A Phase III Randomised, Double-Blind, Parallel Group, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB3 (proposed trastuzumab biosimilar) and Herceptin in Women with Newly Diagnosed HER2 Positive Early or Locally Advanced Breast Cancer in Neoadjuvant Setting

Registry ID: PHRR140616-000205
Secondary Identification Number: SB3-G31-BC; 2013-CT0188

UNIQUE URL

SCIENTIFIC TITLE
A Phase III Randomised, Double-Blind, Parallel Group, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB3 (proposed trastuzumab biosimilar) and Herceptin in Women with Newly Diagnosed HER2 Positive Early or Locally Advanced Breast Cancer in Neoadjuvant Setting

PROJECT DESCRIPTION
The Sponsor plans to conduct the Phase III study prior to the completion of the Phase I study because the similarity in quality and in vivo behavior between SB3 and Herceptin® has already been demonstrated through extensive similarity exercises including physicochemical, biological characterisation studies, in vitro studies and in vivo non-clinical studies in animal models. Moreover, the planned Phase I study is a single-dose study in healthy subjects that mainly focuses on the generation of pharmacokinetics profiles of the Phase III study. Furthermore, in the development of a biosimilar, the purpose of clinical studies is to demonstrate similarity between the investigational medicinal product and the reference product, not to independently establish safety and efficacy profiles of the investigational medicinal product. Therefore, once similarity is demonstrated in quality and in vivo behavior through a step-wise approach, the sponsor believes that it is not necessary to conduct Phase I and Phase III studies in a strictly sequential manner. During recent global Phase III clinical trial application with other biosimilar projects by the Sponsor, the clinical development approach has been accepted from major agencies in Europe, Latin America and Asian countries. In the proposed Phase III study, approximately 498 subjects with HER2 positive early or locally advanced breast cancer will be recruited globally across approximately 87 centres to provide sufficient efficacy data to demonstrate the similarity between SB3 and Herceptin®. The primary objective of the Phase III study is to demonstrate comparable clinical efficacy of SB3 and Herceptin®, in terms of pathologic complete response (pCR) rate of the primary breast tumour in women with human epidermal growth factor 2 (HER2) positive early or locally advanced breast cancer in neoadjuvant setting. The expected study duration per individual subject will be 1 year after randomisation. Subjects will be randomised in a 1:1 ratio to receive either SB3 (=249) or Herceptin® (=249) in neoadjuvant setting for 8 cycles before surgery followed by 10 cycles of adjuvant therapy after surgery. Safety will be monitored by physical examination, vital sign, biochemical and haematological assessment including cardiac function evaluation by ECG, MUGA. Immunogenicity will be assessed at pre-dose of Cycle 1, 5, 9, 14 and 1 month after the last dose of IP. A Data and Safety Monitoring Board (DSMB) will act at an advisory level to monitor safety and tolerability data.
obtained throughout the course of the study. The Sponsor obtained scientific advice for SB3 from European agencies such as MHRA in UK, PEI in Germany and MPA in Sweden on Aug 02, 2012, Nov 28, 2012 and Oct 26, 2012. The responses given by the agencies is included in this application. Approximately 498 subjects will be enrolled in the study of SB3-G31-BC at centers in Europe, Asia and Latin America. From the Philippines, approximately 30 subjects from 7 sites will join this study.

**NUHRA DETAILS**

<table>
<thead>
<tr>
<th>NUHRA Regime</th>
<th>NUHRA Classification</th>
<th>NUHRA Priority</th>
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<tbody>
<tr>
<td>2010 - 2016</td>
<td>Health Technology Development</td>
<td>Drug Discovery and Development</td>
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**PROJECT DURATION**

<table>
<thead>
<tr>
<th>Start Date</th>
<th>Duration in Months</th>
<th>Target Completion Date</th>
<th>Actual Completion Date</th>
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<td>2014-07-21</td>
<td>36</td>
<td>2017-07-21</td>
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**PROJECT STATUS**

Ongoing

**IMPLEMENTING AGENCY (PRIMARY SPONSOR)**

<table>
<thead>
<tr>
<th>Name of Institution</th>
<th>Classification</th>
<th>Region</th>
<th>LTO #</th>
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<tbody>
<tr>
<td>Samsung Biopes Co. Ltd.</td>
<td>Private Business</td>
<td>South Korea</td>
<td>Not Applicable</td>
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**COOPERATING AGENCY (SECONDARY SPONSOR)**

<table>
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<td>Quintiles Philippines, Inc.</td>
<td>Private Business</td>
<td>NCR</td>
<td>CDR-NCR-CRO-2</td>
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**FUNDING AGENCY (SOURCES OF MONETARY OR MATERIAL SUPPORT)**

1. Samsung Biopes Co. Ltd.

**CONTACT FOR PUBLIC QUERIES**

<table>
<thead>
<tr>
<th>Name:</th>
<th>Email Address:</th>
<th>Phone Number:</th>
<th>Postal Address:</th>
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</table>
HEALTH CONDITION(S) OR PROBLEM(S) STUDIED

Breast Cancer

PRIMARY OUTCOMES

The primary objective of the Phase III study is to demonstrate comparable clinical efficacy of SB3 and Herceptin®, in terms of pathologic complete response (pCR) rate of the primary breast tumour in women with human epidermal growth factor 2 (HER2) positive early or locally advanced breast cancer in neoadjuvant setting. The expected study duration per individual subject will be 1 year after randomisation. Subjects will be randomised in a 1:1 ratio to receive either SB3 (=249) or Herceptin® (=249) in neoadjuvant setting for 8 cycles before surgery followed by 10 cycles of adjuvant therapy after surgery.

KEY SECONDARY OUTCOMES

To evaluate the efficacy of SB3 compared to Herceptin® by - total pathological complete...
To evaluate the safety and tolerability of SB3 compared to Herceptin®
To evaluate the pharmacokinetics of SB3 compared to Herceptin®
To evaluate the immunogenicity of SB3 compared to Herceptin®

DATE OF FIRST ENROLLMENT
2014-07-21

RECRUITMENT STATUS
Completed

COUNTRIES OF RECRUITMENT
Bulgaria; Czech Republic; France; Mexico; Philippines; Poland; Romania; Russia; South Korea; Ukraine

RESEARCH CLASSIFICATION
Clinical Trial

PROJECT LOCATION & INSTITUTIONAL ETHICS REVIEW BOARD WHICH APPROVED THE STUDY

<table>
<thead>
<tr>
<th>Project Location</th>
<th>Institutional Ethics Review Board</th>
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<tbody>
<tr>
<td>Perpetual Succour Hospital</td>
<td>Perpetual Succour Hospital Institutional Ethics and Review Board</td>
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<tr>
<td>Cebu Doctors’ University Hospital</td>
<td>Cebu Doctors’ University Hospital Research Ethics Committee (CDUHREC)</td>
</tr>
<tr>
<td>St. Luke’s Medical Center - Quezon City</td>
<td>St. Luke’s Medical Center Institutional Ethics Review Committee</td>
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<tr>
<td>Davao Doctors Hospital</td>
<td>Davao Doctors Hospital Ethics Review Committee</td>
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<tr>
<td>Dr. Pablo O. Torre Memorial Hospital</td>
<td>Dr. Pablo O. Torre Memorial Hospital Research Ethics Review Committee</td>
</tr>
<tr>
<td>National Kidney and Transplant Institute</td>
<td>National Kidney and Transplant Institute Ethics Review Committee</td>
</tr>
<tr>
<td>St. Luke’s Medical Center - Global City</td>
<td>St. Luke’s Medical Center Institutional Ethics Review Committee</td>
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FDA DOCUMENT TRACKING NUMBER
Unspecified

FDA / ERC APPROVAL DATE
AMENDMENT APPROVAL DATES/REASONS

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<tr>
<th>Approval Date</th>
<th>Amendment Classification</th>
<th>Reason</th>
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<tr>
<td>2015-11-10</td>
<td>Amendments related to the protocol</td>
<td>Protocol Amendment 5</td>
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<td>2015-03-10</td>
<td>Protocol Amendment 2 and 3</td>
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<td>2015-03-12</td>
<td>Protocol Amendment 4 and 4.1</td>
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KEY INCLUSION AND EXCLUSION CRITERIA (CT)

Inclusion criteria Subjects must meet all of the following criteria to be eligible for the study: 1. Female aged 18-65 years 2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 3. Non-metastatic, unilateral newly diagnosed primary breast cancer of clinical stage II to III including inflammatory breast cancer with: a. tumour size ≥ 2 cm b. histologically confirmed primary invasive carcinoma of the breast c. HER2-positivity confirmed by a central laboratory or an accredited local laboratory and defined as immunohistochemistry (IHC) 3+ or fluorescence in situ hybridisation (FISH) + 4. Known hormone receptor (oestrogen receptor and progesterone receptor) status 5. Baseline left ventricular ejection fraction (LVEF) ≥ 55% measured by echocardiography or multiple gated acquisition (MUGA) scan 6. Subjects must be able to provide informed consent, which must be obtained prior to any study related procedures Exclusion criteria Subjects meeting any of the following criteria are not eligible for the study: 1. Metastatic (stage IV) or bilateral or multifocal/multicentric breast cancer 2. History of any prior invasive breast carcinoma, except for subjects with a past history of ductal carcinoma in situ (DCIS) and/or lobular carcinoma in situ (LCIS) treated with surgery only 3. Past or current history of malignant neoplasms within 5 years prior to Randomisation, except for curatively treated carcinoma in situ of uterine cervix, basal cell carcinoma of the skin or squamous cell carcinoma of the skin (malignant neoplasms occurring more than 5 years prior to Randomisation are permitted if curatively treated with surgery only) 4. Previous history of radiation therapy, immunotherapy, chemotherapy or biotherapy (including prior HER2 directed therapy) 5. Major surgery within 4 weeks prior to Randomisation and minor surgery within 2 weeks prior to Randomisation (major surgery is defined as surgery which requires general anaesthesia) 6. Serious cardiac illness that would preclude the use of trastuzumab such as: a. history of documented congestive heart failure (CHF) (New York Heart Association, NYHA, class II or greater heart disease) b. LVEF < 55% by echocardiography or MUGA scan c. angina pectoris requiring anti-anginal medication d. evidence of transmural infarction on electrocardiogram (ECG) e. uncontrolled hypertension (systolic > 180 mmHg and/or diastolic > 100 mmHg) f. clinically significant valvular heart disease g. high risk uncontrolled arrhythmias 7. Serious pulmonary illness enough to cause dyspnoea at rest or requiring supplementary oxygen therapy 8. Known history of HBV, HCV or HIV infection 9. Other concurrent serious illnesses that may interfere with planned therapy including severe cardiovascular, pulmonary, metabolic or infectious conditions 10. Known hypersensitivity to the investigational product (IPs), non-IPs or any of the ingredients or excipients of the IPs or non-IPs 11. Known hypersensitivity to murine proteins 12. Known history of dihydropyrimidine dehydrogenase (DPD) deficiency 13. Pre-existing peripheral sensory or motor neuropathy ≥ grade 2, defined by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 14. Any of the following abnormal laboratory tests a. serum total bilirubin > 1.5 × upper limit of normal (ULN); in cases of known Gilberts syndrome, level of total bilirubin within 3 × ULN is permitted b. aspartate transaminase (AST) and/or alanine transaminase (ALT) > 1.5 × ULN c. alkaline phosphatase (ALP) > 2.5 × ULN d. serum creatinine > 1.5 × ULN e. haemoglobin (Hb) < 9 g/dL f. absolute neutrophil count (ANC) < 1500/mm3 (< 1.5 × 109/L) g.
platelets count < 100000/mm³ (< 100 × 10⁹/L)

**STUDY TYPE**

Interventional

**INTERVENTION NAME**

SB3

**INTERVENTION DESCRIPTION**

Subjects will be randomised in a 1:1 ratio to either receive SB3 or Herceptin® in neoadjuvant setting for 8 cycles concurrently with 8 cycles of chemotherapy (4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/ cyclophosphamide). Subjects will then undergo surgery. After surgery, subjects will receive further 10 cycles of adjuvant SB3 or Herceptin® as per randomisation to complete one year of therapy.

**METHOD OF ALLOCATION**

Randomized

**MASKING / BLINDING**

Double Blind

**MASKING DETAILS**

None

**ASSIGNMENT**

Parallel

**PURPOSE**

To demonstrate comparable clinical efficacy of SB3 and Herceptin®, in terms of pathologic complete response (pCR) rate of the primary breast tumour in women with human epidermal growth factor 2 (HER2) positive early or locally advanced breast cancer in neoadjuvant setting.

**PHASE**

Contact #s.: (+632) 8377534, (+632) 8377537, (+632) 8372071-80 loc. 2117, 2112
Email: registry@pchrd.dost.gov.ph
Phase III

**TARGET SAMPLE SIZE (PHILIPPINES)**

30

**ACTUAL SAMPLE SIZE (PHILIPPINES)**

52

**REASON FOR THE DIFFERENCE BETWEEN TARGET & ACTUAL SAMPLE SIZES**

Protocol amended to increase the target size

**DATE OF FIRST ENROLLMENT**

2014-07-21

**RESEARCH UTILIZATION**

None