Clinical Study Protocol

A Long-term Follow-up Study for Cardiac Safety in the Patients with HER2 Positive Early or Locally Advanced Breast Cancer Who Have Completed the SB3-G31-BC

Product	SB3 (proposed trastuzumab biosimilar)	
EudraCT Number	2015-005663-17	
US IND Number (if applicable)	N/A	
Protocol Number	SB3-G31-BC-E	
Version and Effective Date	2.0/Amendment 1	Nov 26, 2018
	1.0	Dec 17, 2015
Sponsor	Samsung Bioepis Co., Ltd. 107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Republic of Korea	

SYNOPSIS

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB3 (proposed trastuzumab biosimilar)
Name of Active Ingredient:	Trastuzumab
Title of Study: A long-term follow-up study for cardiac safety in the patients with human epidermal growth factor receptor 2 (HER2) positive early or locally advanced breast cancer who have completed the SB3-G31-BC	
Protocol No:	SB3-G31-BC-E
Indication:	HER2 positive early or locally advanced breast cancer
Objectives: Primary Objective: The primary objective is to observe the incidence of symptomatic congestive heart failure (CHF) New York Heart Association (NYHA) class II, III, and IV and asymptomatic significant left ventricular ejection fraction (LVEF) decrease in subjects who participated in the SB3-G31-BC trial and treated with SB3 (proposed trastuzumab biosimilar) or Herceptin® as neoadjuvant and adjuvant treatment. Secondary Objectives: The secondary objectives are: • To observe the incidence of cardiac death and other significant cardiac conditions • To observe the long term efficacy of SB3 compared to Herceptin® by - Event-free survival (EFS) and disease-free survival (DFS) - Overall survival (OS)	
Study Design: This is an observational cohort study. **[Cardiac Safety and Survival Cohort]**: The group consists of subjects who completed the SB3-G31-BC trial and provide informed consent for the long-term follow-up of cardiac safety and survival. Subjects who have completed the clinical trial SB3-G31-BC will be asked to consent to participate in this study. Consenting subjects will be enrolled sequentially into the study in accordance with SB3-G31-BC-E trial protocol version 1.0 and will be monitored according to the local clinical practices which are based on the Herceptin® Summary of Product Characteristics (SmPC) or local label. No additional procedures/subject visits in comparison with the usual clinical practice are planned for the study. Data will be collected from medical records for up to 5 years or death, unless they are lost for the follow-up or withdraw the informed consent.	

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Name of Finished Product:	SB3 (proposed trastuzumab biosimilar)
Name of Active Ingredient:	Trastuzumab

[Survival Only Cohort]: The group consists of subjects who participate in this trial among subjects who received the SB3 or Herceptin® in the SB3-G31-BC trial and were not sequentially enrolled into this SB3-G31-BC-E trial as a Cardiac Safety and Survival Cohort.

Subjects who received SB3 or Herceptin® in accordance with the clinical trial SB3-G31-BC and were not sequentially enrolled to SB3-G31-BC-E trial as a Cardiac Safety and Survival Cohort will be asked to consent to participate in this study as a Survival Only Cohort. If prospective data collection is not possible (e.g. when the subject is deceased or lost to follow-up), a waiver of informed consent/authorization will be requested for the retrospective data collection from medical records, where applicable and in accordance with national regulations and local ethics. If informed consent from (ICF) waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent where applicable and approved by institutional review board (IRB)/independent ethics committee (IEC) and in accordance with national regulations.

Data will be collected from medical records for up to 5 years from their last investigational product (IP; SB3 or Herceptin®) administration or death, unless they are lost for the follow-up or withdraw the informed consent. Data for the study will be collected prospectively from the date of the study informed consent signed and data before informed consent will be obtained from medical records retrospectively. If prospective data collection is not possible, data could be collected retrospectively from medical records.

Number of Subjects:

It is planned that approximately 612 subjects will be enrolled.

Target Population:

Patients with HER2 positive early or locally advanced breast cancer who received SB3 or Herceptin® according to clinical trial SB3-G31-BC.

Eligibility Criteria:

[Cardiac Safety and Survival Cohort]

Inclusion criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Subjects who have completed the study treatment of SB3-G31-BC trial according to the protocol.
2. Subjects must provide informed consent.

Exclusion criteria

Subjects unwilling to follow the study requirements are not eligible for the study.

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Name of Active Ingredient:	Trastuzumab

[Survival Only Cohort]

Inclusion criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Subjects who received SB3 or Herceptin® according to the clinical trial SB3-G31-BC.
2. Subjects who provide informed consent. If prospective data collection is not possible (e.g. when the subject is deceased or lost to follow-up), a waiver of informed consent/authorization will be requested for the retrospective data collection from medical records, where applicable and in accordance with national regulations and local ethics. If ICF waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent where applicable and approved by IRB/IEC and in accordance with national regulations.

Exclusion criteria

There is no exclusion criteria for the Survival Only Cohort.

Planned Study Period:

The study will close at 5 years after the last subject has received the last IP (SB3 or Herceptin®) in the setting of clinical trial SB3-G31-BC.

Investigational Products:

SB3 (proposed trastuzumab biosimilar) or European Union sourced Herceptin®

Criteria for Evaluation

Primary endpoint

- The incidence of symptomatic CHF and asymptomatic significant LVEF decrease
  - CHF, defined as NYHA II, III, IV, confirmed by a cardiologist, accompanied by a significant LVEF decrease
  - Significant LVEF decrease, defined as an absolute decline of at least 10% points from baseline LVEF (LVEF at screening of the SB3-G31-BC trial) and resulting LVEF less than 50%

Secondary endpoints

- The incidence of cardiac death and other significant cardiac conditions
  - Cardiac death, defined as death definitely as a result of heart failure, myocardial infarction, or documented arrhythmia, or as probable cardiac death within 24 hours of a

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cardiac event

- EFS, defined as the time from the date of randomisation for the SB3-G31-BC trial to the date where an event occurs. An event is breast cancer recurrence, or progression (local, regional, distant, or contralateral), or death due to any cause.
- DFS, defined as the time from the date of surgery for the SB3-G31-BC trial to the date where an event occurs. An event is breast cancer recurrence (local, regional, distant, or contralateral) or death due to any cause.
- OS, defined as the time from the date of randomisation for the SB3-G31-BC trial to the date of death, regardless of the cause of death. Subjects who were alive at the time of analysis will be censored at the date of the last follow-up assessment.

Statistical Methods

The subject demographics and baseline characteristics from SB3-G31-BC trial will be summarised by treatment group for the Long-term Follow-up Set and Survival Follow-up Set.

The incidence of CHF, asymptomatic LVEF decrease, cardiac death, and other significant cardiac conditions and all other safety data will be summarised descriptively by treatment group in the SB3-G31-BC trial and also listed for the Long-term Follow-up Set.

For time to event data, survival analysis for EFS, DFS, and OS will be performed for the Long-term Follow-up Set and Survival Follow-up Set, respectively. Kaplan-Meier curves will be calculated and displayed by treatment group in the SB3-G31-BC trial. Additionally, the stratified Cox proportional hazard regression model will be applied to estimate hazard ratio (SB3/Herceptin®). The stratification factors are hormone receptor status, breast cancer type, and region. The hazard ratio will be presented along with its *p*-value and corresponding 95% confidence interval (CI).

Exploratory analyses will be conducted to detect any patterns or systemic data issues.

All analyses will be performed periodically and at the end of the study.

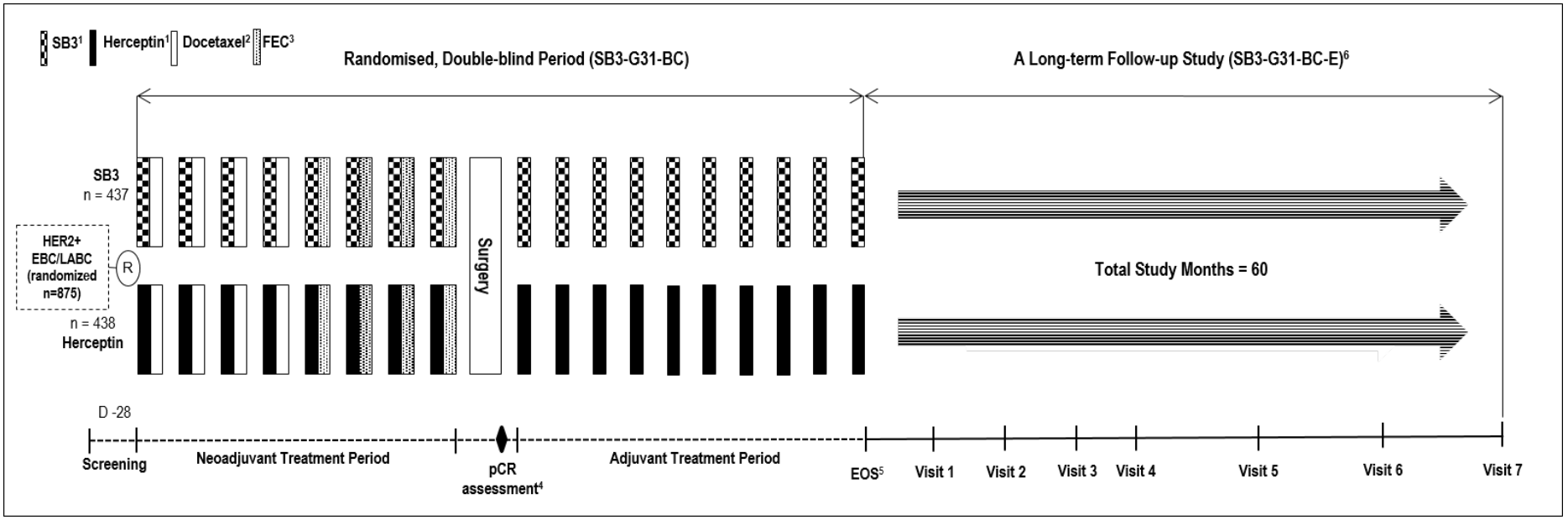

Figure 1. Graphical Study Design

D = day, EBC = early breast cancer, EOS = end of study; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; HER2 = human epidermal growth factor receptor 2; LABC = locally advanced breast cancer, n = number of subjects; LABC = locally advanced breast cancer; pCR = pathological complete response, ® = randomisation

1. Loading dose of 8 mg/kg, and then a maintenance dose of 6 mg/kg every 3 weeks
2. Docetaxel 75 mg/m^2
3. 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2
4. Primary endpoint: Pathologic complete response (pCR) in breast tumour
5. EOS (end of study) means that end of core study (SB3-G31-BC trial) is scheduled 30 days after the last dose of investigational product.
6. After the last SB3 or Herceptin® administration in the SB3-G31-BC trial, subjects will have safety follow-up visits every 6 months for 24 months, then yearly for additional 3 years. For Cardiac Safety and Survival Cohort, subjects will be enrolled sequentially into the study in accordance with SB3-G31-BC-E trial protocol version 1.0 and all data for the study will be collected prospectively. For the Survival Only Cohort, data for the study will be collected prospectively from the date of the study informed consent signed and data before informed consent will be obtained from medical records retrospectively in accordance with recommended schedule of activities. If prospective data collection is not possible, data could be collected retrospectively from medical records.

Table 1. Recommended Schedule of Activities for the Cardiac Safety and Survival Cohort

Assessments	**Follow-up**							
Visit	**ICF**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Month	**-**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
Informed consent[1]	✓							
Physical exam[2]		✓	✓	✓	✓	✓	✓	✓
Mammography			✓		✓	✓	✓	✓
LVEF (ECHO or MUGA scan)[3]		✓	✓	✓	✓	✓	✓	✓
Cardiac events[4, 6]	Continuously							
Breast cancer recurrence/progression[6]	Continuously							
Survival[5, 6]	Continuously							

ECHO = echocardiogram; ICF = informed consent form; MUGA = multiple gated acquisition; LVEF = left ventricular ejection fraction

1. The acceptable time lag from end of study of the SB3-G31-BC trial to obtain the informed consent is one year.
2. Physical exam includes clinical breast exam.
3. LVEF will be measured by 2D ECHO or MUGA scan. The same method should be used for each subject during the SB3-G31-BC trial and this study.
4. Cardiac events will be recorded in case of SB3 or Herceptin® related cardiac toxicities during follow-up.
5. Survival can be followed up by telephone contacts.
6. For the investigation of cardiac events, breast cancer recurrence/progression, and survival, at least scheduled visits, and activities are recommended.

Table 2. Recommended Schedule of Activities for the Survival Only Cohort

Assessments	**Follow-up**							
Visit[2]	**ICF**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Month from Last IP Administration	**-**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
Informed consent[1]	✓							
Breast cancer recurrence/progression[2,3]	Continuously							
Survival[2, 3, 4]	Continuously							

ICF = informed consent form; IP = investigational product

1. Subjects will provide informed consent. If prospective data collection is not possible (e.g. when the subject is deceased or lost to follow-up), a waiver of informed consent/authorization will be requested for the retrospective data collection from medical records, where applicable and in accordance with national regulations and local ethics. If ICF waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent where applicable and approved by institutional review board (IRB)/independent ethics committee (IEC) and in accordance with national regulations.
2. For the investigation of breast cancer recurrence/progression and survival, at least scheduled visits, and activities are recommended.
3. Data will be collected prospectively from the date of the study informed consent signed and data before informed consent will be obtained from medical records retrospectively. If prospective data collection is not possible, data could be collected retrospectively from medical records.
4. Survival can be followed up by telephone contacts.

LIST OF ABBREVIATIONS

ADCC	Antibody dependent cell-mediated cytotoxicity
AE	Adverse event
ASCO	American society of clinical oncology
CHF	Congestive heart failure
CI	Confidence interval
CRO	Contract research organisation
CRF	Case report form
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
EBC	Early breast cancer
EC	Epirubicin/cyclophosphamide
ECHO	Echocardiography
EFS	Event-free survival
EMA	European medicines agency
EOS	End of study
ESMO	European Society for Medical Oncology
FEC	5-fluorouracil, epirubicin, and cyclophosphamide
GCP	Good Clinical Practice
HER2	Human epidermal growth factor receptor 2
IB	Investigator's Brochure
ICF	Informed consent form

ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IP	Investigational product
IRB	Institutional review board
IV	Intravenous
LABC	Locally advanced breast cancer
LVEF	Left ventricular ejection fraction
MUGA	Multiple gated acquisition
NCI-CTCAE v4.0	National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0
MBC	Metastatic breast cancer
NCCN	National comprehensive cancer network
NYHA	New York Heart Association
OS	Overall survival
pCR	Pathologic complete response
PFS	Progression-free survival
PK	Pharmacokinetics
SAE	Serious adverse event
SC	Subcutaneous
SOP	Standard operating procedure
SmPC	Summary of Product Characteristics
tpCR	Total pathologic complete response
TTP	Time to Progression

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LIST OF STUDY STAFF

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Clinical Project Manager	PPD
Clinical Research Physician	PPD
Clinical Development Associate	PPD
Statistician	PPD
Project Safety Lead	PPD
Safety Physician	PPD

1. INTRODUCTION

1.1. Breast Cancer

1.1.1. HER2 Positive Breast Cancer

Breast cancer is the most common cancer in women worldwide. It is also the principle cause of death from cancer among women globally [Siegel, 2013]. Of the total number of patients diagnosed with breast cancer, 20% to 25% have tumours that exhibit human epidermal growth factor receptor 2 (HER2) protein overexpression or gene amplification. HER2 belongs to a family of four transmembrane receptor tyrosine kinases that mediate the growth, differentiation, and survival of cells [Slamon, 1987; Slamon, 1989]. HER2 overexpression is associated with aggressive tumour biology and with poor clinical outcomes compared with tumours that do not have HER2 overexpression [Cooke, 2001].

Trastuzumab (Herceptin®, Roche Registration Limited), a humanised monoclonal antibody that blocks the activity of HER2, improved clinical outcomes in patients with both early and metastatic HER2 positive breast cancer. Lapatinib (Tykerb®, GlaxoSmithKline), HER2 directed tyrosine kinase inhibitor, given in combination with capecitabine, also improved progression-free survival (PFS) in patients who had disease progression on Herceptin®. So far, Herceptin® is the most widely used drug in breast cancer and also the only drug approved for the treatment of early-stage breast cancer.

1.1.2. Current Standard of Neoadjuvant Therapy in HER2 Positive Breast Cancer

While many studies demonstrate high pathologic complete response (pCR) rates and good tolerability with a variety of chemotherapy/Herceptin® combinations, there is no clear consensus on the duration of therapy or whether to include anthracycline, and if anthracycline is included, on whether it should be given concurrently or sequentially with Herceptin®.

The current recommendation of the National Comprehensive Cancer Network (NCCN) guideline is to use paclitaxel plus Herceptin® followed by 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) plus Herceptin®, based on the initial small MD Anderson study [Buzdar, 2005]. European Medicines Agency (EMA) provided the possibility of using neoadjuvant Herceptin® together with anthracyclines when EMA approved Herceptin® to be used as neoadjuvant therapy based on the NOAH study [Gianni, 2010].

Although optimal neoadjuvant regimen cannot be established, it appears that a combination of taxanes and anthracyclines can produce higher pCR rates compared to the taxane only regimen.

1.2. SB3-G31-BC Clinical Trial

1.2.1. Overview of SB3

SB3 has been developed as a similar biological medicinal product to Herceptin® (trastuzumab,

Roche Registration Limited). SB3 and Herceptin® have identical primary structure and the active substance for both products is trastuzumab produced in Chinese Hamster Ovary cell line transformed by recombinant deoxyribonucleic acid (DNA) technology. Trastuzumab (anti-185, rhuMab HER2) is a humanised monoclonal antibody that binds to HER2 protein and inhibits the proliferation of HER2 overexpressing human tumour cells.

SB3 was extensively characterised and compared to Herceptin® using 'state-of-the-art' methods. These studies were in accordance with the principles laid out in the comparability guidelines including the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (revision 1)' [EMEA/CHMP/BWP/247713/2012]. It was demonstrated that SB3 has similar structural and physicochemical characteristics with Herceptin®. In regards to the mechanism of action, SB3 inhibits HER2 expressing human tumour cell proliferation and mediates antibody dependent cell-mediated cytotoxicity (ADCC) against such tumour cells *in vitro* equivalently to Herceptin®.

Biosimilarity between SB3 and Herceptin® was demonstrated through extensive quality and non-clinical similarity exercises, and a Phase I study was conducted in healthy subjects to compare the pharmacokinetics (PK), safety, tolerability, and immunogenicity and a Phase III study has been conducted in subjects with HER2 positive breast cancer to compare the efficacy, safety, PK, and immunogenicity of SB3 to Herceptin®. Information on the safety of SB3 based on the reference product information and non-clinical exercises is presented in the Investigator's Brochure (IB).

1.2.2. Overview of SB3-G31-BC Trial

The SB3-G31-BC clinical trial is a randomised Phase III, double-blind, parallel group, multicentre study to compare the efficacy, safety, PK, and immunogenicity between SB3 and Herceptin® in women with HER2 positive early breast cancer (EBC) or locally advanced breast cancer (LABC) in neoadjuvant setting (EudraCT Number 2013-004172-35). Subjects were 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-FEC). Then subjects underwent surgery. After surgery, subjects received further 10 cycles of adjuvant SB3 or Herceptin® as per randomisation to complete one year of therapy (Figure 1).

The primary objective was to demonstrate comparable clinical efficacy of SB3 and Herceptin®, in terms of pCR rate of the primary breast tumour in women with HER2 positive EBC or LABC in neoadjuvant setting.

The secondary objectives were to evaluate the efficacy of SB3 compared to Herceptin® by total pCR (tpCR) rate, overall clinical response rate, event-free survival (EFS), overall survival (OS), the safety, and tolerability of SB3 compared to Herceptin®, the PK of SB3 compared to Herceptin®, the immunogenicity of SB3 compared to Herceptin®

A total of 875 subjects were randomised; 437 subjects to the SB3 treatment group and 438 subjects to the Herceptin® treatment group. Among them, 380 subjects in the SB3 treatment group and 384

subjects in the Herceptin® treatment group completed the trial.

1.3. Clinical Data of Herceptin®

1.3.1. Herceptin® in Metastatic Breast Cancer

Herceptin® has clinical activity in patients with HER2 positive metastatic breast cancer (MBC), both as single-agent therapy in first-line and salvage settings and in combination with chemotherapy. A pivotal Phase III study demonstrated that the combination of trastuzumab and chemotherapy significantly prolonged time to progression (TTP) and OS compared with chemotherapy alone in patients with HER2 positive MBC [Slamon, 2001]. Similarly, in a randomised Phase II trial, the addition of trastuzumab to docetaxel improved response rate, TTP, and OS compared with docetaxel alone in women with HER2 positive MBC [Marty, 2005]. Therefore, Herceptin® is currently approved for use as monotherapy in patients with HER2 positive MBC who have received one or more chemotherapy regimens and for use in combination with taxane for their metastatic disease.

1.3.2. Herceptin® in Early Breast Cancer (Adjuvant)-Efficacy Results

Herceptin® was investigated in 4 large multicentre, randomised studies in the adjuvant setting. A summary of the results is showed in Table 3. All studies demonstrated that adjuvant Herceptin® treatment for up to 1 year reduced by nearly half the risk of relapse. Also the risk of death was significantly reduced. Based on the results of the HERA trial, Herceptin® was approved for the treatment of patients with HER2-positive EBC following surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy (if applicable).

Table 3. Efficacy of Adjuvant Herceptin® in Breast Cancer

Adjuvant Study	DFS Hazard Ratio (95% CI), *p*-value	OS Hazard Ratio (95% CI), *p*-value	Median Follow-Up
NCCTG N9831 and NSABP B-31			
AC → TH (n = 1872)	0.48 (0.39, 0.59) $p \leq 0.0001$	0.67 (0.48, 0.92) $p = 0.014$	23 months
AC → T (n = 1880)			
HERA [Piccart-Gebhart, 2005]			
Chemo → H (n = 1694)	0.54 (0.43, 0.67) $p < 0.0001$	0.76 $p = 0.26$	12 months
Chemo → Observation (n = 1693)			
BCIRG 006 [Slamon, 2011]			
TCH (n = 1075)	0.75 $p = 0.04$	0.77 $p = 0.04$	65 months
AC → TH (n = 1074)	0.64 $p < 0.001$	0.63 $p < 0.001$	
AC → T (n = 1073)			

A = anthracycline; C = cyclophosphamide; CI = confidence interval; DFS = disease-free survival; H = Herceptin®; n = number of subjects; OS = overall survival; T = docetaxel

1.3.3. Herceptin® in Early Breast Cancer (Adjuvant)-Cardiac Safety Results

Cardiac dysfunction, including congestive heart failure (CHF) is a relevant safety issue related to Herceptin® treatment. The main findings from the HERA trial were:

- The incidence of New York Heart Association (NYHA) class III or IV CHF in patients receiving Herceptin® was low (0.6%) and compares with 0.1% of patients in the observation arm. None of these events was fatal, with the exception of one observation patient who developed CHF class IV leading to death.
- Three percent of the Herceptin® patients had CHF NYHA class I and II during the study compared with 0.5% in the observation arm patients. In the majority of cases, following cessation of Herceptin® treatment with or without standard cardiac medication, stabilization of left ventricular ejection fraction (LVEF) or return towards the baseline value was observed.
- The incidence of cardiac dysfunction (defined as at least one drop in LVEF < 50% and of ≥ 10% points from baseline) was 7.4% in the one-year Herceptin® arm compared with 2.3% in the observation arm.
- The longer-term assessment of trastuzumab-related cardiac adverse events (AEs) for up to 48 months reported that the cumulative incidence of any type of cardiac events increases during the scheduled treatment period of one year but it remains relatively constant thereafter [Procter, 2010].

In the NSABP B-31 trial, the incidence of symptomatic CHF in patients receiving Herceptin® was 4.1% compared to 0.1% in the observation arm. There was one patient who developed CHF class IV leading to death.

In the NCCTG N9831 trial, the incidence of symptomatic CHF in patients receiving Herceptin® was 2.9% compared with 0% of patients in the observation arm. Only one patient in the investigational arm developed CHF class IV leading to death.

Based on results from the BCIRG 006 trial, concomitant administration of Herceptin® with a non-anthracycline based regimen such as docetaxel and carboplatin carries a very low risk of severe CHF (0.3%).

1.3.4. Herceptin® in Early Breast Cancer (Neoadjuvant)-Efficacy Results

Many clinical studies have been conducted or are being conducted to investigate the role of Herceptin® in neoadjuvant setting. The major studies which investigated the efficacy of neoadjuvant Herceptin® are described below. A summary of the study design and efficacy results is showed in Table 4.

Table 4. Neoadjuvant Herceptin® Studies in Breast Cancer

Study	HER2 Positive Patients	Clinical Stage	Chemotherapy	Definition of pCR	pCR Rate
Buzdar (2005)	23	T1-4, N0-2	PH → FECH	ypT0 ypN0	65%
NOAH (2010)	117	LABC, incl. inflammatory	APH → PH → CMFH	ypT0	43%
GeparQuattro (2010)	445	> 1 cm, T1-4, N+if T2, inflammatory	ECH → TH ± X	ypT0/is	32%
TECHNO (2011)	217	> 2 cm or inflammatory	EC → PH	ypT0 ypN0	39%
HannaH (2012)	299	I-IIIc, inflammatory	TH → FECH	ypT0/is	41%

A = anthracycline; C = cyclophosphamide; E = epirubicin; F = 5-floururacil; H = Herceptin®; LABC = locally advanced breast cancer M = methotrexate; P = paclitaxel; pCR = pathologic complete response; T = docetaxel; X = Xeloda®

1.3.5. Herceptin® in Early Breast Cancer (Neoadjuvant)-Cardiac Safety Results

Buzdar AU et al. [Buzdar, 2005]

Herceptin® was given concurrently with preoperative chemotherapy (paclitaxel 225 mg/m^2 every 3 weeks for 4 cycles) followed by FEC (5-fluouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks for 4 cycles). There was no clinical cardiac dysfunction observed and there were no cardiac deaths.

NOAH Study [Gianni, 2010]

Herceptin® was administered concurrently with 10 cycles of neoadjuvant chemotherapy. Chemotherapy regimen consisted of 3 cycles of doxorubicin 60 mg/m^2 and paclitaxel 150 mg/m^2 for followed by and 4 cycles of paclitaxel 175 mg/m^2 followed by an additional 3 cycles of CMF. National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0) grade 2 and 3 LVEF changes were infrequent in both study arms. The safety data suggest that the neoadjuvant regimen used in the NOAH study is tolerated well and has an acceptable cardiac safety profile.

GeparQuattro Study [Untch, 2010]

HER2 positive patients were randomised to receive pre-operative intravenous (IV) Herceptin® concurrently with either epirubicin/cyclophosphamide (EC) followed by docetaxel, or EC followed by docetaxel plus concomitant capecitabine or EC followed by docetaxel followed by capecitabine. There were no cardiac safety concerns in this study. LVEF decreases beyond 45% were not observed, neither was CHF grade 4.

TECHNO Study [Untch, 2011]

Patients were treated with neoadjuvant epirubicin plus cyclophosphamide for 4 cycles, followed by

paclitaxel plus Herceptin® for 4 cycles. Herceptin® was then continued after surgery for a total of 1 year. Cardiac toxicity was reported in eight patients (3.7%) of who six presented with an asymptomatic LVEF decrease and two with symptomatic chronic heart failure.

HannaH Study [Ismael, 2012]

The HannaH study compared PK, efficacy, and safety between subcutaneous (SC) trastuzumab and IV trastuzumab. The incidence of grade 3 to5 AEs was similar between groups. No cases of symptomatic CHF were reported. Six (2.1%) of 298 patients in the IV group and seven (2.4%) of 297 in the SC group had a significant LVEF drop.

1.3.6. Safety Concern in Co-administration of Anthracyclines with Herceptin®

In contrast to the early experiences in MBC, simultaneous neoadjuvant therapy with anthracyclines and Herceptin® appears to have an acceptable cardiac toxicity profile [Slamon, 2011]. Buzdar study did not observe any chronic heart failure (total cumulative dose of epirubicin 300 mg/m^2), [Buzdar, 2007] and only 1 of the 455 patients of the GeparQuattro study (total cumulative dose of epirubicin 360 mg/m^2) developed a persistent decrease in LVEF below 50% during the neoadjuvant therapy [Untch, 2010]. In the NOAH study, only 2 patients (2%) developed symptomatic cardiac failure during 2 year follow-up and both patients responded to cardiac drugs. However, definite requirements before combining Herceptin® and anthracyclines in this setting include careful selection of patients according to pre-existing cardiac diseases and risk factors (such as a higher than normal LVEF before start of treatment), and restriction.

Epirubicin is investigated for concurrent use with Herceptin®; because epirubicin is considered to have cumulative risk of cardiotoxicity up to a 1000 mg/m^2, while doxorubicin has potential cardiotoxic cumulative doses at ≥ 450 mg/m^2. The Hercules study evaluated the cardiac safety of Herceptin® in combination with EC in patients with HER2 positive MBC [Untch, 2010]. Two different doses of epirubicin for 6 cycles were tested (60 mg/m^2 and 90 mg/m^2). The increase in epirubicin dose from 60 mg/m^2 to 90 mg/m^2 was associated with an increase in cardiac events from 15.0% to 23.3%. More specifically, the incidence of CHF NYHA class III/IV increased from 1.7% to 5.0%. However, the dose of epirubicin did not affect the efficacy variables. This result strongly suggests that Herceptin® in combination with low-dose epirubicin is a feasible and may be active regimen for patients with HER2 positive EBC.

1.4. Rationale for the Study

According to the Summary of Product Characteristics (SmPC) of Herceptin®, for patients with EBC, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin®. In patients who receive anthracycline containing chemotherapy further monitoring is recommended yearly up to 5 years from the last administration of Herceptin®, or longer if a continuous decrease of LVEF is observed.

The incidence of symptomatic CHF and asymptomatic significant LVEF decrease was not yet

investigated in the SB3 treated subjectts in neoadjuvant and adjuvant setting. This study will observe the incidence of cardiac event regarding LVEF of SB3 (proposed trastuzumab biosimilar) and Herceptin® in subjects with HER2 positive breast cancer who had completed SB3-G31-BC trial.

This study will evaluate long-term efficacy outcomes to all subjects enrolled in this extension study between treatment groups (SB3 and Herceptin®). EFS, disease-free survival (DFS), and OS will be presented based on the events including breast cancer recurrence/progression and death.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objective is to observe the incidence of symptomatic CHF and significant asymptomatic LVEF decrease in HER2 positive EBC or LABC subjects treated with SB3 or Herceptin® as neoadjuvant and adjuvant treatment.

- CHF is defined as NYHA II, III, and IV confirmed by a cardiologist, accompanied by a significant LVEF decrease.
- Significant LVEF decrease is defined as an absolute decline of at least 10% points from baseline LVEF (LVEF at screening of the SB3-G31-BC trial) and resulting LVEF less than 50%.

2.2. Secondary Objectives

The secondary objectives are:

- To observe the incidence of cardiac death and other significant cardiac conditions
- To observe the long term efficacy of SB3 compared to Herceptin® by
  - EFS and DFS
  - OS

3. STUDY DESIGN

3.1. Overview of Study Design

This is an observational cohort study.

[Cardiac Safety and Survival Cohort]: The group consists of subjects who completed the SB3-G31-BC trial and provide informed consent for the long-term follow-up of cardiac safety and survival.

Subjects who have completed the clinical trial SB3-G31-BC will be asked to consent to participate

in this study. Consenting subjects will be enrolled sequentially into the study in accordance with protocol version 1.0 and will be monitored according to the local clinical practices which are based on the Herceptin® SmPC or local label. No additional procedures/subject visits in comparison with the usual clinical practice are planned for the study.

Baseline data (such as demographics, breast cancer type, TNM stage, medical history, surgical history, pre-treatment LVEF, neoadjuvant and adjuvant treatment, and postoperative radiation therapy) will be transferred from the SB3-G31-BC trial. Follow-up data will be collected from medical records for up to 5 years or death, unless subjects are lost for the follow-up or have withdrew the informed consent.

[**Survival Only Cohort**]: The group consists of subjects who participate in this trial among subjects who received the SB3 or Herceptin® in the SB3-G31-BC trial and were not sequentially enrolled into this SB3-G31-BC-E trial as a Cardiac Safety and Survival Cohort.

Subjects who received SB3 or Herceptin® in accordance with the clinical trial SB3-G31-BC and were not sequentially enrolled to SB3-G31-BC-E trial as a Cardiac Safety and Survival Cohort will be asked to consent to participate in this study as a Survival Only Cohort. If prospective data collection is not possible (e.g. when the subject is deceased or lost to follow-up), a waiver of informed consent/authorization will be requested for the retrospective data collection from medical records, where applicable and in accordance with national regulations and local ethics. If informed consent form (ICF) waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent where applicable and approved by institutional review board (IRB)/independent ethics committees (IEC) and in accordance with national regulations.

Data will be collected from medical records for up to 5 years from their last investigational product (IP; SB3 or Herceptin®) administration or death, unless they are lost for the follow-up or withdraw the informed consent. Data for the study will be collected prospectively from the date of the study informed consent signed and data before informed consent will be obtained from medical records retrospectively. If prospective data collection is not possible, data could be collected retrospectively from medical records.

3.1.1. End of Trial

The study will close at 5 years after the last subject has received the last IP (SB3 or Herceptin®) in the setting of clinical trial SB3-G31-BC.

3.2. Number of Subjects

A total of 875 subjects received the study IP in the SB3-G31-BC trial. Incorporating 20% of refusal rate for consent to this observational study and 10% of lost to follow-up, approximately 612 subjects are expected to be enrolled to this study.

4. STUDY POPULATION

4.1. Overview

[Cardiac Safety and Survival Cohort]

The study population for the Cardiac Safety and Survival Cohort is women who completed in the clinical trial SB3-G31-BC (A Phase III randomised, double-Blind, parallel group, multicentre study to compare the efficacy, safety, PK, and immunogenicity between SB3 [proposed trastuzumab biosimilar] and Herceptin® in women with newly diagnosed HER2 positive EBC or LABC in neoadjuvant setting).

[Survival Only Cohort]

The study population for the Survival Only Cohort is women who received SB3 or Herceptin® in accordance with the clinical trial SB3-G31-BC and were not sequentially enrolled into this SB3-G31-BC-E trial as a Cardiac Safety and Survival Cohort.

4.2. Eligibility Criteria

[Cardiac Safety and Survival Cohort]

Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Subjects have completed the study treatment of the SB3-G31-BC trial according to the protocol.
2. Subjects must provide informed consent.

Exclusion Criteria

Subjects unwilling to follow the study requirements are not eligible for the study for the Cardiac Safety and Survival Cohort.

[Survival Only Cohort]

Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Subjects who received SB3 or Herceptin® according to the clinical trial SB3-G31-BC
2. Subjects who provide informed consent. If prospective data collection is not possible (e.g. when the subject is deceased or lost to follow-up), a waiver of informed consent/authorization will be requested for the retrospective data collection from medical records, where applicable

and in accordance with national regulations and local ethics. If ICF waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent where applicable and approved by IRB/IEC and in accordance with national regulations.

Exclusion Criteria

There is no exclusion criteria for the Survival Only Cohort.

5. STUDY PROCEDURES AND ASSESSMENTS

5.1. Recommended Schedule of Activities for the Cardiac Safety and Survival Cohort (Table 1)

5.1.1. Screening Period and Subjects Numbering (ICF Visit)

All subjects who completed the clinical trial SB3-G31-BC until end of study (EOS) will be asked to consent to participate in this study. The acceptable time lag from EOS of the SB3-G31-BC trial to obtain the informed consent is one year. The subject identification number of the SB3-G31-BC trial will be also used for this study.

5.1.2. Follow-up (Visit 1-7)

Subjects will be followed for 5 years after the EOS of the SB3-G31-BC trial. Each visit is recommended to occur every 6 month in the first 24 months, then yearly (i.e. every 12 months) according to local practice which is based on the SmPC or local label of Herceptin® . The recommended schedule for Visit 1 is 6 months after the last SB3 or Herceptin® administration. There is no pre-defined visit window. The following procedure will be performed during follow-up visits in the routine care setting.

- Physical examination including clinical breast exam
- Mammography
- LVEF measurement (2D echocardiography [ECHO] or multiple gated acquisition [MUGA] scan)
- Monitoring of cardiac events

5.2. Collection of Data for the Cardiac Safety and Survival Cohort

5.2.1. Follow-up Information

Following data will be collected:

- Physical examination including clinical breast exam

- Mammography
- LVEF measurement (2D ECHO or MUGA scan)
- Cardiac disorders: Onset, outcome, and medical intervention indicated or not
  - Symptomatic CHF
  - Asymptomatic LVEF decrease
  - Cardiac death
  - Other significant cardiac conditions (acute myocardial infarction, severe arrhythmia, ischemic heart disease, valvular dysfunction, etc.)
- Recurrence/progression of the breast cancer
- Death (in case scheduled visit is not available, it is allowed to collect survival information by telephone contacts)

For the investigation of cardiac events, breast cancer recurrence/progression, and survival, at least scheduled visits and activities are recommended.
In case of start of any new treatment for recurrent disease, only survival data will be collected.

5.2.2. Cardiac Assessments

This study plans to observe the incidence of symptomatic CHF, asymptomatic significant LVEF decrease, and cardiac death. CHF should be classified according to the NYHA classification (Appendix 1). Symptomatic CHF is defined as NYHA class II, III, IV, confirmed by a cardiologist, accompanied by a significant LVEF decrease. For reference, symptoms that can be associated with CHF are provided in (Appendix 2). Significant LVEF decrease is defined as an absolute decline of at least 10% points from baseline LVEF (LVEF at screening of the SB3-G31-BC trial) and to less than 50%. Cardiac death is defined as death definitely as a result of heart failure, myocardial infarction, or documented arrhythmia or as probable cardiac death within 24 hours of a cardiac event.

LVEF may be measured by 2D ECHO or MUGA scan as specified in the recommended schedule of activities (Table 1) and as medically indicated. The same method should be used for each subject during the SB3-G31-BC trial and this study. Also the assessment by same assessor from the SB3-G31-BC trial is recommended. It is advised that LVEF assessment is performed as per the SmPC or local label of Herceptin® SmPC.

The information about onset, outcome, and medical intervention indicated or not of cardiac events will be collected.

Table 5. Reporting Guideline for Left Ventricular Ejection Fraction Decrease

Observation	Term to be Reported	Grading
Asymptomatic decline in LVEF	N/A	N/A
Asymptomatic significant LVEF decrease (LVEF decline ≥ 10% points from baseline and resulting LVEF < 50%)	Asymptomatic significant LVEF decrease	N/A
Symptomatic significant LVEF decrease	CHF	NYHA

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

5.2.3. Recurrence/Progression and Survival Assessments

This study also plans to observe breast cancer recurrence/progression and death. Follow-up plans after cancer surgery and adjuvant treatment for breast cancer are described in several oncology guidelines including the NCCN guidelines version 1.2015, American Society of Clinical Oncology (ASCO) clinical practice guideline 2012, and European Society for Medical Oncology (ESMO) guidelines. Physical examinations are recommended every 3 to 12 months for the first 5 years, and annually thereafter. Mammography is recommended every 12 months. Diagnosis of breast cancer recurrence/progression will be made by clinical, radiological, or pathological findings.

In this study, EFS is defined as the time from the date of randomisation for the SB3-G31-BC trial to the date where an event occurs and DFS is defined as the time from the date of surgery for the SB3-G31-BC trial to the date where an event occurs. An event is defined as breast cancer recurrence or progression (local, regional, distant, or contralateral), or death due to any cause. OS is defined as the time from the date of randomisation for the SB3-G31-BC trial to the date of death, regardless of the cause of death. Subjects who were alive at the time of analysis will be censored at the date of the last follow-up assessment.

5.3. Recommended Schedule of Activities for the Survival Only Cohort (Table 2)

5.3.1. Subjects Numbering (ICF Visit)

Subjects who received SB3 or Herceptin® in accordance with the clinical trial SB3-G31-BC and were not sequentially enrolled to SB3-G31-BC-E trial as a Cardiac Safety and Survival Cohort will be asked to consent to participate in this study as a Survival Only Cohort. If prospective data collection is not possible (e.g. when the subject is deceased or lost to follow-up), a waiver of informed consent/authorization will be requested for the retrospective data collection from medical records, where applicable and in accordance with national regulations and local ethics. If ICF waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent where applicable and approved by IRB/IEC and in accordance with national regulations. The subject identification number of the SB3-G31-BC trial will be also used for this study.

5.3.2. Follow-up (Visit 1-7)

Subjects will be followed for 5 years after the last administration of IP (SB3 or Herceptin®) in the SB3-G31-BC trial. After enrolment into this trial, each visit is recommended to occur every 6 month in the first 24 months, then yearly (i.e. every 12 months) from the last administration of IP (SB3 or Herceptin®) in the SB3-G31-BC trial according to local practice which is based on the SmPC or local label of Herceptin®. If the recommended visit is already passed at the timing of enrolment, data will be retrospectively collected according to Section 5.4.

5.4. Collection of Data for the Survival Only Cohort

5.4.1. Follow-up Information

Following data will be collected:

- Recurrence/progression of the breast cancer
- Death (in case scheduled visit is not available, it is allowed to collect survival information by telephone contacts)

For the investigation of breast cancer recurrence/progression and survival, at least scheduled visits and activities are recommended.
In case of start of any new treatment for recurrent disease, only survival data will be collected.

5.4.2. Recurrence/Progression and Survival Assessments

Based on the time point of informed consent (or a waiver of informed consent, if applicable) for the study, retrospective and prospective data will be collected as follows.

- Retrospective data collection: Most recent breast cancer recurrence/progression and survival assessment data (whether recurrence/progression occurs or not) between the end of SB3-G31-BC trial and informed consent (or a waiver of informed consent, if applicable) for this extension study will be obtained from medical records retrospectively.
- Prospective data collection: Breast cancer recurrence/progression assessment and survival data after informed consent will be collected prospectively in the same manner as Cardiac Safety and Survival Cohort.

Subjects who were alive at the time of analysis will be censored at the date of the last follow-up assessment.

5.5. Study Treatment

There is no IP or a treatment prescribed by this protocol. Decision about any treatment will be made according to the local practice and at the discretion of the Investigator.

5.6. Unblinding

While this study is ongoing, blindness of SB3 or Herceptin® administered during the SB3-G31-BC trial will be maintained until the data base lock of the SB3-G31-BC trial.

During blinding period, unblinding should be considered when knowledge of the treatment assignment is deemed essential for the subject's care by their Investigator or a regulatory body. If the blind is broken, it may be broken only for the subject in question. If time permits, before requesting that the blind be broken for an individual subject, the Investigator should discuss the situation with the Sponsor via phone or e-mail. The Sponsor must be notified immediately if a subject and/or Investigator is unblinded during the course of the study along with the reason for breaking the blind. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents. This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the date of the unblinding and the relevant IP information.

5.7. Subject Withdrawal

Subjects are free to discontinue the study at any time without giving their reasons. Already collected data will be analysed for this study unless subjects refuse.

A subject must be withdrawn in the event of any of the following:

- Withdrawal of the subject's consent
- Newly diagnosed malignant neoplasm other than breast cancer to be treated during prospective data collection
- Administrative or other reasons

5.8. Premature Discontinuation of the Study

The whole study may be discontinued prematurely in case of the Sponsor's decision that discontinuation of the study is justifiable for medical reasons. Health authorities and IRBs/IECs will be informed about the discontinuation of the study in accordance with applicable regulations.

6. SAFETY MONITORING AND REPORTING

Subjects registered in this study can be waived from the reporting requirement of IP-related serious AEs (SAEs) after EOS described in Section 7 of the protocol for the SB3-G31-BC trial.

6.1. Safety Reporting Requirements for SB3-G31-BC-E

Since SB3-G31-BC-E is to assess the long-term cardiac safety for SB3 or Herceptin®, which is mainly about post-dose cardiac toxicities captured through cardiac assessments described in Section 5.2.2 and not by AE reporting, other non-serious AEs are not intended to be collected

through this study. However, for any type of SAE (cardiac or non-cardiac) that may be determined by the Investigator to be related to the IP then that SAE should be reported through a separate paper SAE report form to the Sponsor and not via the case report form (CRF). (note: AEs should be classified as 'related' if there is a reasonable possibility that the IP caused the AE. This means that there are facts (evidence) or arguments to suggest a causal relationship.) Such IP-related SAEs that occur from the subject's sign of the ICF to the EOS should be reported for the purpose of this study. However, even after the EOS, IP-related SAEs can be reported to the Sponsor separate from this study in the same way.

For more details of AEs including the definition of seriousness, severity, causality and expectedness, please refer to Section 7 of the protocol for the SB3-G31-BC trial.

6.2. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defects
- Is medically important

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation. However, if it is determined that the event may jeopardise the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as SAE.

6.2.1. Serious Adverse Event Reporting

SAEs that are determined to be related to the IP by the Investigator (either cardiac or non-cardiac) must be immediately reported at least within 24 hours of the Investigator becoming aware of the event to the Sponsor or its designated representative using the SAE form provided by the Sponsor. Contact information for SAE reporting will be provided in SAE Report Completion Instruction. In particular, if the reported SAE is fatal or life-threatening, the Sponsor must be notified immediately, irrespective of the extent of available AE information. This timeframe also applies to additional (follow-up) information that becomes available on previously forwarded SAE reports. The sponsor will then follow expedited reporting procedures according to local and international regulations as appropriate.
The Investigator is obligated to pursue and provide information to the Sponsor on such reported

SAEs in accordance with the timeframes for reporting specified above. In addition, the Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the reported SAE, which should be provided in sufficient detail so as to allow for a complete medical assessment of the case and independent determination of causality (as mentioned above, for the scope of this study only IP-related SAEs are expected to be reported). Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. If the reported SAE resulted into the subject's death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative.
All reported SAEs will be followed until event resolution or stabilisation (for chronic events), if possible. For chronic events that does not fully resolve until years later, the outcome should be reported as 'resolved with sequelae' as soon as the event has stabilised or returned to baseline. Follow-up information for the reported SAE should be actively sought and submitted as the information becomes available.

7. STATISTICAL CONSIDERATION AND ANALYTICAL PLAN

This is primarily designed to observe the incidence of symptomatic CHF, asymptomatic significant LVEF decrease, and other cardiac events in breast cancer subjects treated with SB3 or Herceptin® according to the protocol SB3-G31-BC trial. There is no pre-defined hypothesis testing, therefore all analyses will be performed for the observational or exploratory purpose.

All analyses will be performed periodically and at the end of the study.

7.1. Analysis Sets

The following set will be used for the analyses performed in the study:

- Long-term Follow-up Set: This set consists of all subjects who provide informed consent for the long-term follow-up of cardiac safety and survival. This set includes Cardiac Safety and Survival Cohort defined in Section 3.1
- Survival Follow-up Set: This set consists of all subjects who enrolled for this study. This set includes Cardiac Safety and Survival Cohort and Survival Only Cohort defined in Section 3.1.

Subjects will be analysed according to the treatment (SB3 or Herceptin®) received in the SB3-G31-BC trial.

7.2. Statistical Methods and Analytical Plan

7.2.1. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics from the SB3-G31-BC trial will be summarised by treatment group for the Long-term Follow-up Set and Survival Follow-up Set. Continuous

variables will be summarised with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarised with counts and percentage. Relevant medical history from the SB3-G31-BC trial will be summarised by treatment group for the Long-term Follow-up Set and Survival Follow-up Set.

7.2.2. Analysis for Primary and Secondary Objective

The incidence of symptomatic CHF and asymptomatic significant LVEF decrease will be summarized by treatment group for the Long-term Follow-up Set. The incidence of cardiac death and other significant cardiac conditions will be analysed similarly.

For time to event data, survival analysis for EFS, DFS, and OS will be performed for the Long-term Follow-up Set and Survival Follow-up Set respectively. Kaplan-Meier curves will be calculated and displayed by treatment group in the SB3-G31-BC trial. Additionally, the stratified Cox proportional hazard regression model will be applied to estimate hazard ratio (SB3/Herceptin®). The stratification factors are hormone receptor status and breast cancer type, and region. The hazard ratio will be presented along with its *p*-value and corresponding 95% confidence interval (CI).

Exploratory analyses will be conducted to detect any patterns or systemic data issues.

7.3. Sample Size

No formal sample size calculation was done as there is no hypothesis to be tested. A total of 875 subjects received the study IP in the SB3-G31-BC trial. Incorporating 20% of refusal rate for consent to this observational study and 10% of lost to follow-up, approximately 612 subjects are expected to be enrolled to this study.

8. DATA COLLECTION AND MANAGEMENT

8.1. Data Confidentiality

Information about study subjects will be kept confidential. Subject identification information will be labelled with a code number, and will not include the subject's name or other information that could identify them. A list linking the code and the subject's name will be kept in the site files as required by Good Clinical Practice (GCP) to protect the subject's confidentiality.

The coded information will be sent to the Sponsor (or designee) who will analyse it and report the study results both to regulatory and ethical authorities. The Sponsor may also place data on public websites or publish journal articles based upon these results. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes. Care will be taken to prevent subjects being identified through these publications. In addition, data may be shared with other companies or researchers to aid further research into breast cancer. Such data sharing practices will be covered by confidentiality agreements. No-one outside the Investigator site will have access to subject-identifiable information.

8.2. Monitoring

The Sponsor has engaged the services of a contract research organisation (CRO) to perform all monitoring functions within this clinical study. The monitors will work in accordance with the CRO standard operating procedures (SOPs) and have the same rights and responsibilities as monitors from the Sponsor organisation.

During the study, monitors will check that written informed consent has been obtained correctly from subjects and that data are recorded correctly and completely. Monitors will also conduct proper source data verification and verify protocol adherence. Further details on the monitoring processes and the level of source data verification to be performed will be described in the monitoring plan. The monitor will provide written reports to the Sponsor on each occasion they make contact with the Investigator regardless of whether it is by phone or in person.

8.3. Data Handling and Record Keeping

The Investigator must maintain essential study documents (protocol and protocol amendments, completed CRFs, signed ICFs, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the IP or 15 years after completion of the study. These documents should be retained for a longer period if required by the applicable regulatory requirements or the Investigator site, institution or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for the same period of time. These documents may be transferred to another responsible party, deemed acceptable by the Sponsor, and who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records and obtain written permission to do so.

8.4. Database Management

Data generated within this clinical study will be handled according to the relevant SOPs of the data management of the Sponsor (or an appropriate company designated by the Sponsor to perform these activities). The study CRF is the primary data collection instrument for the study. Subject data will be captured in a CRF and reviewed by the monitor in order to check adherence to the protocol and to detect any data inconsistency or discrepancy as per study monitoring plan.

The Investigator must ensure that the clinical data required by the study protocol are carefully reported in the CRF. He/she must also check that the data reported in the CRF correspond to those in the medical records.

Forms should be available during periodic visits by study monitors to enable review for completeness and acceptability. Any correction to the data entered into the CRF must be carried out by the Investigator or a designated member of staff. These changes may be made either on the

initiative of the site staff or in response to monitoring or data queries. Any changes to written and electronic data should be made in a system which can provide an audit trail. The audit trail records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. The Investigator must sign and date the CRF pages as indicated.

Cardiac events will be coded using the Medical Dictionary for Regulatory Activities. The versions of coding dictionaries used will be stated in the clinical study report.

8.5. Quality Control and Quality Assurance

The Investigator and institution will allow the monitors from the Sponsor or its agents and appropriate regulatory authorities direct access to source documents to perform verification. The study site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities.

9. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

9.1. Institutional Review Board or Independent Ethics Committee

The Investigator and the Sponsor will follow all local laws and regulations relating to contact with and approvals from the IRB/IEC.

The Investigator must provide the Sponsor with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the Investigator site. The Investigator will supply documentation to the Sponsor relating to the annual renewal of the protocol from the IRB/IEC and any approvals of revisions to the ICF or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC on a regular basis and in accordance with the timelines required locally. Upon completion of the study, the Investigator will provide the ethics committee with a report on the outcome of the study if required by local regulations.

9.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, the ICH guidelines, GCP, the Declaration of Helsinki (2013) and all applicable and current regulatory requirements.

9.3. Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject enters into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the

subject is free to withdraw from the study at any time. Written consent will be given by the subject after the receipt of detailed information on the study. The Investigator is responsible for ensuring that informed consent is obtained from each subject and for obtaining the appropriate signatures. The Investigator will provide each subject with a copy of the signed and dated ICF and this will be documented in the subject's source notes. When prospective data collection is not possible (e.g. when the subject is deceased or lost to follow-up), waiver of informed consent/authorization will be requested for the retrospective collection where applicable and approved by IRB/IEC and in accordance with national regulations. If ICF waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent on data-handling procedures where applicable and approved by IRB/IEC and in accordance with national regulations.

If it is not possible for the subject or next of kin (if applicable) to physically come to site for an in-person informed consent discussion, informed consent process will be performed remotely where applicable and approved by IRB/IEC and in accordance with national regulations. In such cases, the Investigator will discuss the study information and consent by a means other than face to face communication. If the subject or next of kin (if applicable) are interested to participate in study, the investigator or designee will send two copy of ICFs for subject. The subject or next of kin (if applicable) can request additional phone call with investigator in case of question and discuss. The subject or next of kin (if applicable) will send the two written consent to the site. Upon receipt of two signed ICFs, the investigator will sign the ICF and place 1 copy in the Investigator Study File and send 1 copy back to the subject or next of kin (if applicable).

9.4. Financing and Insurance

Samsung Bioepis is the Sponsor of this study and will be providing the finances to cover the operation of the study. Details of financial agreements are provided in the Clinical Study Agreements with the Investigator sites and in contracts with other companies involved in the running of the study.

The Sponsor has obtained suitable insurance for this study. A copy of the insurance details will be provided to each Investigator who will be responsible for providing the IRB/IEC with these details according to local requirements.

10. PUBLICATION POLICY

The Sponsor supports the efforts of health authorities to increase the transparency of medical research conducted in human subjects. The Sponsor will comply with the guidelines of regulatory authorities with regards to public registration and disclosure of clinical study data.

The clinical study data collected during the study are confidential and proprietary to the Sponsor. The Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed abstract or presentation.

Any publications from this study should be approved by the Sponsor prior to publication or presentation. The rights of the Investigator with regard to publication of this study are described in the Clinical Study Agreement.

11. REFERENCES

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Untch M, Rezai M, Loibl S, et al. Neoadjuvant treatment with trastuzumab in her2-positive breast cancer: Results from the geparquattro study. *J Clin Oncol.* 2010; 28 (12): 2024-2031.

APPENDICES

Appendix 1: Criteria for New York Heart Association Functional Classification

Class	Patient Symptoms
Class I	No limitation of physical activity. No symptoms (fatigue, palpitation, or dyspnoea) with ordinary physical activity
Class II	Slight limitation of physical activity Comfortable at rest, but symptomatic (fatigue, palpitation, or dyspnoea) at ordinary physical activity
Class III	Marked limitation of physical activity Comfortable at rest, but symptomatic (fatigue, palpitation, or dyspnoea) at less than ordinary activity
Class IV	Unable to perform any physical activity Symptomatic (fatigue, palpitation, or dyspnoea) at rest, and discomfort with any ordinary physical activity If any physical activity is undertaken, discomfort is increased.

Reference:

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix 2: Framingham Criteria for Congestive Heart Failure

A definite diagnosis of CHF requires that a minimum of two major or one major and two minor criteria be present concurrently. The presence of other conditions capable of producing the symptoms and signs (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or nephrotic syndrome) are considered in evaluating the findings.

This criteria is provided as a checklist. However, participating clinicians make decision on diagnosis of symptomatic CHF.

Major Criteria:

- Paroxysmal nocturnal dyspnea or orthopnea
- Distended neck veins (in other than the supine position)
- Rales
- Increasing heart size by X-ray
- Acute pulmonary edema
- Ventricular S (3) gallop
- Increased central venous pressure (> 16 cm water at right atrium)
- Hepatojugular reflux
- Weight loss > 4.5 kg in 5 days in response to CHF treatment

Minor criteria:

- Bilateral ankle edema
- Night cough
- Dyspnea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Decrease in vital capacity by one-third from maximum record
- Tachycardia (120 beats per minute or more)

Reference:

Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol*. 1993; Oct. 22(4 Suppl A):6A-13A.

CHANGE HISTORY OF PROTOCOL AMENDMENT

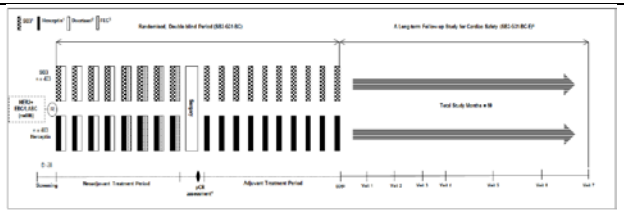
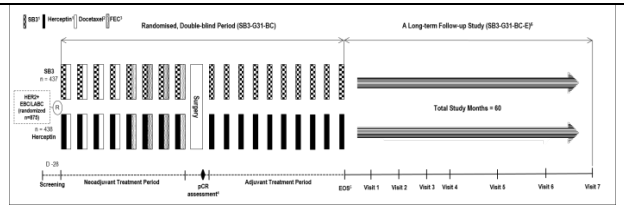
Amendment 1: Version 2.0, Nov 26, 2018

Section Affected	Original Content	Amended/New Content	Rationale
SYNOPSIS – Objectives and 2.2. Secondary Objectives	• To observe the long term efficacy of SB3 compared to Herceptin® by - event-free survival	• To observe the long term efficacy of SB3 compared to Herceptin® by - Event-free survival (EFS) and **disease-free survival (DFS)**	To add DFS in secondary endpoint
SYNOPSIS – Study Design and 3.1. Overview of Study Design	N/A	**[Cardiac Safety and Survival Cohort]: The group consists of subjects who completed the SB3-G31-BC trial and provide informed consent for the long-term follow-up of cardiac safety and survival.**	To add cohort definition in accordance with updated study design
SYNOPSIS – Study Design and 3.1. Overview of Study Design	Consenting subjects will be enrolled sequentially into the study and will be monitored according to the local clinical practices which are based on the Herceptin® SmPC or local label.	Consenting subjects will be enrolled sequentially into the study **in accordance with protocol version 1.0** and will be monitored according to the local clinical practices which are based on the Herceptin® SmPC or local label.	To add description for clarification of each cohort
SYNOPSIS – Study Design and 3.1. Overview of Study Design	N/A	**[Survival Only Cohort]: The group consists of subjects who participate in this trial among subjects who received the SB3 or Herceptin® in the SB3-G31-BC trial, were not sequentially enrolled into this SB3-G31-BC-E trial as a Cardiac Safety and Survival Cohort. Subjects who received SB3 or Herceptin® in accordance with the clinical trial SB3-G31-BC and were not sequentially enrolled to SB3-G31-BC-E trial**	To add cohort definition and detailed explanation in accordance with updated study design

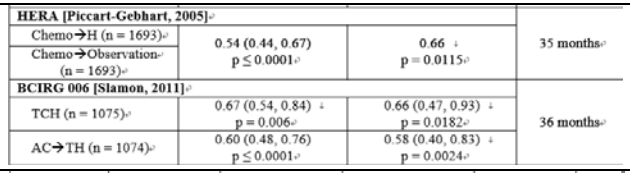
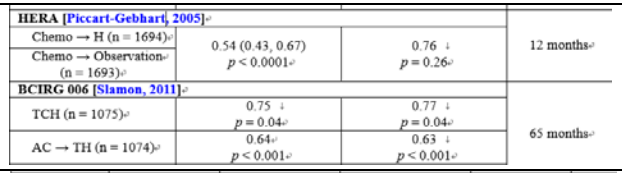
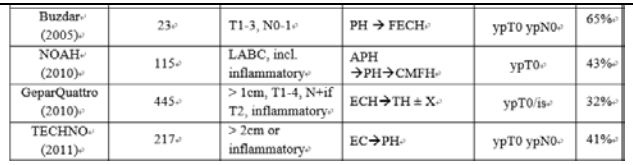
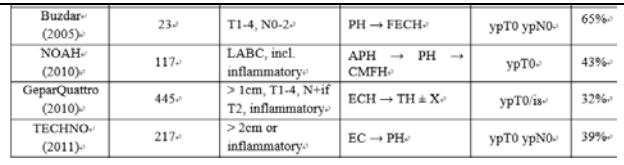
Section Affected	Original Content	Amended/New Content	Rationale
		as a Cardiac Safety and Survival Cohort will be asked to consent to participate in this study as a Survival Only Cohort. If prospective data collection is not possible (e.g. when the subject is deceased or lost to follow-up), a waiver of informed consent/authorization will be requested for the retrospective data collection from medical records, where applicable and in accordance with national regulations and local ethics. If ICF waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent where applicable and approved by institutional review board (IRB)/independent ethics committee (IEC) and in accordance with national regulations. **Data will be collected from medical records for up to 5 years from their last investigational product (IP; SB3 or Herceptin®) administration or death, unless they are lost for the follow-up or withdraw the informed consent. Data for the study will be collected prospectively from the date of the study informed consent signed and data before informed consent will be obtained from medical records retrospectively. If prospective data collection is not possible, data could be collected retrospectively from medical records.**	
SYNOPSIS – Number	It is planned that approximately 579 subjects will be enrolled.	It is planned that approximately ~~**579**~~ **612** subjects will be enrolled.	To reflect updated study design

Section Affected	Original Content	Amended/New Content	Rationale
of Subjects			
SYNOPSIS – Eligibility Criteria and 4.2. Eligibility Criteria	N/A	**[Survival Only Cohort]** **<u>Inclusion criteria</u>** **Subjects must meet all of the following criteria to be eligible for the study:** **1. Subjects who received SB3 or Herceptin® according to the clinical trial SB3-G31-BC.** **2. Subjects (or legal representative, if applicable) who provide informed consent. If subjects were lost to follow-up or died after the end of SB3-G31-BC trial and prospective data collection is not possible, a waiver of informed consent/authorization will be requested for the retrospective data collection from medical records, where applicable and in accordance with national regulations and local ethics. If ICF waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent where applicable and approved by IRB/IEC and in accordance with national regulations.** **<u>Exclusion criteria</u>** **There is no exclusion criteria for the Survival Only Cohort.**	To add eligibility criteria for Survival Only Cohort in accordance with updated study design
SYNOPSIS – Planned Study Period	Enrolment is expected to last approximately 10 months. The study will close at 5 years after the last patient has	**~~Enrolment is expected to last approximately 10 months.~~** The study will close at 5 years after the	To reflect updated study design

Section Affected	Original Content	Amended/New Content	Rationale
	been enrolled (Figure 1).	last **~~patient~~ subject** has **~~been enrolled (Figure 1).~~received the last IP (SB3 or Herceptin®) in the setting of clinical trial SB3-G31-BC.**	
SYNOPSIS – Criteria for Evaluation	N/A	• **DFS, defined as the time from the date of surgery for the SB3-G31-BC trial to the date where an event occurs. An event is breast cancer recurrence (local, regional, distant, or contralateral) or death due to any cause.**	To add definition of DFS
SYNOPSIS – Statistical Methods and 7.2.2. Analysis for Primary and Secondary Objective	The incidence of CHF, asymptomatic LVEF decrease, cardiac death, and other significant cardiac conditions and all other variables will be summarised descriptively by SB3-G31-BC treatment group and also listed. For time to event data, Kaplan-Meier curves will be calculated and displayed by SB3-G31-BC treatment group. Median survival times and the corresponding 95% CI will be also provided.	**The subject demographics and baseline characteristics from SB3-G31-BC trial will be summarised by treatment group for the Long-term Follow-up Set and Survival Follow-up Set.** The incidence of CHF, asymptomatic LVEF decrease, cardiac death, and other significant cardiac conditions and all other **~~variables~~ safety** data will be summarised descriptively by SB3-G31-BC treatment group **in the SB3-G31-BC trial and also listed for the Long-term Follow-up Set.** For time to event data, **survival analysis for EFS, DFS, and OS will be performed for the Long-term Follow-up Set and Survival Follow-up Set, respectively.** Kaplan-Meier curves will be calculated and displayed by treatment group **in the SB3-G31-BC trial. Additionally, the stratified Cox proportional hazard regression model will be applied to estimate Hazard ratio**	To reflect updated study design

Section Affected	Original Content	Amended/New Content	Rationale
		(SB3/Herceptin®). The stratification factors are hormone receptor status and breast cancer type, and region. The hazard ratio will be presented along with its *p*-value and corresponding 95% confidence interval (CI). Kaplan-Meier curves will be calculated and displayed by SB3-G31-BC treatment group. ~~Median survival times and the corresponding 95% CI will be also provided.~~ **Exploratory analyses will be conducted to detect any patterns or systemic data issues.**	
Figure 1			To reflect updated study design
Figure 1	6. After the last SB3 or Herceptin® administration, subjects will have safety follow-up visits every 6 months for 24 months, then yearly for additional 3 years.	6. After the last SB3 or Herceptin® administration **in the SB3-G31-BC trial,** subjects will have safety follow-up visits every 6 months for 24 months, then yearly for additional 3 years. **For Cardiac Safety and Survival Cohort, subjects will be enrolled sequentially into the study in accordance with SB3-G31-BC-E trial protocol version 1.0 and all data for the study will be collected prospectively. For the Survival Only Cohort, data for the study will be collected prospectively from the date of the study informed consent signed and data before**	To reflect updated study design

Section Affected	Original Content	Amended/New Content	Rationale
		informed consent will be obtained from medical records retrospectively in accordance with recommended schedule of activities. If prospective data collection is not possible, data could be collected retrospectively from medical records.	
Table 1	Table 1. Recommended Schedule of Activities	Table 1. Recommended Schedule of Activities **for the Cardiac Safety and Survival Cohort**	To reflect updated study design
Table 1	6. For the investigation of cardiac events, breast cancer recurrence/progression, and survival, at least scheduled visits and activities are recommended. And also there will be additional unscheduled visits IF there is suspicion of such events.	6. For the investigation of cardiac events, breast cancer recurrence/progression, and survival, at least scheduled visits and activities are recommended. ~~**And also there will be additional unscheduled visits IF there is suspicion of such events.**~~	To reflect updated study design
Table 2	N/A	Added	To reflect updated study design
LIST OF STUDY STAFF	Previous study staffs	Current study staffs at the time of protocol amendment	To update study staffs
1.2.2. Overview of SB3-G31-BC Trial	A total of 806 subjects (403 per treatment arm) were randomised in the study. Each subject will be on clinical study for approximately 12 months, corresponding to 8 cycles of neoadjuvant therapy before surgery followed by 10 cycles of adjuvant therapy after surgery. Post therapy, subjects will be followed at 30 days after last dose of IP. As clinical study has not been completed up to date, clinical data is currently not available.	~~**A total of 806 subjects (403 per treatment arm) were randomised in the study. Each subject will be on clinical study for approximately 12 months, corresponding to 8 cycles of neoadjuvant therapy before surgery followed by 10 cycles of adjuvant therapy after surgery. Post therapy, subjects will be followed at 30 days after last dose of IP. As clinical study has not been completed up to date, clinical data is currently not available.**~~ **A total of 875 subjects were randomised; 437 subjects**	To update information in accordance with SB3-G31-BC trial

Section Affected	Original Content	Amended/New Content	Rationale
		to the SB3 treatment group and 438 subjects to the Herceptin® treatment group. Among them, 380 subjects in the SB3 treatment group and 384 subjects in the Herceptin® treatment group completed the trial.	
Table 3			To update data in accordance with the reference
Table 4			To update data in accordance with the reference
1.4. Rationale for the Study	N/A	**This study will evaluate long-term efficacy outcomes to all subjects enrolled in this extension study between treatment groups (SB3 and Herceptin®). EFS, disease-free survival (DFS), and OS will be presented based on the events including breast cancer recurrence/progression and death.**	To reflect updated study design
3.1.1. End of Trial	N/A	**The study will close at 5 years after the last subject has received the last IP (SB3 or Herceptin®) in the setting of clinical trial SB3-G31-BC.**	To add definition of end of trial
3.2. Number of Subjects and 7.3. Sample Size	More than 716 out of 806 subjects are expected to complete study treatment in SB3-G31-BC trial. Incorporating 20% of refusal rate for consent to this	~~**More than 716 out of 806 subjects are expected to complete study treatment in SB3-G31-BC trial.**~~ **A total of 875 subjects received the study IP in the SB3-G31-**	To reflect updated study design

Section Affected	Original Content	Amended/New Content	Rationale
	observation study, approximately 573 subjects over 10 months are expected to be enrolled to this study.	**BC trial.** Incorporating 20% of refusal rate for consent to this observational study **and 10% of lost to follow-up,** approximately ~~**573**~~ **612 subjects** ~~**over 10 months**~~ are expected to be enrolled to this study.	
4.1. Overview	N/A	**[Survival Only Cohort]** **The study population for the Survival Only Cohort is women who received SB3 or Herceptin® in accordance with the clinical trial SB3-G31-BC and were not sequentially enrolled into this SB3-G31-BC-E trial as a Cardiac Safety and Survival Cohort.**	To reflect updated study design
5.2.1. Follow-up Information	For the investigation of cardiac events, breast cancer recurrence/progression, and survival, at least scheduled visits and activities are recommended. And also there will be additional unscheduled visits IF there is suspicion of such events.	For the investigation of cardiac events, breast cancer recurrence/progression, and survival, at least scheduled visits and activities are recommended. ~~**And also there will be additional unscheduled visits IF there is suspicion of such events.**~~	To reflect updated study design
5.2.3. Recurrence/Progression and Survival Assessments	In this study, EFS is defined as the time from the date of randomisation for SB3-G31-BC to the date where an event occurs.	In this study, EFS is defined as the time from the date of randomisation for the SB3-G31-BC trial to the date where an event occurs **and DFS is defined as the time from the date of surgery for the SB3-G31-BC trial to the date where an event occurs**	To add definition of DFS
5.3. Recommended Schedule of Activities for the Survival Only Cohort (Table 2)	N/A	Section 5.3 including 5.3.1 and 5.3.2 was added.	To reflect updated study design
5.4. Collection of Data for the Survival Only	N/A	Section 5.4 including 5.4.1 and 5.4.2 was added.	To reflect updated study design

Section Affected	Original Content	Amended/New Content	Rationale
Cohort			
5.7. Subject Withdrawal	• Newly diagnosed malignant neoplasm other than breast cancer to be treated**.**	• Newly diagnosed malignant neoplasm other than breast cancer to be treated **during prospective data collection.**	To reflect updated study design
6. SAFETY MONITORING AND REPORTING	N/A	**Subjects registered in this study can be waived from the reporting requirement of IP-related serious AEs (SAEs) after EOS described in Section 7 of the protocol for the SB3-G31-BC trial.**	To clarify safety reporting
7.1. Analysis Sets	Long-term Follow-up set: this set consists of all subjects who provide informed consent for this study. Subjects will be analysed according to the treatment received in SB3-G31-BC.	• Long-term Follow-up Set: This set consists of all subjects who provide informed consent **for the long-term follow-up of cardiac safety and survival. This set includes Cardiac Safety and Survival Cohort defined in Section 3.1** • **Survival Follow-up Set: This set consists of all subjects who enrolled for this study. This set includes Cardiac Safety and Survival Cohort and Survival Only Cohort defined in Section 3.1.** **Subjects will be analysed according to the treatment (SB3 or Herceptin®) received in the SB3-G31-BC trial.**	To reflect updated study design
7.2.1. Demographics and Baseline Characteristics	Subject demographics and baseline characteristics from SB3-G31-BC will be summarised by treatment group. … Relevant medical history from SB3-G31-BC will be summarised by treatment group.	Subject demographics and baseline characteristics from the SB3-G31-BC trial will be summarised by treatment group for the Long-term Follow-up Set **and Survival Follow-up Set.** … Relevant medical history from the SB3-G31-BC trial will	To reflect updated study design

Section Affected	Original Content	Amended/New Content	Rationale
		be summarised by treatment group **for the Long-term Follow-up Set and Survival Follow-up Set.**	
7.2.2. Analysis for Primary and Secondary Objective	The incidence of symptomatic CHF and asymptomatic significant LVEF decrease will be summarized by treatment group.	The incidence of symptomatic CHF and asymptomatic significant LVEF decrease will be summarized by treatment group **for the Long-term Follow-up Set.**	To reflect updated study design
9.3. Informed Consent	Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.	Written consent ~~**must**~~ **will** be given by the subject ~~**and/or legal representative,**~~ after the receipt of detailed information on the study. **The Investigator is responsible for ensuring that informed consent is obtained from each subject and for obtaining the appropriate signatures. The Investigator will provide each subject with a copy of the signed and dated ICF and this will be documented in the subject's source notes. When prospective data collection is not possible (e.g. when the subject is deceased or lost to follow-up), waiver of informed consent/authorization will be requested for the retrospective collection where applicable and approved by IRB/IEC and in accordance with national regulations. If ICF waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent on data-handling procedures where applicable and approved by IRB/IEC and in accordance with national regulations.** **If it is not possible for the subject or next of kin (if applicable) to physically come to site for an in-person**	To reflect updated study design

Section Affected	Original Content	Amended/New Content	Rationale
		informed consent discussion, informed consent process will be performed remotely where applicable and approved by IRB/IEC and in accordance with national regulations. In such cases, the Investigator will discuss the study information and consent by a means other than face to face communication. If the subject or next of kin (if applicable) are interested to participate in study, the investigator or designee will send two copy of ICFs for subject. The subject or next of kin (if applicable) can request additional phone call with investigator in case of question and discuss. The subject or next of kin (if applicable) will send the two written consent to the site. Upon receipt of two signed ICFs, the investigator will sign the ICF and place 1 copy in the Investigator Study File and send 1 copy back to the subject or next of kin (if applicable).	
All sections	The latest Manual of Style (version 3.0) of Samsung Bioepis was not fully applied.	Updated in accordance with Manual of Style version 3.0 by Samsung Bioepis	Administrative update irrelevant to study design and/or procedures

PROTOCOL SIGNATURE PAGES

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Expert

Protocol Title: A Long-term Follow-up Study for Cardiac Safety in the Patients with HER2 Positive Early or Locally Advanced Breast Cancer Who Have Completed the SB3-G31-BC

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

Name: PPD SB3 Clinical Research Physician

Institution: Samsung Bioepis Co., Ltd.

Signature: PPD Date: PPD

(Month, Day, Year)

SIGNATURE PAGE

Declaration of the Principal/Coordinating Investigator

Protocol Title: A Long-term Follow-up Study for Cardiac Safety in the Patients with HER2 Positive Early or Locally Advanced Breast Cancer Who Have Completed the SB3-G31-BC

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Principal/Coordinating Investigator

Name: _____

Institution: _____

Signature: _____ Date: _____
(Month, Day, Year)

Statistical Analysis Plan

Protocol No.: SB3-G31-BC-E

A Long-term Follow-up Study for Cardiac Safety in the Patients with HER2 Positive Early or Locally Advanced Breast Cancer Who Have Completed the SB3-G31-BC

Sponsor: Samsung Bioepis Co., Ltd.

Author: PPD

Protocol Version: SB3-G31-BC-E_Version 2.0/Amendment 1, Nov 26, 2018

SAP Version: SAP_SB3-G31-BC-E_Addendum 2_2021-01-26

Signature Page

Prepared by

PPD

Statistician *Signature* *Date(YYYY-MM-DD)*

Reviewed by

PPD

STAT Manager *Signature* *Date(YYYY-MM-DD)*

PPD

STAT Director *Date(YYYY-MM-DD)*

PPD

PPD

Statistician, Samsung Bioepis *Signature* *Date(YYYY-MM-DD)*

Approved by

PPD

Director, Samsung Bioepis *Signature* *Date(YYYY-MM-DD)*

History of Revision

Protocol No.	SB3-G31-BC-E	**Sponsor**	Samsung Bioepis Co., Ltd.
		CRO	LSK Global PS
Approval Date	**Amended Version**	**Reason**	
2018-01-16	Addendum 1	1. Wording change for "Significant LVEF decrease" 2. 'Asymptomatic significant LVEF decrease' is redefined. 3. Description of summary of significant LVEF decrease is included in section 10.1. 4. Explanation on interim analysis is modified since the frequency of analyses can be adjusted by the sponsor's decision. 5. Table 14.3-2.2 is combined with Table 14.3-2.1.	
2021-01-26	Addendum 2	1. To reflect the amendment of protocol (version 2.0) - Updating study design - Adding survival follow-up set - DFS is defined as secondary endpoint 2. Adding contents about premature discontinuation of the study	

List of Contents

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

BMI	Body Mass Index
BSA	Body Surface Area
CHF	Congestive heart failure
CI	Confidence interval
DFS	Disease-free survival
EBC	Early breast cancer
ECHO	Echocardiography
EFS	Event-free survival
EOS	End of study
HER2	Human epidermal growth factor receptor 2
ICF	Informed consent form
IP	Investigational product
LABC	Locally advanced breast cancer
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multiple gated acquisition
NYHA	New York Heart Association
PT	Preferred Term
OS	Overall survival
pCR	Pathologic complete response
SAS	Statistical Analysis System
SOC	System Organ Class
SmPC	Summary of product characteristics

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to observe the incidence of symptomatic congestive heart failure (CHF) New York Heart Association (NYHA) class II, III, and IV and asymptomatic significant Left Ventricular Ejection Fraction (LVEF) decrease in subjects who participated in the SB3-G31-BC trial and treated with SB3 (proposed trastuzumab biosimilar) or Herceptin® as neoadjuvant and adjuvant treatment.

- Symptomatic CHF is defined as NYHA II, III, and IV, confirmed by a cardiologist, accompanied by a significant LVEF decrease.
- Significant LVEF decrease is defined as an absolute decline of at least 10 % points from baseline LVEF (LVEF at screening of SB3-G31-BC trial) and resulting LVEF less than 50%

2.2 Secondary Objective

The secondary objectives are:

- To observe the incidence of cardiac death and other significant cardiac conditions
- To observe the long term efficacy of SB3 compared to Herceptin® by
  - Event-free survival and disease-free survival
  - Overall survival

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an observational cohort study.

[Cardiac Safety and Survival Cohort]: The group consists of subjects who completed the SB3-G31-BC trial and provide informed consent for the long-term follow-up of cardiac safety and survival.

Subjects who have completed the clinical trial SB3-G31-BC will be asked to consent to participate in this study. Consenting subjects will be enrolled sequentially into the study in accordance with SB3-G31-BC-E trial protocol version 1.0 and will be monitored according to the local clinical practices which are based on the Herceptin® SmPC or local label. No additional procedures/subject visits in comparison with the usual clinical practice are planned for the study.

Baseline data (such as demographics, breast cancer type, TNM stage, medical history, surgical history, pre-treatment LVEF, neoadjuvant and adjuvant treatment, postoperative radiation therapy) will be transferred from the SB3-G31-BC study. Follow-up data will be collected from medical records for up to 5 years or death, unless subjects are lost for the follow-up or have withdrew the informed consent.

[Survival Only Cohort]: The group consists of subjects who participate in this trial among subjects who received the SB3 or Herceptin® in the SB3-G31-BC trial and were not sequentially enrolled into this SB3-G31-BC-E trial as a Cardiac Safety and Survival Cohort. All subjects in Bosnia & Herzegovina and APAC countries including India are solely applicable for the Survival Only Cohort.

Subjects who received SB3 or Herceptin® in accordance with the clinical trial SB3-G31-BC and were not sequentially enrolled to SB3-G31-BC-E trial as a Cardiac Safety and Survival Cohort will be asked to consent to participate in this study as a Survival Only Cohort. Cardiac and other safety assessment will be performed in subjects who provide informed consent for follow-up of cardiac safety and all data will be collected prospectively. If prospective data collection regarding breast cancer recurrence and survival status is not possible (e.g. when the subject is deceased or lost to follow-up), a waiver of informed consent/authorization will be requested for the retrospective data collection from medical records, where applicable and in accordance with national regulations and local ethics. If informed consent form (ICF) waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent where applicable and approved by institutional review board (IRB)/independent ethics committees (IEC) and in accordance with national regulations.

Data will be collected from medical records for up to 5 years from their last investigational product (IP; SB3 or Herceptin®) administration or death, unless they are lost for the follow-up or withdraw the informed consent. Data for the study will be collected prospectively from the date of the study informed consent signed and data before informed consent will be obtained from medical records retrospectively. If prospective data collection regarding breast cancer recurrence and survival status is not possible, data could be collected retrospectively from medical records.

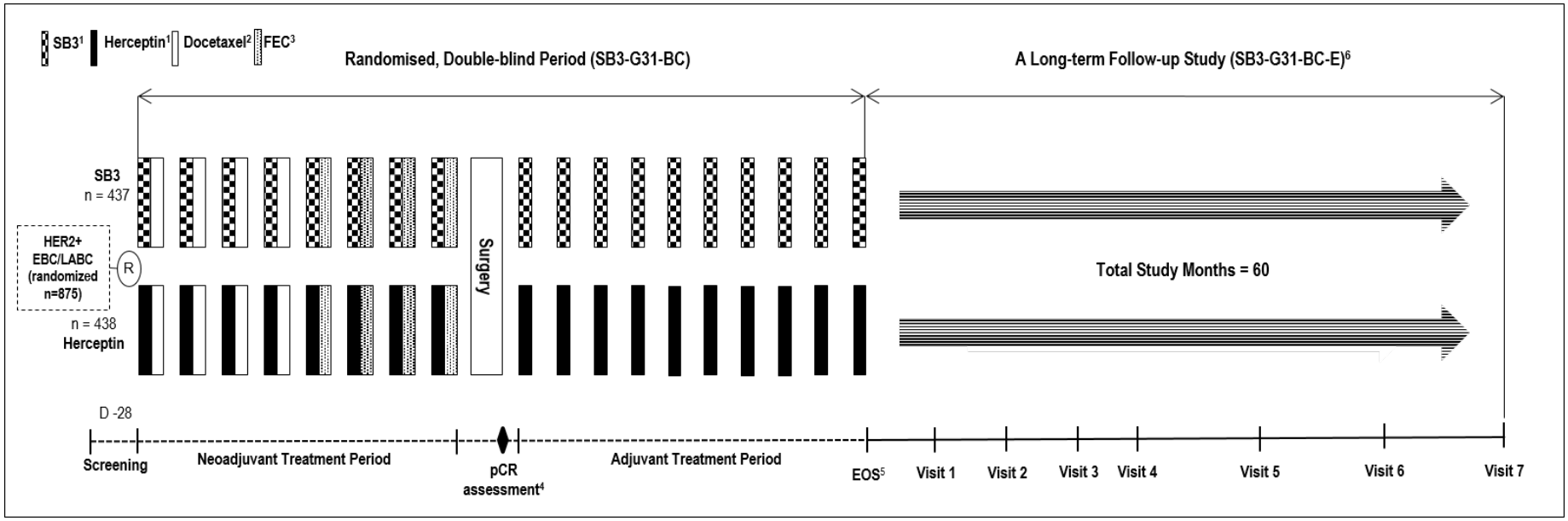


Figure 1. Graphical Study Design

D = day, EBC = Early breast cancer, EOS = end of study; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; HER2 = human epidermal growth factor receptor 2; LABC = Locally advanced breast cancer, n = number of subjects; LABC = locally advanced breast cancer; pCR = pathological complete response, ® = randomisation

1. Loading dose of 8 mg/kg and then a maintenance dose of 6 mg/kg every 3 weeks
2. Docetaxel 75 mg/m^2
3. 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2
4. Primary endpoint: pathologic complete response (pCR) in breast tumour
5. EOS (End of Study) that means end of core study (SB3-G31-BC) is scheduled 30 days after the last dose of Investigational product (IP).
6. After the last SB3 or Herceptin® administration, subjects will have safety follow-up visits every 6 months for 24 months, then yearly for additional 3 years. For Cardiac Safety and Survival Cohort, subjects will be enrolled sequentially into the study in accordance with SB3-G31-BC-E trial protocol version 1.0 and all data for the study will be collected prospectively. For the Survival Only Cohort, data for the study will be collected prospectively from the date of the study informed consent signed and data before informed consent will be obtained from medical records retrospectively in accordance with recommended schedule of activities. If prospective data collection is not possible, data could be collected retrospectively from medical records.

3.2 Study Duration

The study will close at 5 years after the last subject has received the last IP (SB3 or Herceptin®) in the setting of clinical trial SB3-G31-BC

The whole study may be discontinued prematurely in case of the Sponsor's decision that discontinuation of the study is justifiable for medical reasons. Health authorities and IRBs/IECs will be informed about the discontinuation of the study in accordance with applicable regulations.

3.3 Dosage, Administration and Schedule

There is no investigational product or a treatment in this trial. Decision about any treatment will be made according to the local practice and at the discretion of investigator.

3.4 Randomisation and Unblinding

All subjects in SB3-G31-BC-E were unblinded after data base lock for SB3-G31-BC trial.

3.5 Schedule of Study

Recommended Schedule of Activities for the Cardiac and Survival Cohort

Assessments	**Follow-up**							
Visit	**ICF**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Month	**-**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
Informed consent[1]	✓							
Physical exam[2]		✓	✓	✓	✓	✓	✓	✓
Mammography			✓		✓	✓	✓	✓
LVEF (ECHO or MUGA scan)[3]		✓	✓	✓	✓	✓	✓	✓
Cardiac events[4, 6]	Continuously							
Breast cancer recurrence/progression[6]	Continuously							
Survival[5, 6]	Continuously							

ECHO = echocardiogram; ICF = informed consent form; MUGA = multiple gated acquisition; LVEF = left ventricular ejection fraction

1. The acceptable time lag from EOS of SB3-G31-BC to obtain the informed consent is one year.
2. Physical exam includes clinical breast exam.
3. LVEF will be measured by 2D echocardiography or MUGA scan. The same method should be used for each subject during SB3-G31-BC & this study.
4. Cardiac events will be recorded in case of SB3 or Herceptin® related cardiac toxicities during follow-up.
5. Survival can be followed up by telephone contacts.
6. For the investigation of cardiac events, breast cancer recurrence/progression, and survival, at least scheduled visits and activities are recommended.

Recommended Schedule of Activities for the Survival Only Cohort

Assessments	Follow-up							
Visit[2]	ICF	1	2	3	4	5	6	7
Study Month from Last IP Administration	-	6	12	18	24	36	48	60
Informed consent[1]	✓							
Physical exam*, [2, 3]		✓	✓	✓	✓	✓	✓	✓
Mammography*, [2]			✓		✓	✓	✓	✓
LVEF (ECHO or MUGA scan) *, [2, 4]		✓	✓	✓	✓	✓	✓	✓
Cardiac events*, [2, 5, 6]	Continuously							
Breast cancer recurrence/progression[6, 7]	Continuously							
Survival[6, 7, 8]	Continuously							

ECHO = echocardiogram; ICF = informed consent form; IP = investigational product; MUGA = multiple gated acquisition; LVEF = left ventricular ejection fraction
Note: All subjects in Bosnia & Herzegovina and APAC countries including India are solely applicable for the Survival Only Cohort.
*: Physical exam, mammography, LVEF (ECHO or MUGA scan), and cardiac events are collected in India only.

1. Subjects will provide informed consent. If prospective data collection is not possible (e.g. when the subject is deceased or lost to follow-up), a waiver of informed consent/authorization will be requested for the retrospective data collection from medical records, where applicable and in accordance with national regulations and local ethics. If ICF waiver for the deceased subject is not allowed, their next-of-kin (if applicable) will be informed accordingly, and will be asked to give their consent where applicable and approved by institutional review board (IRB)/independent ethics committee (IEC) and in accordance with national regulations.
2. Cardiac and other safety assessment will be performed in subjects who provide informed consent for follow-up of cardiac safety and all data will be collected prospectively.
3. Physical exam includes clinical breast exam.
4. LVEF will be measured by 2D ECHO or MUGA scan. The same method should be used for each subject during the SB3-G31-BC trial and this study.
5. Cardiac events will be recorded in case of SB3 or Herceptin® related cardiac toxicities during follow-up.
6. For the investigation of cardiac events, breast cancer recurrence/progression and survival, at least scheduled visits, and activities are recommended.
7. Data will be collected prospectively from the date of the study informed consent signed and data before informed consent will be obtained from medical records retrospectively. If prospective data collection is not possible, data could be collected retrospectively from medical records.
8. Survival can be followed up by telephone contacts.

3.6 Determination of the Sample Size

No formal sample size calculation was done as there is no hypothesis to be tested. A total of 875 subjects received the study IP in the SB3-G31-BC trial. Incorporating 20% of refusal rate for consent to this observation study and 10 % of lost to follow-up, approximately 612 subjects are expected to be enrolled to this study.

4. ANALYSIS SETS

The following sets will be used for the analyses performed in the study. Subjects will be analysed according to the treatment received in SB3-G31-BC trial.

4.1 Long-term Follow-up set

Long-term follow-up set: This set consists of all subjects who provide informed consent for the long-term follow-up of cardiac safety and survival. This set includes Cardiac Safety and Survival Cohort defined in the Section 3.1.

4.2 Survival Follow-up set

Survival Follow-up Set: This set consists of all subjects who enrolled for this study. This set includes Cardiac Safety and Survival Cohort and Survival Only Cohort defined in Section 3.1.

5. DOCUMENTATION OF VARIABLES

5.1 Analysis Variables

5.1.1 Primary Objective Endpoint

The primary objective is to observe the incidence of symptomatic CHF and asymptomatic significant LVEF decrease in HER2 positive EBC or LABC subjects treated with SB3 or Herceptin® as neoadjuvant and adjuvant treatment.

(1) Symptomatic CHF

Symptomatic CHF is defined as the following criteria:

- An absolute decline of at least 10 % points from baseline LVEF and resulting LVEF less than 50% on the “LVEF (echo or MUGA scan)” page on the eCRF, and
- Selected as cardiac events of “Symptomatic CHF (NYHA class II, III, IV)” on the page of ‘Cardiac events’ in eCRF

Incidence rate will be calculated using following formula.

- Incidence rate of symptomatic CHF = $\frac{\text{Number of subjects with symptomatic CHF}}{\text{Number of subjects in the Long-term follow-up set}} \times 100$

(2) Asymptomatic significant LVEF decrease

Asymptomatic significant LVEF decrease is defined as the following criteria:

- An absolute decline of at least 10 % points from baseline LVEF and resulting LVEF less than 50% on the “LVEF (echo or MUGA scan)” page on the eCRF, and
- Not selected as cardiac events of “Symptomatic CHF (NYHA class II, III, IV)” on the ‘Cardiac events’ page on the eCRF.

Incidence rate will be calculated using following formula.

- Incidence rate of asymptomatic significant LVEF decrease = $\frac{\text{Number of subjects with asymptomatic significant LVEF decrease}}{\text{Number of subjects in the Long-term follow-up set}} \times 100$

5.1.2 Secondary Objective Endpoints

The secondary objectives are to observe the incidence of cardiac death and other significant cardiac conditions and to observe the long term efficacy of SB3 compared to Herceptin® by event-free survival, disease-free survival and overall survival.

(1) Cardiac Death

Cardiac death is defined as death definitely as a result of heart failure, myocardial infarction, or documented arrhythmia or as probable cardiac death within 24 hours of a cardiac event, which is “Cardiac death” of “Primary cause of death” item on the End of Follow-up page in eCRF. Incidence rate will be calculated using following formula.

- Incidence rate of cardiac death $= \frac{\text{Number of subjects with cardiac death}}{\text{Number of subjects in the Long-term follow-up set}} \times 100$

(2) Other Cardiac Event

Other cardiac event is defined as acute myocardial infarction, severe arrhythmia, ischemic heart disease, valvular dysfunction and other significant cardiac conditions. on the “Cardiac events” page in eCRF.

If cardiac events of significant LVEF decrease are recorded as “other significant cardiac conditions” to the “Cardiac events” of cardiac events page in eCRF, they will be excluded from the analysis.

Incidence rate will be calculated using following formula.

- Incidence rate of other cardiac event $= \frac{\text{Number of subjects with other cardiac event}}{\text{Number of subjects in the Long-term follow-up set}} \times 100$

(3) Event-Free Survival (EFS)

EFS is defined as the time from the date of randomisation for SB3-G31-BC trial to the date where an event occurs. An event is breast cancer recurrence or progression (local, regional, distant or contralateral) or death due to any cause. Breast cancer recurrence is identified as the record with “Yes” to the item “Was the breast cancer recurred?” on the “Breast Cancer recurrence” page or “Yes” to the item “Was the breast cancer recurrence/progression confirmed between the end of SB3-G31-BC trial and the informed consent for this SB3-G31-BC-E study?” on the “Retrospective data collection” in the eCRF.

Subjects who did not have recurrence or progression or who were alive at the time of analysis will be censored at the date of the last follow-up assessment (breast cancer recurrence, physical examination, or mammography assessment).

- EFS

- Status = 0, if recurrence or progression or died due to any cause

  = 1 (censored), if alive at the last follow-up assessment, and no recurrence or progression until the last follow-up assessment

Duration (months) = [date of recurrence confirmed, progression, death or the last follow-up assessment (censored), whichever occurs first – the date of randomisation for SB3-G31-BC + 1] / [365.24/12]

Refer to **Table 5.1** for detailed censoring and event date options and outcomes for EFS.

Table 5.1. Outcome and event/censored dates for EFS analysis

Situation	Date	Outcome
Progression occurred during SB3-G31-BC trial	Date of progression	Event (Progression)
Recurrence occurred during SB3-G31-BC trial	Date of recurrence	Event (Recurrence)
No breast cancer assessment after the end of SB3-G31-BC trial.	Date of the last evaluable clinical response in SB3-G31-BC trial	Censored
Subject had breast cancer assessment after the end of SB3-G31-BC trial and breast cancer not recurred.	Date of the most recent breast cancer assessment with normal result	Censored
Recurrence or progression occurred between the end of SB3-G31-BC trial and the informed consent for SB3-G31-BC-E trial.	Date of recurrence/ progression confirmed	Event (Recurrence/progression)
Recurrence occurred during the SB3-G31-BC-E trial and progression not occurred.	Date of recurrence	Event (Recurrence)
Subject early terminated by death and progression or recurrence were not occurred.	Date of death	Event (Death)

- Breast cancer assessment includes physical examination and mammography assessment with normal results
- For subjects without post-baseline clinical response assessment, randomisation date will be used as the censoring date.

(4) Disease-Free Survival (DFS)

DFS is defined as the time from the date of surgery for the SB3-G31-BC trial to the date where an event occurs. An event is breast cancer recurrence or death due to any cause. Breast cancer recurrence is identified as the record with “Yes” to the item “Was the breast cancer recurred?” on the “Breast Cancer recurrence” page or “Yes” to the item “Was the breast cancer recurrence/progression confirmed between the end of SB3-G31-BC trial and the informed consent for this SB3-G31-BC-E study?” on the “Retrospective data collection” in the eCRF.

Subjects who did not have recurrence or who were alive at the time of analysis will be censored at the date of the last follow-up assessment (breast cancer recurrence, physical examination, mammography assessment).

➢ DFS

- Status = 0, if recurrence or died due to any cause

  = 1 (censored), if alive at the last follow-up assessment, and no recurrence until the last follow-up assessment

Duration (months) = [date of recurrence confirmed, death or the last follow-up assessment (censored), whichever occurs first – the date of surgery for SB3-G31-BC + 1] / [365.24/12]

Refer to **Table 5.2** for detailed censoring and event date options and outcomes for DFS.

Table 5.2. Outcome and event/censored dates for DFS analysis

Situation	Date	Outcome
Recurrence occurred during SB3-G31-BC trial	Date of recurrence	Event (Recurrence)
No breast cancer assessment after the end of SB3-G31-BC trial.	Date of the last evaluable clinical response in SB3-G31-BC trial	Censored
Subject had breast cancer assessment after the end of SB3-G31-BC trial and breast cancer not recurred.	Date of the most recent breast cancer assessment with normal result	Censored
Breast cancer recurred after the end of SB3-G31-BC trial and progression not occurred.	Date of recurrence	Event (Recurrence)
Subject early terminated by death and progression or recurrence were not occurred.	Date of death	Event (Death)

- Breast cancer assessment includes physical examination and mammography assessment with normal results
- For subjects without post-baseline clinical response assessment, randomisation date will be used as the censoring date.

(5) Overall Survival (OS)

OS is defined as the time from the date of randomisation for SB3-G31-BC trial to the date of death which is identified as the record with a response of “Death” to the item "Main reason for early termination” on the End of Follow-up page of the eCRF, “Dead” to the time “Subject survival status” on the Survival page, or with a response of “Fatal” to the item “Outcome” on the Cardiac events page, regardless of the cause of death.

Subjects who were alive at the time of analysis will be censored at the date of the last follow-up visit (including the date of study completion if a subject completes the study) or the last phone contact successfully completed.

➢ OS

- Status = 0, if died from any cause

  = 1 (censored), if alive until the last follow-up

- Duration (months) = [date of death or the last follow-up visit (censored), whichever occurs first – the date of randomisation for SB3-G31-BC + 1] / [365.24/12]

6. SUBJECT DISPOSITION

The number of subjects who consent to participate in this follow-up study, completed or early terminated from the study will be summarised by treatment group for the Long-term Follow-up Set and Survival Follow-up Set. The reasons for early termination will be summarised and the listing will be provided. The number of subjects who died and the reason for death will be summarised and the listing will be provided. Also, the number of subjects included in the analysis set will be summarised and the listing of study disposition will be provided.

Subject disposition in the study will be presented in the following tables, figure and listing.

- *T. Subject Disposition by Treatment Group – Long-term Follow-up Set*
- *T. Subject Disposition by Treatment Group – Survival Follow-up Set*
- *T. Number (%) of Subjects in the Analysis Sets by Treatment Group – Survival Follow-up Set*
- *T. Summary of Safety Observation Duration – Long-term Follow-up Set*
- *T. Summary of Safety Observation Duration – Survival Follow-up Set*
- *F. Subject Disposition by Treatment Group – Long-term Follow-up Set*
- *F. Subject Disposition by Treatment Group – Survival Follow-up Set*
- *L. Subject Disposition*

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject demographics and baseline disease characteristics from SB3-G31-BC will be summarised by treatment group for the Long-term Follow-up Set and Survival Follow-up Set. Continuous variables will be summarised with descriptive statistics (n, mean, standard deviation, median, minimum, maximum). Categorical variables will be summarised with counts and percentage.

Demographics

- Continuous variables: Age(years), Height(cm), Weight(kg), Body Surface Area (BSA) (m^2), Body Mass Index (BMI) (kg/m^2), LVEF(%) at screening of SB3-G31-BC study

- Categorical variables: Age group(<20,<30,.. ,<60,≥60years) Gender(Male, Female), Race(White, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, Other), Ethnicity(Hispanic or Latino, Chinese, Indian (Indian subcontinent), Japanese, Mixed Ethnicity, Other), Region(Region 1 (Korea),Region 2 (Malaysia, Mexico, Philippines, Vietnam), Region 3 (Bosnia and Herzegovina, Ukraina), Region 4 (Bulgaria, Czech Republic, France, Romania), Region 5 (Poland), Region 6 (India), Region 7 (Russian Federation)), Child bearing potential(Yes, No), Menopausal status(Yes, No), ECOG performance status(0, 1, >1), ECG result(Normal, Abnormal NCS, Abnormal CS)

Baseline disease characteristics

- Categorical variables: Name of diagnosis(Invasive carcinoma of breast, Carcinoma in situ (non-invasive) of breast), Number of breast tumour lesions(One, More than one), Histopathological tumour classification(Invasive ductal carcinoma NOS, Invasive lobular carcinoma, Other), Clinical T stage(cT0, cTis, cT1, cT2, cT3, cT4), Clinical N stage(cN0, cN1, cN2, cN3), Clinical M stage(cM0, cM1), Clinical TNM staging(Stage 0,

Stage I, Stage IIA, Stage IIB, Stage IIIA, Stage IIIB, Stage IIIC, Stage IV), Breast cancer type(Operable, Locally advanced, Inflammatory), Hormone receptor status(ER+/PR+, ER+/PR-, ER-/PR+, ER-/PR-), Sentinel lymph node biopsy performed prior to treatment(Positive, Negative, Not determined)

Data will be summarised in the following tables.

- *T. Demographic Characteristics by Treatment Group – Long-term Follow-up Set*
- *T. Demographic Characteristics by Treatment Group – Survival Follow-up Set*
- *T. Baseline Disease Characteristics by Treatment Group – Long-term Follow-up Set*
- *T. Baseline Disease Characteristics by Treatment Group – Survival Follow-up Set*
- *L. Demographics Characteristics of SB3-G31-BC*
- *L. Disease Stage at Screening of SB3-G31-BC*

8. MEDICAL HISTORY

All collected continuing medical conditions and medical/surgical history data from SB3-G31-BC will be summarised by treatment group for the Long-term Follow-up Set and Survival Follow-up Set. Continuing medical condition was identified the items with 'Ongoing' status. They will be summarised according to the System Organ Class(SOC) and Preferred Term(PT) using Medical Dictionary for Regulatory Activities (MedDRA)version 16.1, and the number and percentage(%) of subjects will be presented for SOC and PT.

Data will be summarised in the following tables.

- *T. Medical and Surgical History by Primary System Organ Class, Preferred Terms and Treatment Group – Long-term Follow-up Set*
- *T. Medical and Surgical History by Primary System Organ Class, Preferred Terms and Treatment Group – Survival Follow-up Set*
- *T. Continuing Medical Conditions by Primary System Organ Class, Preferred Terms and Treatment Group – Long-term Follow-up Set*
- *T. Continuing Medical Conditions by Primary System Organ Class, Preferred Terms and Treatment Group – Survival Follow-up Set*
- *L. Medical History and Continuing Disease*
- *L. Surgical History*

9. EFFICACY EVALUATION

9.1 Event-Free Survival, Disease-Free Survival and Overall Survival

(1) Event-Free Survival

(2) Disease-Free Survival

(3) Overall Survival

For time to event data, survival analysis for EFS, DFS, and OS will be performed for the Long-term Follow-up Set and Survival Follow-up Set respectively. Kaplan-Meier curves will be

calculated and displayed by treatment group in the SB3-G31-BC trial. Median survival times and the corresponding 95% CI will also be provided. EFS, DFS, OS rates will be estimated using the Kaplan-Meier method and the corresponding 95% CI will be calculated. Additionally, the stratified Cox proportional hazard regression model will be applied to estimate Hazard ratio (SB3/Herceptin). The stratification factors are hormone receptor status and breast cancer type, and region. The hazard ratio will be presented along with its p-value and corresponding 95% CI.

For DFS analysis, only subjects who have had surgery after completion of 8 cycles in SB3-G31-BC trial will be included in the analysis.

The analysis results will be summarised in the following tables, figures and listing.

- *T. Analysis of Event-Free Survival – Long-term Follow-up Set*
- *T. Analysis of Event-Free Survival – Survival Follow-up Set*
- *T. Analysis of Disease-Free Survival – Long-term Follow-up Set*
- *T. Analysis of Disease-Free Survival – Survival Follow-up Set*
- *T. Analysis of Overall Survival – Long-term Follow-up Set*
- *T. Analysis of Overall Survival – Survival Follow-up Set*
- *F. Analysis of Event-Free Survival – Long-term Follow-up Set*
- *F. Analysis of Event-Free Survival – Survival Follow-up Set*
- *F. Analysis of Disease-Free Survival – Long-term Follow-up Set*
- *F. Analysis of Disease-Free Survival – Survival Follow-up Set*
- *F. Analysis of Overall Survival – Long-term Follow-up Set*
- *F. Analysis of Overall Survival – Survival Follow-up Set*
- *L. Subjects with Breast Cancer Recurrence*
- *L. Time to Event Parameters by Subjects*

10. SAFETY EVALUATION

10.1 Symptomatic CHF and Asymptomatic significant LVEF decrease

(1) Symptomatic CHF

(2) Asymptomatic significant LVEF decrease

The incidence of symptomatic CHF and asymptomatic significant LVEF decrease will be summarised by treatment group for the Long-term follow-up Set. The number and percentage of subjects and the number of events (for symptomatic CHF) will be presented.

As the upper level of those two cardiac events, incidence of significant LVEF decrease, which is defined as an absolute decline of at least 10 % points from baseline LVEF and resulting LVEF less than 50% on the “LVEF (echo or MUGA scan)” page on the eCRF, will also be summarised by treatment group.

The analysis results will be summarised in the following tables.

- *T. Incidence of Symptomatic Congestive Heart Failure (CHF) and Asymptomatic Significant Left Ventricular Ejection Fraction (LVEF) Decrease – Long-term Follow-up Set*

10.2 Cardiac Death and Other Cardiac Event

(1) Cardiac Death

(2) Other Cardiac Event

The incidence of cardiac death and other cardiac events will be analysed similarly with primary objective analyses. The number and percentage of subjects and the number of events (for other cardiac event) will be presented. Acute myocardial infarction, severe arrhythmia, ischemic heart disease, valvular dysfunction and other significant cardiac conditions will be summarised as number of subjects.

The analysis results will be summarised in the following tables and listing.

- *T. Incidence of Cardiac Death – Long-term Follow-up Set*
- *T. Incidence of Other Cardiac Event – Long-term Follow-up Set*
- *L. Subjects with Cardiac Events*

10.3 Other Safety Measures

10.3.1 Left Ventricular Ejection Fraction

For LVEF, descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) will be presented by each visit as well as for change from baseline (LVEF at screening of SB3-G31-BC).

Moreover, the worst value during overall study period where 'worst' indicates the lowest value during overall study period, including SB3-G31-BC and SB3-G31-BC-E, will be summarised by treatment group. The worst value of LVEF will be categorised in '≥ 50', '≥ 45 and < 50', '< 45'. The '≥ 45 and < 50' will be broken down into 'Decrease of < 10 points from baseline' and 'Decrease of ≥ 10 points from baseline'.

The LVEF will be summarised in the following table and listed.

- *T. Summary of Left Ventricular Ejection Fraction (LVEF) (%) by Visit and Treatment– Long-term Follow-up Set*
- *T. Summary of Worst Value for Left Ventricular Ejection Fraction (LVEF) (%) during Overall Study Period from Screening of SB3-G31-BC by Treatment Group – Long-term Follow-up Set*
- *T. Incidence of Significant Change in Worst Value of LVEF during Overall Study Period from Screening of SB3-G31-BC – Long-term Follow-up Set*
- *L. Echocardiogram/MUGA Scan (LVEF)*

10.3.2 Others

The following safety measures will be provided:

Physical examination (Listing only)

Mammography (Listing only)

- *L. Physical examination*
- *L. Mammography*

11. ADDITIONAL EVALUATION

11.1 Subgroup Analysis

No subgroup analysis is planned in this study.

12. GENERAL PRESENTATION OF SUMMARIES AND ANALYSES

12.1 Significance Level

Statistical test will be conducted at a two-sided 5% significance level, if necessary.

12.2 Summary Statistics

Continuous data will be summarised with descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) and categorical data will be presented with frequency (N) and percentage (%).

12.3 Decimals

Mean, standard deviation, median, minimum, maximum for descriptive statistics of continuous data, and percentage for categorical data, will be presented down to 2 decimal places.

12.4 Statistical Analysis Methods

Not applicable

12.5 Relative Study Day

Study Day in days will be calculated from Day 1 of Cycle 1 date in SB3-G31-BC study and it will be used to show start/stop day of assessments or event.

- If the date of the event is on or after the Day 1 of Cycle 1 date in SB3-G31-BC study, day = event date – first study drug date + 1.

- If the date of the event is prior to the Day 1 of Cycle 1 date in SB3-G31-BC study, day = event date – first study drug date.

If the event date was partially missing, the date will appear partial or missing in the listings and study day will be calculated after partial date imputation as described in section 13.3 Handling of Incomplete Date.

12.6 Baseline

For analysis of LVEF, the last measurement prior to the time of the first IP administration of SB3-G31-BC will be used as baseline.

12.7 Study Period and Visit Window Definitions

Unless specifically mentioned, each endpoint by time point will be summarised for regular visits.

Visit Name	Actual Point	Visit Label
Screening of SB3-G31-BC	Date of Screening for SB3-G31-BC	Screening of SB3-G31-BC (BL)
ICF Visit	Date of Informed Consent for SB3-G31-BC-E	
Visit 1	6 months	Visit 1 (6 months)
Visit 2	12 months	Visit 2 (12 months)
Visit 3	18 months	Visit 3 (18 months)
Visit 4	24 months	Visit 4 (24 months)
Visit 5	36 months	Visit 5 (36 months)
Visit 6	48 months	Visit 6 (48 months)
Visit 7	60 months	Visit 7 (60 months)

12.8 Software for Statistical Analysis

SAS® Version 9.4 or higher, SAS institute, Cary, NC, USA

13. DATA HANDLING COVENTIONS

13.1 Handling of Missing Data

For all endpoints, observed data will be used for analysis without imputation of missing values, and data that was censored without occurrence of the event will be handled as censoring.

13.2 Repeated or Unscheduled Assessments

Generally, data recorded at the nominal visit will be presented for by-visit summary. Repeated or unscheduled assessment will not be included in the by-visit summaries.

Repeated or unscheduled assessment will be included when defining the asymptomatic significant LVEF decrease and the worst value of LVEF.

Listings will include scheduled, unscheduled, repeated and early termination data in chronological order along with scheduled visits.

13.3 Handling of Incomplete Date

For survival analysis, if the date of death is partially missing, such as day or month, date comparison will be made by imputing the missing date. If the day of the date is unknown (i.e., date is “YYYY/MM/UK”), it will be imputed as ‘01’.If the month of the date is unknown (i.e., date is “YYYY/UK/UK”), it will be imputed as ‘01/01’. If the date of death is completely missing, it will be imputed as the last date to confirmed survival.

For cardiac events, if start date of an event is partially missing, such as day or month, date comparison will be made by imputing the missing date. If the day of the start date is unknown (i.e., date is “YYYY/MM/UK”), it will be imputed as ‘01’.If the month of the start date is unknown (i.e., date is “YYYY/UK/UK”), it will be imputed as ‘01/01’. If start date of an event is completely missing, it will be censored at the date of the last follow-up visit. If stop date is partially missing,

it will be imputed as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown).

For recurrence date, if the date is partially missing, such as day or month, date comparison will be made by imputing the missing date. If the day of the date is unknown (i.e., date is "YYYY/MM/UK"), it will be imputed as '01'.If the month of the date is unknown (i.e., date is "YYYY/UK/UK"), it will be imputed as '01/01'. If the recurrence date is completely missing, it will be the last follow-up date prior to the date of visit confirmed the recurrence.

For the date of end of participation, if the subject was early terminated due to death, the date of end of participation will be the date of death which is completed imputation.

13.4 Character Values of Clinical Laboratory Evaluation

No clinical laboratory evaluation is planned in this study.

14. INTERIM ANALYSIS

Analyses will be conducted once a year from 2017 to 2021. However, the frequency of the analyses can be adjusted by the sponsor's decision.

15. CHANGE FROM PROTOCOL

Unlike the analysis plan of the protocol section 7.2.2, the exploratory analyses will not be conducted.

16. SAS PROCEDURE FOR TESTING

16.1 Test of Survival Time

Cox Proportional Hazard Regression Model

```
PROC PHREG DATA=dataset;
   CLASS treatment hormone_receptor_status breast_cancer_type region/REF=first;
   MODEL Time*event(1)= treatment / TIES=EFRON ALPHA=0.05 RL;
   STRATA hormone_receptor_status breast_cancer_type region;
RUN;
```

Kaplan-Meier Estimation for Median Survival or Survival Rate at Certain Timepoints

```
PROC LIFETEST DATA=dataset conftype=linear METHOD=KM PLOTS = SURVIVAL
ALPHA=0.05;
   TIME Time*event(1);
   STRATA treatment;
RUN;
```

17. REFERENCES

Not applicable

Appendix. Mock-up TFL