# Samfenet

Ministry of Food and Drug Safety

**APPROVED**

| PART A - ADMINISTRATIVE INFORMATION | | |
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| **Entered by:** | **Biosimilar Product Information** | |
| MAH | **Name of the biosimilar medicinal product** | Samfenet |
| MAH | **MAH** | Samsung Bioepis Co. Ltd.,<br>Yeonsu-gu Cheomdan-daero 107<br>Incheon, Republic of Korea |
| NRA | **Authorisation / Licence number** | Samsung Bioepis Co. Ltd.,/4 |
| MAH / NRA | **API manufacturing facilities and batch release site for the finished product** (if applicable) | N/A<br>Confidential – Not Released |
| MAH | **Name of the active substance** | Trastuzumab (INN) |
| MAH | **Pharmaco-therapeutic group** | ATC code: L01XC03 |
| MAH | **Substance category** | Monoclonal antibody |
| MAH | **Pharmaceutical form** | Powder for concentrate for solution for infusion<br>White to pale yellow lyophilized powder |
| MAH | **Quantitative composition** | 150 mg/vial |
| MAH | **Route of administration** | Intravenous infusion |
| MAH | **Packaging/material** | Glass vial |
| MAH | **Package size(s)** | 1 vial/pack |
| MAH | **Local legal basis** | Pharmaceutical Affairs Act article 42 and Enforcement for the drug safety article 4 |
| MAH | **Local biosimilar guidelines** | Guidelines on the Evaluation of Biosimilar Product (MFDS, 2014) |
| MAH | **Date of authorisation/licensing of biosimilar** | 8 November 2017 |
| | **Reference Biotherapeutic Product (RBP) Information** | |
| MAH | **Name of the RBP** | Herceptin |
| MAH | **Authorised indications for RBP** | Metastatic breast cancer |

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| | | Early breast cancer<br>Metastatic gastric cancer |
| MAH | **Pharmaceutical form** | Powder for concentrate for solution for infusion<br>White to pale yellow lyophilized powder |
| MAH | **Quantitative composition** | 150 mg/vial |
| MAH | **Route of administration** | Intravenous infusion |
| MAH | **Packaging/material** | Glass vial |
| MAH | **Package size(s)** | 1 vial/pack |
| MAH | **Authorisation (Licence) number (of RBP)** | Roche Korea/76 |
| MAH | **Date of authorisation (of RBP)** | 19 July 2005 |
| MAH | **Authorisation (Licence) Holder (of RBP)** | Roche Korea |
| MAH | **Source of RBP (or other comparator) for comparability exercise** | Republic of Korea<br>European Union<br>United States |
| MAH / NRA | **Availability of the RBP assessment report (Korean)/link** | https://www.nifds.go.kr/brd/m_88/list.do?itm_seq_1=&srchTp=0&srchWord=%ED%97%88%EC%85%89%ED%8B%B4#none |
| | **Summary of outcomes** | |
| MAH | **Comparability exercise to demonstrate similarity to RBP** | Physicochemical and biological characterization study<br>Comparative *in vitro* and *in vivo* non-clinical studies (PK/PD study)<br>Comparative clinical studies(PK, efficacy, safety and immunogenicity) |
| NRA | **Availability of full assessment report (Korean)/link** | https://www.nifds.go.kr/brd/m_88/list.do?itm_seq_1=&srchTp=0&srchWord=%EC%82%BC%ED%8E%98%EB%84%B7#none |
| MAH | **Indications applied for** (if different to RBP) | Metastatic breast cancer<br>Early breast cancer<br>Metastatic gastric cancer) |
| NRA | **Authorised indications for biosimilar** | Metastatic breast cancer<br>Early breast cancer<br>Metastatic gastric cancer |

MAH (Marketing Authorisation Holder) or Sponsor
NRA (National Regulatory Authority) i.e. CA (Competent Authority)

| PART B - SUBMITTED DATA AND REVIEWER SUMMARY | |
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| **Procedure: Initial Application** | |
| MAH | **Quality data. Composition of the biosimilar product(s)** |
| | Trastuzumab 150 mg<br>L-Histidine Hydrochloride monohydrate<br>L-Histidine<br>Trehalose dehydrate<br>Polysorbate 20 |
| MAH | **Quality data. State-of-the-art methods** |
| | **Structural Characteristics**<br>- Primary Structure: Molecular weight, amino acid sequencing, N-terminal sequencing, C-terminal sequencing, peptide mapping, disulfide bond location determination, free sulfhydryl group quantification, met oxidation, deamidation<br>- High order structure<br><br>**Physicochemical Tests**<br>- Purity and impurity profiles, charge variants, N-glycan profile, protein content<br><br>**Biological activities**<br>- *In vitro* bioactivity: Anti-proliferation assay, ADCC<br>- Binding activity: HER2, FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, FcRn, C1q<br>- Additional biological assay: Surface HER2 expression level, HER2 ECD shedding, inhibition of AKT phosphorylation, *in vitro* angiogenesis assay, combination treatment with chemotherapy, CDC assay |
| NRA | **Quality data assessment outcome** |
| | Comprehensive head-to-head characterization studies performed using state-of-the-art orthogonal analytical tests demonstrated that all major quality attributes of Samfenet with respect to the primary and higher order structures, glycan profile, purity and impurities, charges variants, quantity, biological properties, immunochemical properties were comparable to those of Herceptin. The similarity range was defined using the sufficient batches of EU Herceptin, and the bridging data demonstrated the equivalence of EU Herceptin, US Herceptin and KR Herceptin.<br>Due to the complex heterogeneity in the structure of Herceptin, slight differences were found in deamidation, N-glycan profile, non-glycosylated heavy chain (NGHC), charge variant compared to Herceptin; lower levels of deamidation at Asn30 in light chain, higher levels of mannose glycan, NGHC, and acidic variants. However, those differences were not considered clinically meaningful since those had no impact on the biological activities related to the primary mechanism of action including binding affinity to HER2. In addition, although the differences were observed in antibody-dependent cell-mediated cytotoxicity (ADCC) compared to EU Herceptin batches manufactured lately, Samfenet demonstrates similarity to sufficient numbers of reference products batches.<br>Overall, based on the totality of evidence with respect to all quality characteristics and global clinical studies, the biosimilarity of Samfenet to Herceptin was concluded. |

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| MAH | **Mechanism of action** |
| | Samfenet (trastuzumab) is a humanized monoclonal antibody that binds with high affinity and specificity to the extracellular domain of HER2. |
| MAH | **Nonclinical data. *In vitro* studies** |
| | Non-clinical studies conducted during the development of Samfenet include anti-proliferation effect on HER2 overexpressing tumor cells, ADCC/CDC activity, HER2 binding activity, FcγRI binding assay, FcγRIIa binding assay, FcγRIIb binding assay, FcγRIIIa binding assay, FcγRIIIb binding assay, FcRn binding assay, C1q binding assay, surface HER2 expression level measurement, HER2 ECD shedding, inhibition of AKT phosphorylation, *in vitro* angiogenesis assay, combination treatment with chemotherapy. |
| MAH | **Nonclinical data. *In vivo* studies** |
| | ***In vivo* pharmacological study**<br>Anti-tumor activity of Samfenet, EU Herceptin, and US Herceptin on tumor growth inhibition in human breast cancer cell xenograft growth in mice at dose levels of 1, 5, and 15 mg/kg weekly for 4 weeks.<br><br>**Pharmacokinetics/Toxicokinetics**<br>PK/TK similarity assessments between Samfenet and EU Herceptin and US Herceptin in female cynomolgus monkeys following a 4-week repeat dose intravenous administration at a dose level of 25 mg/kg/day once a week.<br><br>**Toxicity study (including TK)**<br>4-week repeat dose toxicity study of Samfenet, EU Herceptin and US Herceptin by intravenous in cynomolgus monkeys at a dose level of 25 mg/kg/day once a week (conducted in accordance with GLP). |
| NRA | **Nonclinical data assessment outcome** |
| | 1. *In vitro* studies<br>See Quality assessment data outcome.<br><br>2. *In vivo* studies<br>*In vivo* pharmacological study (inhibition of tumor xenograft growth in mice) showed similar pharmacodynamic properties between Samfenet and EU or US Herceptin treated groups.<br><br>A repeat-dose toxicity study in cynomolgus monkeys showed similar PK ($C_{max}$, $T_{max}$ and $AUC_{0-t}$) and TK profiles between Samfenet and EU or US Herceptin treated groups.<br><br>In the repeat-dose toxicity study, Samfenet, EU Herceptin and US Herceptin were well tolerated with no physiology-related effects. There was no difference detected in immunogenicity profiles between Samfenet and EU or US Herceptin treated groups. |
| | **CLINICAL STUDIES** |

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| | **- include relevant study data from the following (not all may be required) which have been included to demonstrate biosimilarity.**<br>• **Pharmacokinetic, PK**<br>• **Pharmacodynamic, PD**<br>• **Efficacy,**<br>• **Safety,**<br>• **Immunogenicity.** |
| MAH | **Clinical data. PK studies** |
| | • Summary of design: A randomized, double-blind, three-arm, parallel group, single-dose, Phase I study to compare PK in healthy male subjects<br>(Randomized subjects (N=109): 36 healthy male subjects each in Samfenet and US Herceptin treatment group and 37 healthy male subjects in EU Herceptin treatment group)<br>• Objective and primary endpoint: Demonstration of equivalence PK in terms of area under the concentration-time curve (AUC) from time zero to infinity ($AUC_{inf}$), $AUC_{last}$, $C_{max}$ between Samfenet and Herceptin in healthy male volunteers after the single dose injection.<br>• Dose used: 6 mg/kg of Samfenet or Herceptin (EU sourced and US sourced)<br>• Length of the study: Maximum of 8 weeks |
| NRA | **Clinical data. PK data assessment outcome** |
| | The primary PK results: The 90% CIs of the geometric LSMean ratios of Samfenet to EU/US Herceptin for the PK parameters ($AUC_{inf}$, $AUC_{last}$ and $C_{max}$) were comparable between the Samfenet and EU/US Herceptin treatment groups.<br>Samfenet and EU Herceptin showed comparability between the two products as the 90% CIs of the geometric mean ratios for $AUC_{inf}$, $AUC_{last}$ and $C_{max}$ were 0.969, 0.971 and 1.001, respectively, and these were all within the acceptance range of 80-125%.<br>Samfanet and US Herceptin showed comparability between the two products as the 90% CIs of geometric mean ratios for $AUC_{inf}$, $AUC_{last}$ and $C_{max}$ were 0.930, 0.934, 0.988, respectively, and these were all within the acceptance range of 80-125%. |
| MAH | **Clinical data. PD studies** |
| | No specific PD study was conducted. |
| NRA | **Clinical data. PD data assessment outcome** |
| | Not applicable |
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| MAH | **Clinical data. Efficacy studies** |
| | **Study Number: SB3-G31-BC**<br>• Summary of design: A randomized double-blind, parallel group, multicenter Phase III study to compare the efficacy, safety, PK and immunogenicity between Samfenet and EU Herceptin in women with HER2-positive early breast cancer (EBC) or locally advanced breast cancer (LABC). Eligible patients were randomized in a 1:1 ratio to receive either Samfenet or EU Herceptin in a neoadjuvant setting for 8 cycles concurrently with 8 cycles of chemotherapy (4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/cyclophosphamide). These patients then underwent surgery. After |

surgery, the patients received additional 10 cycles of adjuvant Samfenet or Herceptin as per randomization to complete 1 year of treatment.

(Randomized patients (N=875): 437 patients in Samfenet treatment group and 438 patients in EU Herceptin treatment group)

- Objective and primary endpoint: Demonstration of comparable clinical efficacy between Samfenet and EU Herceptin in terms of pathological complete response (pCR) rate of the primary breast tumor (bpCR) in women with HER2 positive EBC or LABC in neoadjuvant setting
- Secondary objective: Evaluation of comparable efficacy between Samfenet and EU Herceptin in terms of total pathological complete response (tpCR) rate, overall response rate (ORR), event-free survival (EFS), and overall survival (OS).
- Dose used: 8 mg/kg (loading dose), then 6 mg/kg (maintenance dose) every 3 weeks
- Cycle: a total of 18 cycles (8 cycles of neoadjuvant therapy and 10 cycles of adjuvant therapy)

NRA

**Clinical data. Efficacy data assessment outcome**

The difference in bpCR rate was analyzed for the primary analysis. Equivalence was declared when the 95% CI of the difference in the bpCR rate between treatments was entirely contained within the equivalence margin of [−13%, 13%]. The 95% CIs for the difference was estimated in the Per-protocol Set (PPS). In addition, two-sided 95% CI for the ratio was estimated for the PPS and full analysis set (FAS) as supportive analyses.

In the PPS, the bpCR rate was 51.7% (208/402) in the Samfenet treatment group and 42.0% (167/398) in the EU Herceptin treatment group. The adjusted difference in bpCR rate (Samfenet/EU Herceptin) was 10.70% and the 95% CI of the difference was [4.13%, 17.26%], which was not contained within the pre-defined equivalence margin [-13%, 13%].

| Analysis set | Treatment (N) | bpCR rate | Adjusted Difference | 95% CI |
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| **PPS** | Samfenet (N=402) | 51.7% | 10.70% | [4.13%, 17.26%] |
| | Herceptin (N=398) | 42.0% | | |
| **FAS** | Samfenet (N=437) | 51.1% | 9.86% | [3.41%, 16.31%] |
| | Herceptin (N=438) | 41.9% | | |

After the similarity assessments, additional Herceptin lots were analysed by the Applicant for the monitoring purpose. During the analysis, it was noted that an apparent shift was found in ADCC activity for many of the more recent batches of EU Herceptin. The apparent shift in ADCC activity in the batches of EU Herceptin might have contributed to the observed differences in the efficacy between the Samfenet and EU Herceptin treatment groups. An alternative statistical analysis excluding the patients who received ADCC-shifted EU Herceptin lots was performed. The result showed that the difference in bpCR response rate between Samfenet and EU Herceptin was within the margin.

Thus, the difference in the bpCR rate that were possibly associated with the shifts in ADCC

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| | activity of the EU Herceptin was viewed as not being clinically significant considering its small magnitude and the fact that the small incremental change in bpCR is unlikely to impact the clinically relevant endpoints such as EFS and OS. The difference in bpCR rate did not lead to any clinically meaningful difference, and therapeutic equivalence between Samfenet and Herceptin was demonstrated in terms of efficacy. | |
| MAH | **Clinical data. Safety/ Immunogenicity studies** (specify population, dose used, length of the study and comparability margins) | |
| | Safety and immunogenicity data were collected from all clinical studies: SB3-G11-NHV and SB3-G31-BC. | |
| NRA | **Clinical data. Safety/ Immunogenicity data assessment outcome** | |
| | 1. Safety<br>The overall safety profiles were similar between Samfenet and Herceptin treatment groups.<br><br>2. Immunogenicity<br>The overall immunogenicity profiles were similar between the Samfenet and Herceptin treatment groups. | |
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| MAH | **Interchangeability data** | |
| | < No additional data were provided > | |
| MAH | **Additional information about the comparability exercise** | Not applicable |
| MAH | **Post-authorization measures** | |
| | Re-examination study in Korea<br>- Period: 8 November 2017~ 7 November 2021 | |
| NRA | **Post-authorization risk measures: assessment outcome.** | |
| | Post-marketing surveillance study (re-examination study) plan was considered to be acceptable. Number of subjects of Samfenet for re-examination study met the MFDS criteria (over 400). | |
| MAH | **Availability of additional relevant information in the local language/ link** | Not applicable |

| **PART C - REVIEWER CONCLUSIONS** | |
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| NRA | **Conclusions on biosimilarity, approval** |

The data provided by the Applicant were in line with the local legislation, guidelines and international guidelines.

Quality

The biosimilar manufacturer has developed and validated a process capable of consistently manufacturing a product of appropriate quality, with satisfactory control of impurities. Manufacturing operations are carried out according to cGMP requirements.

The quality attributes of high relevance for clinical safety and efficacy, e.g. physicochemical characteristics and biological activities of Samfenet were comparable to those of the reference biotherapeutic product Herceptin.

Nonclinical
No major differences in nonclinical data were observed for Samfenet compared to the reference

biotherapeutic product Herceptin.

Clinical Studies

The Phase I and Phase III studies conducted in in healthy volunteers and EBC or LABC patients provided robust evidences to show that there are no clinically meaningful differences between Samfenet and the reference biotherapeutic product Herceptin.

Safety: Adverse drug reactions (ADRs) observed with Samfenet were in the same range as the ADRs observed with the reference biotherapeutic product Herceptin.

Immunogenicity: The proportion of the patients who developed anti-drug antibodies (ADA) with Samfenet was generally similar to the proportion of the patients who developed ADA with the reference biotherapeutic product Herceptin.

Extrapolation of indications: Based on the totality of evidence, all indications requested for Samfenet (see Section A, summary of outcomes) were considered to be approvable.

Risk Management
The risk management plan was considered acceptable.

Overall Conclusion
Satisfactory assurance of biosimilarity was demonstrated using an appropriate comparability exercise. The biosimilar product Samfenet was considered approvable.