determine whether the data package is acceptable for filing an application for the use of Herceptin SC in patients with HER2-positive breast cancer as an alternative to the established Herceptin IV formulation.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Rajesh Venugopal, Senior Regulatory Project Manager at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: October 17, 2017/12:00 PM – 1:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: PIND 109168
Product Name: Herceptin® (trastuzumab) solution for subcutaneous injection
Indication: Adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer:

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel;
- as part of a treatment regimen with docetaxel and carboplatin;
- as a single agent treatment following multi-modality anthracycline-based therapy.

For the treatment of metastatic breast cancer:

- in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer; and
- as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Laleh Amiri-Kordestani, MD
Meeting Recorder: Rajesh Venugopal

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Laleh Amiri Kordestani, MD, Medical Team Leader, DOP1
Jennifer Gao, MD, Medical Reviewer, DOP1
Joyce Cheng, PhD, Biostatistics Reviewer, OB/DBV
Shenghui Tang, PhD, Biostatistics Team Leader, OB/DBV
Xianhua Cao, PhD, Clinical Pharmacology Reviewer, DCP V

Qi Liu, PhD, Clinical Pharmacology Team Leader, DCP V
Todd Palmby, PhD, Pharm/Tox Supervisor, DHOT
Ching-Jey (George) Chang, PhD, Pharm/Tox Reviewer, DHOT
LCDR Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS, Team Leader, OSE, OMEPRM, DMEPA
Tingting Gao, PharmD, Reviewer, OSE, OMEPRM, DMEPA
Wendy Weinberg, PhD, Lab Chief, Division of Biotechnology Review and Research I**,** OBP
Andrea George, PhD, Reviewer, Division of Biotechnology Review and Research I, OBP
Frances Fahnbulleh, RPh, PharmD, Safety RPM, OSE
Christina Marshall, MS, Regulatory Health Project Manager for Safety, DOP1
Rajesh Venugopal, MPH, MBA, Senior Regulatory Project Manager, DOP1
Rui Li, OB1, edata

SPONSOR ATTENDEES
Martin Morrissey, Life Cycle Leader, Herceptin
Dominik Heinzmann, PhD, Global Development Team Leader
Ann Marie Lucchesi, a.i. Global Regulatory Lead
Jing He, MD, PhD, Clinical Science Leader
Luis Herraez-Baranda, PhD, Clinical Scientist
Amit Garg, PhD, Senior Scientist, Clinical Pharmacology
Maria Solonets, MD, Safety Science Leader,
Wolfgang Richter, PhD, Pharmacokinetics Dynamics Metabolism Leader
Rebecca Elliott, MSc, Bioanalytical Sciences
Allison Guy, MSc, Regulatory Program Manager
Anh Nguyen, MSc, PharmD, Associate Regulatory Program Manager

BACKGROUND

Purpose of Meeting

The purpose of the meeting is to discuss the development program for the Herceptin SC formulation containing rHuPH20 and to determine whether the data package is acceptable for filing an application for the use of Herceptin SC in patients with HER2-positive breast cancer as an alternative to the established Herceptin IV formulation.

Objectives of Meeting

- To obtain Agency feedback on the acceptability of the nonclinical development program, including studies conducted with rHuPH20 and with the Herceptin SC formulation containing rHuPH20, to support a BLA for Herceptin SC

- To obtain Agency feedback on the acceptability of the clinical development program to support a BLA for the use of Herceptin SC for HER2-positive breast cancer

- To reach agreement with the Agency that the available data support the Sponsor's plan to file an original BLA

Indication

The proposed indications for Herceptin SC are the same as those approved in the US for Herceptin IV for HER2-positive breast cancer:

- For the adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer
    - As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel;
    - As part of a treatment regimen with docetaxel and carboplatin; and
    - As a single agent treatment following multi-modality anthracycline-based therapy
- For the treatment of metastatic breast cancer
    - In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer; and
    - As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Product Name

Herceptin (trastuzumab) solution for subcutaneous injection (Herceptin SC)

Product Description

This is a co-formulation of Herceptin and recombinant human hyaluronidase (rHuPH20) and is a new dosage form of Herceptin IV which was approved by the FDA on September 25, 1998 (BLA 103792). Trastuzumab is a full-length 1328 amino acid recombinant humanized IgG1 kappa monoclonal antibody that targets the extracellular domain of human epidermal growth factor receptor 2 (HER2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity.

The recombinant human hyaluronidase rHuPH20 is a glycosylated single-chain protein made up of 447 amino acids. rHuPH20 is a member of the family of neutral- and acid-active ß-1,4-glycosyl hydrolases that depolymerize hyaluronic acid and enhances SC permeation and leads to improved absorption. On December 2, 2005, Halozyme Therapeutics, Inc., received FDA approval for recombinant human hyaluronidase, rHuPH20 (Hylenex, for injection). The recommended dose of Hylenex is 150 USP units for (SC) administration.

Regulatory History

June 21, 2010, EOP2 Type B meeting: Clinical development plan discussion.

- FDA stated primary endpoint for establishing clinical benefit is DFS. PK endpoint of C_{trough} at cycle 7 is exploratory given there is no established exposure-response relationship for trastuzumab. (b) (4)

- FDA disagreed with proposed margin for non-inferiority of HannaH study. SAP must be revised.

- SAP should include proposal for analysis of primary endpoint for both PPP and ITT population.

- FDA and Genentech agreed on definition of DFS and EFS.

- Immunogenicity on PK profile, efficacy, and safety must be evaluated.

- Genentech stated a more sensitive anti-trastuzumab antibody assay has been developed. FDA stated the assay protocol, validation protocol and report must be submitted for review.

- 300-600 patient safety database required for Herceptin SC formulation for BLA submission.

- Cardiac safety should be secondary endpoint.

- *December 8, 2009, Type C meeting:* CMC development plan discussion. FDA had concerns HannaH is being developed outside of US without FDA consultation.

Foreign Regulatory Status

- Overall: Herceptin SC approved in over 80 countries worldwide
- EMA/EU: approved August 26, 2013
- Australia: approved March 13, 2015
- Ongoing applications (b) (4)

Clinical Protocols

The following Sponsor provided table lists the core studies conducted with Herceptin SC:

Table 1 Core Studies of Herceptin SC Development Programme

Herceptin SC Study	Sample Size	Number of Subjects Dosed with Herceptin SC	Number of Herceptin SC Cycles	Duration of Follow-Up (Median Time in Months)
BP22023	70 [a]	58 [a]	1 [a]	4.8
BO22227 (HannaH)	299/297 [b]	297	18/18 [b]	71.4/70.8 [b]
MO22982 (PrefHER)	248/240 [c]	244/239 [c]	4/14 [c]	35.3/36.6 [c]
MO28048 (SafeHER)	1,867/710 [d]	1,864/709 [d]	18/18 [d]	23.7/14.9 [d]
TOTAL		3,411	—	—

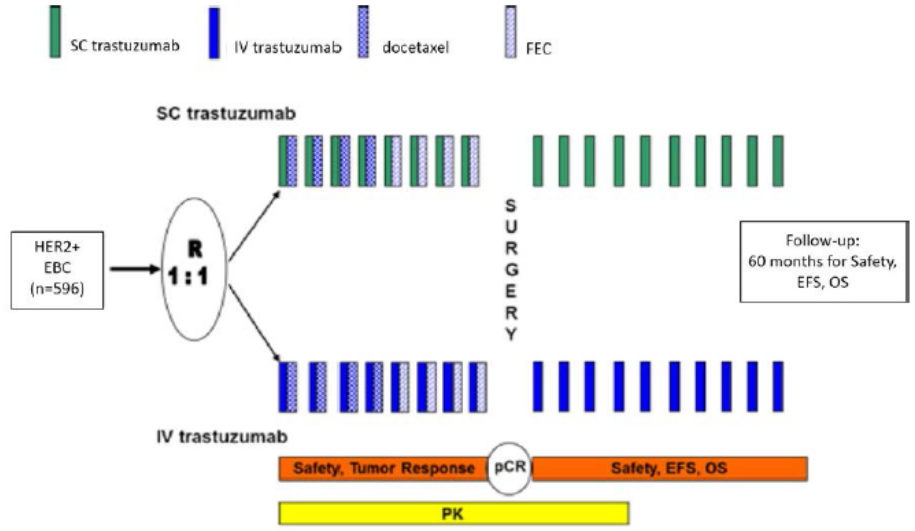
N/A = not applicable; SC = subcutaneous; SID = single-use injection device.
[a] Single-dose study: 40 female patients with breast cancer and 18 healthy male volunteers.
[b] Herceptin IV arm and Herceptin SC arm, respectively.
[c] In Cohort 1 and Cohort 2, respectively.
[d] Cohort A (Herceptin SC Vial) and Cohort B (Herceptin SC SID), respectively.

1. **Study BP22023 (Phase 1 study, completed)** was a Phase 1, open-label, two-part, PK, dose-finding and confirmation study in 18 healthy male volunteers and 40 female patients with breast cancer to identify the dosing regimen. Ultimately, 600 mg every 3 weeks fixed dose was chosen.

2. **Study BO22227 (HannaH, completed)** is a randomized, open-label, multicenter, Phase 3, non-inferiority study in the neoadjuvant-adjuvant HER2-positive EBC setting to look at the PK, efficacy, and safety of Herceptin SC 600 mg every 3 weeks fixed dose regimen vs. Herceptin IV. The co-primary endpoints were to demonstrate non-inferior serum trastuzumab exposure (pre-dose cycle 8 C_{trough} level) and non-inferior efficacy (pCR defined as absence of invasive neoplastic cells in the breast) rate of Herceptin SC. The non-inferiority margin for the geometric mean ratio for the C_{trough} value was chosen as 0.8, the lower bound of the bioequivalence range recommended in the EMA guidelines for bioequivalence. The difference in pCR rate was chosen as the endpoint, with a non-inferiority margin of 12.5% selected to ensure the lower bound of the indirect 95% CI for the difference of pCR rates between Herceptin IV and chemotherapy alone was above 0.

   The study design is shown below.

Figure 2 Study BO22227 (HannaH) Design



EBC = early breast cancer; EFS = event-free survival; FEC = 5-fluorouracil, epirubicin and cyclophosphamide; HER2+ = human epidermal growth factor receptor 2 positive; IV = intravenous; mths = months; OS = overall survival; pCR = pathologic complete response; PK = pharmacokinetic; R = randomization; SC = subcutaneous.

Results from HannaH:

- **pCR:** pCR primary endpoint was met for the per protocol population. The pCR rates were 40.7% Herceptin IV vs. 45.4% Herceptin SC, with an absolute difference of 4.7% which is within the pre-defined NI margin of -12.5%. Similar results were seen in the ITT population (absolute difference 4.8%).

- **C_{trough} at cycle 7/pre-dose cycle 8:** C_{trough} primary endpoint was met for the per protocol population. The geometric mean ratio of C_{trough} SC/IV was 1.33, which was above the pre-specified NI margin of 0.8.

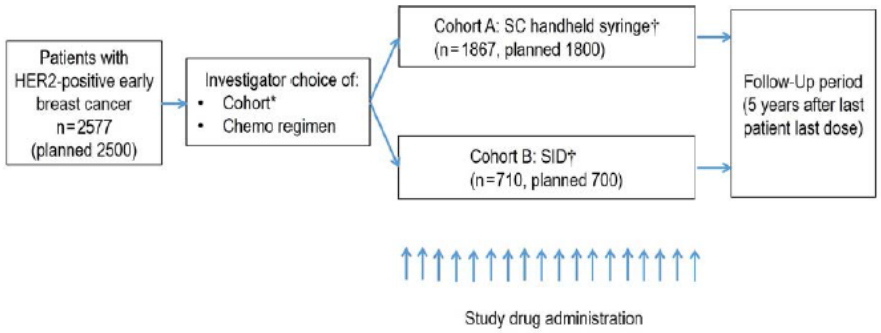
3. **Study MO28048 (SafeHER, ongoing)** is a Phase 3, prospective, two-cohort, non-randomized, open-label study planned to enroll ~2500 patients with HER2-positive EBC at 520 centers in 60 countries. Patients were assigned to one of two cohorts at the investigators' discretion depending on availability of the cohorts for recruitment:

    - Cohort A: 1867 patients received Herceptin SC at a fixed dose of 600 mg using a handheld syringe with hypodermic needle for a total of up to 18 cycles

    - Cohort B: 710 patients received Herceptin SC at a fixed dose of 600 mg using a SID for a total of up to 18 cycles

    The Sponsor stated in the briefing document that the SID (single-use injection device) is not intended to be marketed and thus, data from Cohort B will not be included in the planned BLA submission. The study design is shown below.

Figure 9 Study MO28048 (SafeHER) Design



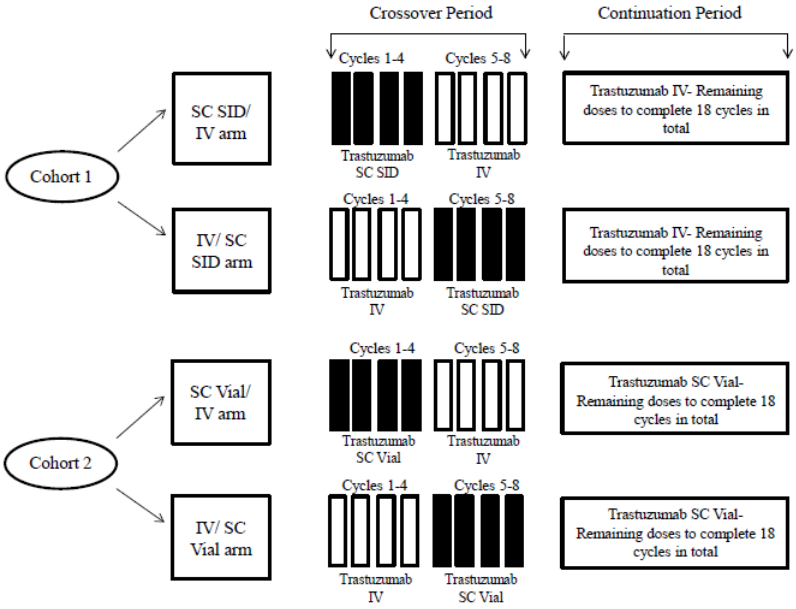
HER2=human epidermal growth factor receptor 2; SC=subcutaneoues; SID=single-use injection device.
Cohort A: Herceptin SC was injected by an HCP, into the thigh over a period of approximately 5 minutes, using a conventional handheld syringe with a gauge 25 or 27 hypodermic needle.
Cohort B: Herceptin SC was injected into the thigh over a period of approximately 5 minutes using the SID.

Results from SafeHER:

- Efficacy results immature due to short FU (~20 months on average for the cohorts)
- Safety results similar so far but ongoing study

4. **Study MO22982 (PrefHER, completed)** is a Phase 3, randomized, open-label, two-cohort, two-arm, crossover study designed to look at patient preference for injection of Herceptin SC or infusion of Herceptin IV every 3 weeks in the neoadjuvant setting. The study design is shown below.

Figure 11 Study MO22982 (PrefHER) Design



IV=intravenous; SC=subcutaneous; SID=single-use injection device.

Only results from Cohort 2 (SC vial arm) will be included with the BLA submission, as the SC SID used in Cohort 1 is not intended to be marketed.

Results from PrefHER:

- Patients preferred SC, HCP satisfied with SC (especially time savings)
- 3-year EFS at final cut-off Dec 2015 comparable between the cohorts
- Safety comparable between the cohorts

5. Two additional studies have been completed looking at hyaluronidase (R04-0851) and rHuPH20 (HALO-104-104). HALO was an open-label Phase 1 study in healthy volunteers of rHuPH20 diluted at 2 different dose levels. The primary objective was to look at the safety and tolerability of rHuPH20 IV. PK was a secondary endpoint. Twenty-four (24) patients completed the study. No safety signals observed.

DISCUSSION

1. *Does FDA agree that the results from the nonclinical pharmacology, pharmacokinetic, and toxicology studies conducted with rHuPH20 and with the Herceptin SC formulation containing rHuPH20 are adequate to support the BLA for Herceptin SC formulation and route of administration?*

   FDA Response: The nonclinical studies summarized in your meeting package for rHuPH20 and the Herceptin SC formulation appear appropriate to support submission of a BLA for the Herceptin SC formulation. The final adequacy of your nonclinical studies to support a BLA approval will be determined during our review of your BLA.

   Meeting Discussion: No discussion took place.

2. *Does FDA agree that the PK and clinical data provided from Study BP22023, Study BO22227 (HannaH) and MO28048 (SafeHER) adequately support the use of the Herceptin SC 600 mg q3w fixed dose regimen for patients with HER2-positive BC?*

   FDA Response: Yes. The PK data collected from Study BP22023, Study BO22227 (HannaH) and MO28048 (SafeHER) seems acceptable to support the use of the Herceptin SC 600 mg every 3 weeks fixed dose regimen for the proposed indication. However, the adequacy of the PK data to support the BLA application will be a review issue.

   Meeting Discussion: No discussion took place.

3. *Does FDA agree the efficacy and safety data from Study BO22227 (HannaH), supported by Study MO28048 (SafeHER) and Study MO22982 (PrefHer), provide sufficient evidence to support the proposed HER2-positive breast cancer indications for Herceptin SC, which are the same as those approved for Herceptin IV in the US?*

FDA Response: Possibly. This will be a review issue. This may require an Oncologic Drugs Advisory Committee (ODAC) meeting.

Meeting Discussion: The Agency reiterated the need for ODAC will be a review issue.

4. *Does FDA agree that the efficacy data to be submitted in support of the Herceptin SC BLA may be presented separately for the individual studies BO22227 (HannaH), MO28048 (SafeHER) and MO22982 (PrefHer) in the Summary of Clinical Efficacy (SCE), and that a separate pooled efficacy analysis is not required? Given that the data from the individual studies will be included in the SCE, does the Agency agree with the Sponsor's proposal that the Integrated Summary of Efficacy (ISE) in Module 5 will cross-refer to the SCE in Module 2?*

FDA Response: Yes.

Meeting Discussion: No discussion took place.

5. *Does FDA agree that the safety data presented in the Summary of Clinical Safety (SCS) for the individual studies for Herceptin SC, BO22227 (HannaH), MO28048 (SafeHER) and MO22982 (PrefHER), are sufficient to reflect the safety profile of Herceptin SC in HER2-positive breast cancer and that a separate pooled safety analysis is not required? Given that the data from the individual studies will be included in the SCS, does the Agency agree with the Sponsor's proposal that the Integrated Summary of Safety (ISS) in Module 5 will cross-refer to the SCS in Module 2?*

FDA Response: No. Include a pooled safety analysis with your BLA submission. In addition, you should provide pooled safety and immunogenicity analyses of patients who received monotherapy with either Herceptin IV or SC without concurrent chemotherapy. We do not agree with cross-referencing.

Meeting Discussion: The Sponsor's proposed pooling strategy and immunogenicity plan are acceptable to the Agency. In addition, the Agency requested that the pulmonary toxicity and embryo fetal toxicity be added to the pooled safety analysis output. The Sponsor will submit the individual study dataset as well as the pooled safety dataset.

6. *Does FDA agree with the MAH's proposed contents and formats of the raw and derived datasets for the studies included in the BLA?*

FDA Response: Yes. Page 40 of the briefing packet states for study BO22227 "in 85% of cases, local institutional practices prevented the local pathologist from knowing a study patient's treatment assignment". This implies in 15% of cases, the local pathologist was aware of the treatment arm the patient was assigned. In your BLA submission, clearly identify in the dataset and CSR in which cases the pathologist was blinded versus not blinded.

Meeting Discussion: No discussion took place.

7. *Does FDA agree that Herceptin IV and Herceptin SC have distinguishable approved marketed presentations and that the presented risk mitigation measures are sufficient to control the risk of medication errors?*

Table 43 Packaging Information for Herceptin IV and Herceptin SC Vials

Packaging Information	Herceptin IV	Herceptin SC
Content	(b) (4)	
Product Color (Vertical strip left of product name)		
Strength Bar (also on vial label)		
Vial Size		
Vial Flip Cap		
Vial Label		

IV = intravenous; SC = subcutaneous.

FDA Response: Your proposed risk management strategy appears reasonable. However, given the considerations of potential confusion between subcutaneous and intravenous formulations, we recommend that you submit a comprehensive risk analysis with your BLA. The use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, and the potential negative clinical consequences of use errors and task failures. It may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and a similar comparator product for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product. Include your risk analysis and comparative analyses in your BLA submission. The acceptability will be a review issue.
We note you propose to use a new proprietary name for your subcutaneous formulation and you refer to your proposed product as "Herceptin SC" in your meeting package. However, it is unclear whether you intend to use "Herceptin SC" or develop an alternate proprietary name. Please note that that the proprietary name "Herceptin SC" has not been evaluated by the Agency for your proposed product, however, the abbreviation "SC" is on the ISMP List of Error-Prone Abbreviations Symbols, and Dose Designations.[1] Therefore, we recommend against the use of the abbreviation

[1] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

"SC" in the proprietary name. We recommend you submit your proposed proprietary name to the Agency for review under the IND as soon as possible. The acceptability of your proposed proprietary name will be a review issue. If you require information on submitting a request for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

•Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022 (https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf)

Meeting Discussion: The Sponsor may submit the proprietary name request under their pre-IND number 109168. The Agency finds this acceptable.

8. *Since the FDA advice received in June 2010 for Herceptin SC, Rituxan Hycela has been approved by FDA with rHuPH20 as a permeation enhancer.*

   a) *As rHuPH20 plays the same role in both the Rituxan Hycela and Herceptin SC formulations, does FDA agree that rHuPH20 can also be considered as a permeation enhancer in the Herceptin SC formulation and that Herceptin SC is not considered a combination product?*

FDA Response: We understand that Herceptin SC is a co-formulation of trastuzumab and recombinant human hyaluronidase (rHuPH20). Trastuzumab is a full-length 1328 amino acid recombinant humanized IgG1 kappa monoclonal antibody and rHuPH20 is a glycosylated single-chain protein composed of up to 447 amino acids. Unless it is cross-labeled, copackaged, or prefilled with a delivery device, such as a syringe, Herceptin SC is not a combination product as defined in 21 CFR 3.2(e).

Meeting Discussion: No discussion took place.

   b) *Does FDA agree that the marketing application for Herceptin SC should be filed as an original BLA?*

FDA Response: Yes.

Meeting Discussion: No discussion took place.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 27, 2017, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological

products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
    a. Site number
    b. Principal investigator
    c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
    d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
    a. Number of subjects screened at each site
    b. Number of subjects randomized at each site
    c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
    a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
    b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

   b. Subject listing for treatment assignment (randomization)

   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued

   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol

   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

   f. By subject listing, of AEs, SAEs, deaths and dates

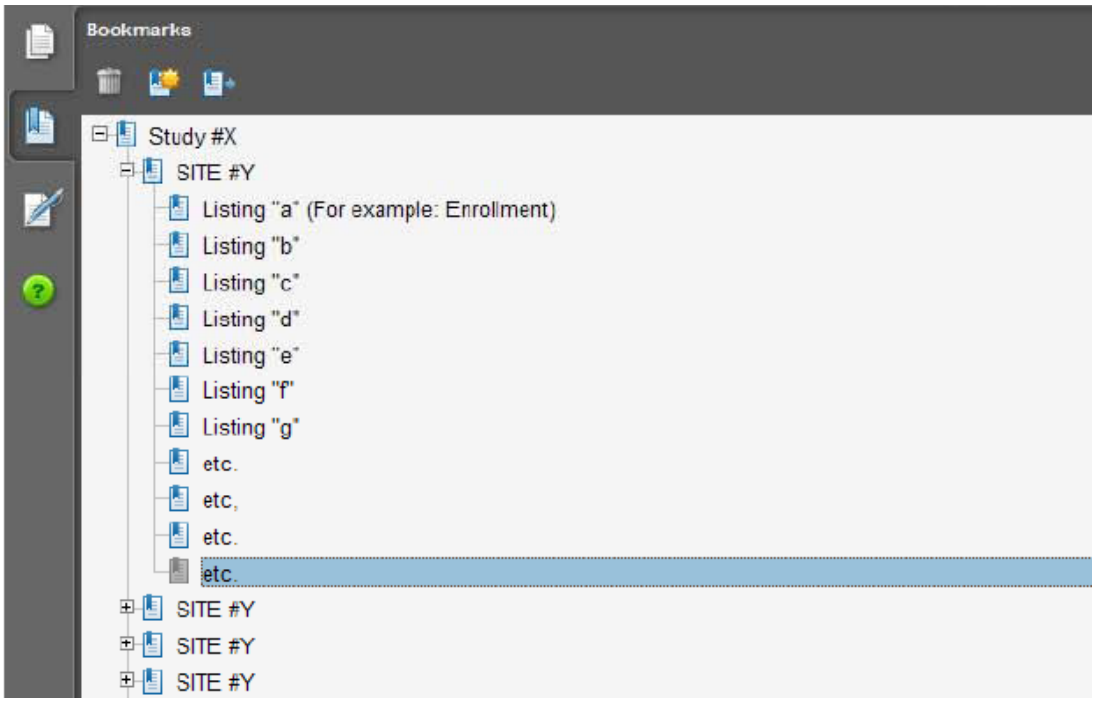
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

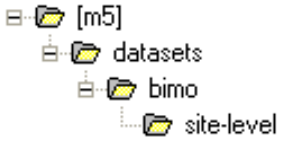
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[2]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[2] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ATTACHMENTS AND HANDOUTS

A copy of the slide presentation during the meeting is attached.

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJESH VENUGOPAL
11/16/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 4517 & PIND 109168

Genentech Incorporated
Attention: Michelle H. Rohrer, Ph.D.
VP, Regulatory Affairs
1 DNA Way, MS #241B
South San Francisco, CA 94080

Dear Dr. Rohrer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Trastuzumab [Humanized Monoclonal Antibody (Genentech) to p185HER2/neu]" and to pre-submission for "Trastuzumab and recombinant human hyaluronidase (rHuPH20) for SC administration."

We also refer to the meeting held on June 21, 2010, between representatives of your firm and the FDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4236.

Sincerely,

{See appended electronic signature page}

Mona Patel, Pharm.D.
Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

FOOD AND DRUG ADMINISTRATION

Meeting Date and Time:	June 21, 2010
Meeting Type:	Type B
Meeting Category:	EOP2
Meeting Location:	White Oak, 1417
Application Number:	IND 4517 and pIND 109168
Product Name:	trastuzumab and recombinant human hyaluronidase (rHuPH20) for SC administration
Received Briefing Package	May 21, 2010
Sponsor Name:	Genentech
Meeting Requestor:	Michelle H. Rohrer, Ph.D.
Meeting Chair:	Genevieve Schechter, M.D.
Meeting Recorder:	Mona Patel, Pharm.D.

Meeting Attendees:

FDA Attendees

Patricia Keegan, M.D., Director, DBOP/OODP/CDER
Joseph Gootenberg, M.D., Deputy Director, DBOP/OODP/CDER
Mona Patel, Pharm.D., Regulatory Project Manager, DBOP/OODP/CDER
Karen Jones, Chief of Project Management Sataff, DBOP/OODP/CDER
Genevieve Schechter, M.D., Lead Medical Officer, DBOP/OODP/CDER
Jacinta Arrington, M.D., Medical Officer, DBOP/OODP/CDER
William Pierce, Pharm.D., Senior Clinical Analyst, DBOP/OODP/CDER
Reena Philip, Ph.D., Biologist, Team Leader, OIVD/DIHD/CDRH
Kun He, Ph.D., Statistical Reviewer, Team Leader, OTS/OB/DBV
Xiaoping (Janet) Jiang, Ph.D., Statistician, OTS/OB/DBV
Nikhil Thakur, Ph.D., Reviewer, ODE/DAGID/GHDB
Andrew McDougal, Ph.D., Pharmacologist/ Toxicologist, DBOP/OODP/CDER
Michael Orr, Ph.D., DABT, Pharmacologist/ Toxicologist, DBOP/OODP/CDER
Wendy Weinberg, Ph.D., Chemistry, Manufacturing & Controls Reviewer, Team Leader DMA/OBP/OPS/CDER

Caryl Giuliano, Ph.D., IOTF Fellow, Chemistry, Manufacturing & Controls Reviewer, DMA/OBP/OPS/CDER
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, OTS/OCP/CDER
Sarah Schrieber, Pharm.D., Clinical Pharmacologist, OTS/OCP/CDER

External Attendees

Erin Jones, Regulatory Affairs
Fan Zhang, Ph.D., Associate Director, Biostatistics
Jennifer Visich, Clinical Pharmacology
Johannes Schmidt, SC Development Life Cycle Leader
Fabio Bisordi, Global Regulatory Leader
Harald Weber, Clinical Science Leader
Susanne Muehlbauer, Clinical Scientist
Beate Bittner, SC Development Subteam Leader
Wolfgang Richter, Pre-clinical DMPK
Markus Stephen-Gueldner, Pre-clinical Toxicology
Mona Shing, Clinical Development

1.0 BACKGROUND

On February 5, 2010, Genentech requested a Type C, meeting to discuss the proposed preclinical and clinical development plan for a new trastuzumab formulation (trastuzumab for subcutaneous (SC) administration) containing recombinant human hyaluronidase (rHuPH20) and intended for SC use only. A general development (type C) meeting was held on December 8, 2009, to discuss the CMC development plan. FDA identified this meeting as a Type B, EOP2 meeting to discuss the clinical development plan.

Trastuzumab is a full-length, 1328-amino acid, humanized IgG1 k monoclonal antibody produced in Chinese hamster ovary (CHO) cells and is directed against the human epidermal growth factor receptor 2 (HER2). Herceptin (trastuzumab) was approved on September 15, 1988 as a 440 mg lyophilized powder supplied in multi-use vials for IV administration. Herceptin is indicated for the treatment of HER2 over-expressing breast cancer, either as adjuvant therapy alone or in combination with chemotherapy and for the treatment of metastatic breast cancer either alone or in combination with chemotherapy.

rHuPH20 is a member of the family of neutral- and acid-active ß-1,4-glycosyl hydrolases that depolymerize hyaluronic acid. On December 2, 2005, Halozyme Therapeutics, Inc., received FDA approval for recombinant human hyaluronidase, rHuPH20 (Hylenex, for injection). The recommended dose of Hylenex is 150 USP units for (SC) administration. Hylenex is approved for the same DESI indications as the animal-derived hyaluronidase products, i.e., as an adjuvant to increase the absorption and dispersion of other injected drugs; for SC fluid administration; and as an adjunct in SC urography for improving resorption of radiopaque agents. The proposed trastuzumab SC formulation will contain rHuPH20 at a concentration of 2000 U/mL.

In the briefing package, Genentech states that Roche completed the nonclinical program for the trastuzumab SC formulation. Pre-clinical study result summaries are included in the briefing

package. The following doses of the trastuzumab SC formulation were administered by the SC route in these studies: ≤ 3.5 million U/kg rHuHP20 (vehicle control solution) in cynomolgus monkeys; ≤108 mg trastuzumab formulated in 6000 U rHuHP20/mL in minipigs in a local tolerability study, and 30 mg/kg trastuzumab formulated in 12,000 U/mL rHuHP20 in a 13 week, repeat-dose toxicity study in cynomolgus monkeys.

In the Hylenex NDA# 021859, three toxicology studies using rHuPH20 were included: one single-dose general toxicity study in rats and two repeat-dose studies in monkeys. In both monkey studies, the no-observed-adverse-effect levels via the SC route of injection were reported to be the highest doses tested (45,000 Units [approximately 0.45 mg] per injection in the ascending dose study and 38,800 Units [approximately 0.388 mg] per injection in the single/repeat dose study).

Genentech completed a 7-day repeat-dose toxicity study of rHuPH20 by either the SC or IV route of administration in cynomolgus monkeys.

A 9-month repeat-dose toxicity study of rHuPH20 in cynomolgus monkeys examined the local and systemic tolerability of rHuPH20 over the dose range of 0.02-2.0 mg/kg. Reproductive endpoints measured in the 9-month general toxicology study in cynomolgus monkeys included testosterone and luteinizing hormone levels, testicular volume, menstrual cycle durations in all females, semen collection and analysis in all males, ovary, prostate, seminal vesicle, and testes organ weights, and histopathology of the epididymis, ovaries, prostate, seminal vesicles, testes, uterus, and vagina.

The evaluation of the subcutaneous administration of rHuPH20 in mice was performed in an embryofetal toxicity study (segment II) and a pre- and post-natal development study (segment III). In the embryofetal toxicity study, mice were administered rHuPH20 subcutaneously at doses of 3, 9, and 18 mg/kg (1.8 million U/kg). Genentech states that the observed reductions in fetal weight and increases in the number of late resorptions in the 9 and 18 mg/kg dosage groups provide evidence that rHuPH20 is potentially embryofetotoxic at these doses. In the pre- and postnatal development study, mice were subcutaneously administered rHuPH20 at doses of 3, 6, and 9 mg/kg and Genentech provided summary data.

Clinical Summary:

Study BP22023 was an open-label, two-part, multi-center, dose-finding and dose- confirmation study. The primary objective of the study was to identify a dose of the trastuzumab SC formulation which results in comparable exposure (as measured by C_{trough}) to an approved dose of Herceptin administered intravenously (IV). The secondary objective was to assess the safety and tolerability of SC trastuzumab formulation. Part 1 of Study BP22023, completed in February 2009, consisted of 5 cohorts. Cohorts 1 and 2 (six healthy males and six women with HER 2 positive breast cancer, respectively) received a single dose Herceptin 6 mg/kg IV. Cohorts 3, 4, and 5, received a single dose of 6, 8 or 10 mg/kg of trastuzumab SC formulation, respectively. Adverse events reported in Cohort 1 (Herceptin) were mild to moderate headache and mild acne while adverse events in Cohorts 3-5, who received the SC trastuzumab formulation, were mild to moderate headache, upper respiratory infection and flu-like illness.

Dosing was completed in May 2009 for Part 2 of Study BP22023, a safety and tolerability, two-dose, multiple-dosing comparison of the trastuzumab SC formulation in women with HER-2 positive breast cancer. . In cohort A, 20 patients were dosed with trastuzumab SC at 8 mg/kg, and in cohort B, 20 patients were dosed with trastuzumab SC at 12 mg/kg. Safety information includes 181 adverse events (AEs) in 39 patients. Adverse events were reported as mild to moderate headache, diarrhea, lethargy, and injection site erythema. No serious AEs were reported within thirty days of study drug administration.

This meeting package includes a clinical study, Study BO22227 (HANNAH), an ongoing, randomized, open-label, multicenter, multinational, study intended to establish that the proposed dose of the trastuzumab SC formulation maintains trastuzumab levels above a specified threshold (trough levels) and yields comparable activity in the neoadjuvant setting to that of Herceptin, and to assess safety and tolerability of the SC formulation. The study population consists of women with stages I-III, HER-2-positive early breast cancer (EBC) or locally advanced breast, and inflammatory breast cancer. More than 200 of the proposed 552 patients in the study sample size have been enrolled at the time of the meeting package submission (during the meeting, Genentech stated that more than 300 patients have been enrolled as of June 21, 2010). Herceptin or Trastuzumab (IV or SC) is given in the neoadjuvant/ adjuvant setting. Subjects are randomized (1:1) to receive Herceptin (initial dose of 8mg/kg followed by 6 mg/kg every 3 weeks) or the investigational trastuzumab SC formulation at a dose of 600 mg every three weeks in conjunction with pre-operative (neoadjuvant) chemotherapy consisting of docetaxel 75 mg/m^2 every 21 days for four cycles followed FEC (5- fluorouracil 500 mg/m^2 , epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2 administered every 21 days) for four cycles. After completion of surgery, Herceptin or trastuzumab SC formulation will be administered as adjuvant therapy every three weeks for up to 1 year. Randomization will be stratified by stage of disease and estrogen receptor status. Patients will be followed for safety and efficacy for approximately 2 years after the end of treatment or until disease recurrence/death, whichever occurs earlier.

The two co-primary endpoints of this ongoing study are the pharmacokinetic endpoint of observed trough concentration (C_{trough}) at Cycle 7 and an activity primary endpoint pathological complete response (pCR). For the pharmacokinetic (PK) co-primary endpoint, the null hypothesis would be rejected if the lower bound of the 90% confidence interval (CI) for the mean ratio of C_{trough} SC to C_{trough} IV is equal to or greater than 0.8. For the pCR endpoint, the null hypothesis would be rejected if the lower limit of the one-sided 97.5% CI for the difference of the pCR rate using the continuity correction of Anderson and Hauck is above 12.5% (absolute percentage points) with the estimate pCR effect in the control arm of ~40%.

The meeting briefing packages were received May 21, 2010.

Meeting Purpose:

- To receive regulatory/scientific input with respect to non-clinical and clinical development activities required in order to bridge from the approved Herceptin to trastuzumab SC formulation.

- Gain agreement with the Agency on the details of the proposed non-clinical and clinical studies in order to obtain approval for a line extension for the trastuzumab SC formulation in all approved Herceptin indications.

Draft comments were forwarded to Genentech on June 21, 2010.

3.0 DISCUSSION

FDA General Comment: Clinical development of this product should be conducted under a new Investigational New Drug (IND) Application. FDA has not yet determined whether marketing approval should be sought under a separate Biologics License Application (BLA) or as a supplement to STN BL 103792, however factors such as the differences in formulation, route of administration, and pharmacokinetic profile from Herceptin will be considered. Proposals for minimizing risks to patients, specifically risks of medication errors, should be provided in the marketing application. FDA also encourages Genentech to initiate discussion of risk management plans prior to clinical development.

Discussion during the Meeting: FDA stated that the answers below have been given in the context of the product to be regulated as a biologic in which halozyme is an excipient. However due to differences between this product and Herceptin, a new presubmission will be established for the new formulation of trastuzumab that Genentech is proposing to develop as noted during the December 8, 2009, meeting to discuss the Chemistry, Manufacturing & Controls (CMC) plan for trastuzumab with rHuPH20 SC. FDA stated that whether rHuPH20 will be considered an excipient or as an active drug component is still being evaluated within the Agency; if halozyme is determined to be an active drug, this product (trastuzumab and rHuPH20 for subcutaneous administration) will be a combination product. Genentech agreed that investigations for this product be conducted under a separate IND. FDA stated that since the study is not being conducted in the U.S., the pre-meeting materials and communications will remain as a pre-IND submission. The presubmission will convert to an IND upon submission of the clinical protocol. Genentech indicated that they do not intend to submit the protocol in support of an active IND, but will provide study information to the pre-IND and submit final results in the marketing application.

Post-Meeting Addendum: FDA has confirmed that the trastuzumab and rHuPH20, intended for subcutaneous administration, is a combination product, in which the biologic product (trastuzumab) will provide the primary mode of action. Therefore, product development must be conducted under a new IND and request for marketing approval would be submitted under an original BLA rather than as a supplement to the existing BLA for Herceptin. FDA provided information regarding the June 18, 2010 administratively created presubmission (pre-IND 109168) to Genentech via electronic communication on June 23, 2010, from Dr. Mona Patel of this Office to Erin Jones of Genentech. A letter should be submitted to pIND 109168 authorizing FDA to cross-reference materials in IND 4517 in support of the new product. The letter of cross-reference should cite the specific information and include date(s) of submission, volume(s) and page numbers of the materials to be referenced in support of pIND 109168.

Discussion During Meeting:

Sponsor Submitted Questions and FDA Response:

1. *Does the Agency agree that the proposed non-clinical toxicology package is adequate to support the supplemental application for trastuzumab's SC formulation route of administration? In particular, does the Agency agree that:*

   a. *A dedicated Segment 1 study for effects on female and male fertility and early embryonic development for rHuPH20 is not required?*

      FDA Response: Yes, for the proposed indication.

   b. *A Segment II study for effects on embryo-fetal development for rHuPH20 in one species (mouse) is appropriate?*

      FDA Response: Yes, for the proposed indication.

   c. *A carcinogenicity study for rHuPH20 is not required?*

      FDA Response: Yes, for the proposed indication.

   d. *Separate safety pharmacology studies for rHuPH20 are not required (CNS, respiratory and cardiovascular endpoints are included in the 39-week general toxicity study in cynomolgus monkeys?*

      FDA Response: Yes, for the proposed indication.

   e. *One 13-week toxicity study in cynomolgus monkeys with the trastuzumab SC formulation to compare and bridge safety endpoints obtained by IV dosing is adequate?*

      FDA Response: While the 13-week toxicity study in cynomolgus monkeys appears reasonable to support the supplemental application, the adequacy of the data is a review issue that will be determined at the time the data is submitted in the supplemental application.

      Discussion During Meeting: Genentech acknowledged FDA's responses to items 1a-e and no further discussion on these items occurred during the meeting.

2. *Does the Agency agree that non-clinical pharmacology and pharmacokinetic studies conducted with rHuPH20 and trastuzumab SC formulation containing rHuPH20 are adequate to support the supplemental application for trastuzumab's SC formulation route of administration?*

   FDA Response: While in general, Genentech's overall nonclinical pharmacology and pharmacokinetic studies conducted with the rHuPH20 product and the trastuzumab SC formulation appears reasonable to support the supplemental application, the adequacy of the data is a review issue that will be determined at the time these data are submitted in the marketing application.

Discussion During Meeting: Genentech acknowledged FDA's response to item 2 and no further discussion on this item occurred during the meeting.

3. *Does the Agency agree that the proposed clinical program, including the design, patient population, strategy to investigate immunogenicity, endpoints and planned analyses of the ongoing pivotal Phase III clinical study BO22227 is adequate to support a supplemental application for trastuzumab's SC formulation route of administration?*

FDA Response:

No, the FDA has the following issues with the proposed study.

a. The study included in this meeting package proposes to establish clinical benefit of a fixed dose of the subcutaneous trastuzumab formulation for (b) (4) adjuvant therapy of (b) (4) HER2-positive breast cancer. (b) (4) .

The appropriate primary endpoint for establishing clinical benefit in this population would be disease free survival (DFS), not pCR, which is the primary endpoint of the study protocol, BO22227, included in this package. Follow-up for disease recurrences should be of a timeframe adequate to detect a clinically important difference between arms should one exist. In addition, survival information on all participants must be collected although the survival information may not be mature at the time of the regulatory submission. The proposed pharmacokinetic endpoint of observed trough concentration (C_{trough}) at Cycle 7 would be considered as an exploratory endpoint since exposure-response relationship has not been established for trastuzumab.

Discussion During Meeting: (b) (4)

The NOAH study is an open-label, randomized (1:1), comparative study of neoadjuvant/adjuvant chemotherapy with or without trastuzumab in 235 patients with HER2-positive breast cancer (117 patients randomized to trastuzumab plus chemotherapy vs. 118 patients randomized to chemotherapy alone) and a parallel group of 99 patients with HER2-negative breast cancer who received chemotherapy alone. The primary endpoint of the NOAH trial is event (disease)-free survival (EFS). Genentech claims that pathologic complete response rates (pCR), a secondary endpoint of the NOAH study will be validated as a surrogate for EFS.

In addition, data from the MD Anderson study (a 42- patient, randomized Phase 2 study of neoadjuvant therapy with or without trastuzumab) and a German study

(GeparQuattro in which 453 HER2-positive patients were enrolled) may be submitted (b) (4) to establish/support the surrogacy of effects on pCR rates as predictive of effect on EFS.

(b) (4) Genentech will submit the results of non-inferiority (NI) study, Study BO22227, intended to establish that new product (trastuzumab/rHuPH20) is non-inferior to Herceptin, based on the co-primary endpoints of pCR and EFS. Since the data from pCR will be available sooner, Genentech proposed that the application be filed based on these data with EFS results to be submitted subsequently. FDA requested that Genentech submit the protocol and results from the MD Anderson and German studies to the pIND submission and in the proposed BLA.

b. As with any intended claim for non-inferiority, sufficient information regarding the treatment effect of the control, Herceptin, in the adjuvant setting derived from a meta-analysis of well controlled randomized clinical studies using trastuzumab in combination with the same/a similar chemotherapy regimen in the same or similar population is required. In addition, adequate justification for the non-inferiority margin selected and a demonstration that this margin would preserve a clinically important fraction of the treatment effect on DFS is required. See the following guidance document:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf

Discussion During Meeting: FDA stated that an application based on Study BO22227 (HANNAH) may be problematic for several reasons. The effect size is based on the data from only two randomized studies, one of 235 patients and one with 42 patients, making the estimate of the effect size unreliable. FDA also noted that the chemotherapy regimens and the chemotherapy schedules for the two studies that Genentech proposes to use to establish the NI effect size are different from that proposed for the BO22227 study. Genentech replied that the drugs were in the same class, and that the non-inferiority margin of 12.5% (absolute difference in pCR rates) is based on the lowest of the lower bounds of the confidence intervals of differences between trastuzumab/chemotherapy and chemotherapy alone arms from the two historical studies. In addition, this NI margin is sufficient to conclude that at least some treatment effect is preserved (i.e., complete loss of the treatment effect could be excluded). Based on demonstration that the treatment effect is not entirely lost, the BO22227 study would be considered successful by Genentech. FDA did not agree with Genentech's justification of the proposed margin. FDA advised Genentech that sufficient justification for the proposed effect size must be submitted, that the proposed margin for NI must be revised in order to preserve a clinically important fraction of the clinical benefit of trastuzumab, and that the BO22227 study will probably need to be resized based on a more conservative NI margin if this study is to be used for regulatory purposes. FDA also stated, as three hundred patients

are already enrolled on BO22227, the statistical plan must be revised if this study is to provide support for the approval of the new trastuzumab/rHuPH20 product. FDA advised Genentech to expeditiously submit the revised statistical plan to the FDA for review. FDA advised Genentech to review the guidance on NI trials. Genentech agreed to take FDA's recommendations under advisement.

c. If an appropriately designed NI study is conducted which fails to provide evidence of a favorable risk:benefit, a second study may be required.

Discussion During Meeting: GNE agreed with FDA's response 3c and no further discussion of item 3.c. occurred during the meeting.

d. The definition of the per-protocol population for a NI study in early breast cancer would include patients who have completed both pre-surgery and all of the twelve month post surgery trastuzumab therapy. In addition, all protocol violations which would exclude subjects from the protocol population must be defined in the statistical analytical plan prior to initiation of the study.

Discussion During Meeting: Genentech indicated that they understood that the per-protocol definition for the adjuvant setting will need to include patients who completed all of the neoadjuvant and adjuvant therapy. (b) (4) FDA advised that a definitive analysis of the comparison of disease-free survival from Study BO22227 will probably be required prior to a final regulatory action.

e. The statistical analytical plan should include a proposal for analysis of the primary endpoint in both the per protocol population and in the intent-to-treat (ITT) population.

Discussion During Meeting: GNE agreed to provide a statistical analytical plan which will include a proposal for analysis of the primary endpoint in both the per-protocol population and in the intent-to-treat (ITT) population.

f. FDA accepts the following definition for the composite endpoint of DFS in early breast cancer: the time from randomization to the earliest occurrence of invasive loco-regional recurrence, invasive contra-lateral breast cancer, distant metastases or death from any cause.

Discussion During Meeting: Genentech stated that FDA's criteria for a DFS-defining event (as stated in 3.f.) is identical to the criteria for an event free survival (EFS)-event in the BO22227 protocol. Genentech confirmed that the definition of disease progression for both the NOAH study and BO22227 study is the FDA accepted definition.

g. Additionally, your development plan should include a plan to adequately evaluate the impact of immunogenicity on the pharmacokinetic profile, efficacy and safety of the trastuzumab SC formulation.

Discussion During Meeting: GNE agreed to provide a development plan which will include a plan to adequately evaluate the impact of anti-product immunogenicity on the pharmacokinetic profile, efficacy and safety of the trastuzumab/rHuPH20 product. Genentech stated that the DSMB is monitoring carefully for adverse events related to increased immunogenicity.

h. FDA notes the statement that a more sensitive anti-trastuzumab antibody assay has been developed. The assay protocol, as well as the validation protocol and report should be submitted for FDA review. Relate levels of antibody found to interfere with the assay to pharmacokinetic findings and the clinical time-points at which samples are collected for analysis.

Discussion During Meeting: Genentech stated that details of the assay will be provided for review. Genentech noted that the assay is sensitive enough to detect 200 ng/mL anti-product antibodies in the presence of 50 mcg/mL of Herceptin in plasma samples.

4. (b) (4)

5. Does the agency agree that rHuPH20 contained in trastuzumab SC can be classified as permeation/absorption enhancer?

FDA Response: Please clarify the intent of this question and the implication of this classification. The ability of rHuPH20 to affect the absorption of trastuzumab should be demonstrated clinically or supported by adequate scientific justification and other sources of data.

Discussion During Meeting: FDA noted that the proposed trastuzumab product may be designated as a combination product. Genentech stated that it would be logististically

difficult to do a human study to demonstrate the effects of rHuPH20 on the absorption of trastuzumab due to the volumes that would be needed to be administered of trastuzumab subcutaneously in the absence of the rHuPH20 to achieve similar serum levels as that with trastuzumab with rHuPH20. Genentech stated it will be more feasible to conduct a single dose study in healthy volunteers in which differing volumes of traztuzumab-rHuPH20 were administered and C_{trough} measured could be performed. Genentech stated that several pre-clinical studies addressed this issue. FDA advised Genentech to submit all of the studies with the rationale for use of only preclinical data for review so that FDA can determine if a clinical study also will be required.

6. *Does the agency agree that the pharmacokinetic, efficacy and safety comparability of the SC route of administration to the IV route, as demonstrated in the Phase III "clinical bridging study" BO22227 conducted in patients with early breast cancer, supports a route of administration amendment that can be applied to all approved trastuzumab indications?*

FDA Response: No, such an approach relies heavily on exposure / response and dose response relationships which have not been adequately characterized for Herceptin. Therefore, information from this study is highly unlikely to be applicable to all approved Herceptin indications.

Discussion During Meeting: FDA stated the co-primary endpoint of C_{trough} at month 7 is an exploratory endpoint as no data from any study has been submitted to demonstrate that C_{trough} correlates with clinical benefit. Genentech stated that the selection of the dose for the trastuzumab/rHuPH20 product was based on the C_{trough} levels observed in 90% of patients treated with trastuzumab administered intravenously every three weeks (at the approved dose). Genentech confirmed that the PK analysis method measures total trastuzumab and can not differentiate between bound to shed antigen (HER2) and free Herceptin. Genentech stated that most of the Herceptin is assumed to be initially bound, but rapidly becomes free so that at steady state the majority of the trastuzumab is thought to be free. C_{trough} is thought to represent the trastuzumab steady state concentration. FDA stated that while C_{trough} may be an accurate measure of steady state, the correlation with clinical benefit has not been established. There are no data that the FDA has reviewed which establishes a dose-response relationship based on C_{trough}. Genentech agreed that such a relationship has not been established.

7. *Does the Agency agree with the extent of the database to be submitted for regulatory approval and the overall submission strategy?*

FDA Response: No, a 300 – 600 patient safety database would be required for the trastuzumab SC formulation.

Discussion During Meeting: Genentech stated that the safety data for the trastuzumab/rHuPH20 product is limited to the single dose study, the multidose study (39 patients), and the BO222227 study (~270 patients available for safety assessment of the subcutaneous formulation). FDA stated that the acceptability of the safety database should be re-visited when more safety information are available (i.e., at the pre-BLA meeting).

ADDITIONAL FDA COMMENTS:

8. The clinical protocol should include the requirement for physical exam and vital signs to be performed on day 1 of each cycle of chemotherapy and/ or trastuzumab therapy.

   Discussion During Meeting: Genentech noted FDA's comment 8. No further discussion occurred during the meeting.

9. Provide a discussion in the background section of the clinical protocol regarding the expected disease recurrence rate and time of recurrence based on the population proposed for enrollment in this study. What percentage will be expected to have disease recurrence based on stage at enrollment? What percentage are expected to progression during the pre-surgical therapy? What percentage are expected to be cured following therapy?

   Discussion During Meeting: Genentech stated that about 10% of the patients enrolled in BO22227 have inflammatory breast cancer and the other 90% appeared to split evenly between early T_1 and more advanced T_4 lesions. FDA noted that the patients enrolled on Study BO22227 should be followed until the median DFS is reached for safety reasons. This time period may be longer than the two year follow-up proposed in the study protocol. Genentech agreed with FDA's recommendation and stated that median disease free survival would be determined before submission of a marketing application.

10. Include the evaluation of cardiac safety as a secondary endpoint for the study protocol. Include a plan to analyze the cardiac safety on this study. At a minimum, patients should have echocardiogram/ multi gated acquisition scan (ECHO /MUGA) pre-treatment, at the end of docetaxel therapy, at the end of 5FU (fluorouracil), epirubicin and cyclophosphamide (FEC) therapy, at the completion of trastuzumab therapy, and at any time patient becomes symptomatic. Follow-up over time for patients who develop left-ventricular ejection fraction (LVEF) dysfunction on study should also be included in this plan.

    Discussion During Meeting: No discussion occurred for comment 10 during the meeting.

11. Discuss whether the study will be conducted in part in the US. If not, a discussion of the applicability of this study to the US population must be included in the marketing application.

    Discussion During Meeting: FDA noted that Comments 11, 12, 13, and 14 relate to the impact of these variables on the results of the non-inferiority study. A non-inferiority study must be rigorously controlled for any variable that could impact the endpoint of DFS. FDA advised Genentech to provide a written response explaining how these variables are controlled in Study BO22227.

12. Discuss how variability in the local radiation therapy practice with regard to the primary endpoint of disease free survival will be controlled. Provide information about the degree of variability locally for each disease stage.

Discussion During Meeting: See discussion under Comment #11.

13. Discuss how the effect of anti-estrogen / aromatase inhibitors on the primary endpoint of DFS will be controlled.

Discussion During Meeting: See discussion under Comment #11.

14. Discuss how the effect of different surgical procedures on the endpoint of DFS will be controlled.

Discussion During Meeting: See discussion under Comment #11.

15. Discuss the use of chest x-ray and liver scans as the primary imaging modality for detection of disease and disease progression. Please discuss the difference in initial disease evaluation / follow-up evaluations between the US and ex-US sites and its impact on the endpoint of DFS.

Discussion During Meeting: No discussion occurred for comment 15 during the meeting.

16. In the BO22227 final clinical study report, include safety tables stratified by body weight as a way to assess whether patients with lower body weight have a higher incidence of adverse events.

Discussion During Meeting: No discussion occurred for comment 16 during the meeting.

17. Please provide complete information regarding the specific test kits which will be used by the central laboratory for HER2 identification by FISH and/or IHC, including which guidelines will be used to interpret the results, e.g., manufacturer instructions, ASCO/CAP or other medical associate guidelines.

Discussion During Meeting: No discussion occurred for comment 17 during the meeting.

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3.0 ISSUES REQUIRING FURTHER DISCUSSION

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4.0 ACTION ITEMS

There are no action items requiring further discussion.

5.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for these meeting minutes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-109168	ORIG-1	GENENTECH INC	Trastuzumab [SC formulation containing recombinant human hyaluronidase (rHuPH20)]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONA G PATEL
07/21/2010