Onbevzi

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Onbevzi
MAH	**MAH**	Samsung Bioepis Co. Ltd., 76, Songdogyoyuk-ro, Yeonsu-gu Incheon, Republic of Korea
NRA	**Authorisation / Licence number**	Samsung Bioepis Co. Ltd., / 8
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Not Released
MAH	**Name of the active substance**	Bevacizumab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: L01XC07
MAH	**Substance category**	Monoclonal antibodies
MAH	**Pharmaceutical form**	Clear to slightly opalescent, colorless to pale brown solution
MAH	**Quantitative composition**	100 mg/vial 400 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 drug safety article 4
MAH	**Local biosimilar guidelines**	Guidelines on the Evaluation of Biosimilar Products (MFDS 2014)
MAH	**Date of authorisation/licensing**	11 March 2021

	of biosimilar	
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Avastin
MAH	**Authorised indications for RBP**	Metastatic colorectal cancer (mCRC) Metastatic breast cancer Non-small cell lung cancer (NSCLC) Advanced and/or metastatic renal cell cancer (mRCC) Glioblastoma Epithelial ovarian, fallopian tube, or primary peritoneal cancer Cervical cancer
MAH	**Pharmaceutical form**	Clear to slighthly opalescent, colorless to pale brown solution
MAH	**Quantitative composition**	100mg / vial 400mg / 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 / 92
MAH	**Date of authorisation (of RBP)**	12 September 2007
MAH	**Authorisation (Licence) Holder (of RBP)**	Roche Korea Co., Ltd.
MAH	**Source of RBP (or other comparator) for comparability exercise**	Republic of Korea European Union United States
MAH / NRA	**Availability of the RBP assessment report** (language)/**link**	https://nedrug.mfds.go.kr/pbp/CCBAC02/getItem?totalPages=2&limit=10&page=2&title=%EC%95%84%EB%B0%94%EC%8A%A4%ED%8B%B4&jdgmnResultInfoSeq=6370
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including data form : physicochemical, biological characterization, *in vitro*, *in vivo non-clinical studies*, PK, efficacy, safety and immunogenicity studies

NRA	**Availability of full assessment report** (language)/**link**	https://nedrug.mfds.go.kr/pbp/CCBAC02/getItem?totalPages=351&limit=10&searchYn=true&page=1&title=%EC%98%A8%EB%B2%A0%EB%B8%8C&jdgmnResultInfoSeq=20210000077
MAH	**Indications applied for** (if different to RBP)	The indications applied for were all authorized for RBP (see section Authorised indications for RBP).
NRA	**Authorised indications for biosimilar**	Metastatic colorectal cancer (mCRC) Metastatic breast cancer Non-small cell lung cancer (NSCLC) Advanced and/or metastatic renal cell cancer (mRCC) Glioblastoma Epithelial ovarian, fallopian tube, or primary peritoneal cancer Cervical cancer

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

PART B - SUBMITTED DATA AND REVIEWER SUMMARY	
Procedure: <Initial Application>	
MAH	**Quality data. Composition of the biosimilar product(s)**
	Bevacizumab 100 mg, Bevacizumab 400 mg Trehalose dihydrate Sodium acetate trihydrate Acetic acid Polysorbate 20 Water for injection
MAH	**Quality data. State-of-the-art methods**
	Structural Chracteristics - Primary structure : Molecular weight, Amino acid sequence, N-terminal sequence analysis, C-terminal sequence analysis, Peptide mapping, Met oxidation, Deamidation, Glycation, Disulfide bond analysis, Free sulfhydryl group quantification - High order structure analysis **Physicochemical Test** - Purity and Impurities, Charge variants, Hydrophobic variants, N-glycan profile, Protein concentration **Biological properties** - HUVEC anti-proliferation assay, VEGF neutralization assay, VEGFR phosphorylation

	inhibition assay, HUVEC anti-migration assay, HUVEC anti-survival assay, ADCC assay, CDC assay **Immunochemial properties** - VEGF-A(165, 121, 189) binidng assay, FcRn binding assay, VEGF-A specificity, Fc gamma Receptor(FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb) binding assay, C1q binding assay
NRA	**Quality data assessment outcome**
	Comprehensive head-to-head comparability studies performed using state-of-the art analytical procedures demonstrated that all major quality attributes of Onbevzi were comparable to those of Avastin with respect to physiochemical, biological and immunochemical properties. The similarity range was determined using the sufficient characterization data from EU Avastin, and the bridging data demonstrated the equivalence of EU Avatin, US Avastin and KR Avastin. There were slight differences in N-/C-terminal sequences, charge and hydrophobic variants, glycan profiles. The diffrences were appropriately justified to have no impact on the biological activity of Onbevzi. · Additional N- and C-terminal sequence variants were found in Onbevzi. However, the relative content of these variants was too low and it did not anticipate to have an impact on biological activites and safety. · Differences were observed for charge profiles by CEX-HPLC and hydrophobic profiles by HI-HPLC. However, those difference were not considered clinically meaningful, since those have no impact on the biolotical activities, as demonstrated in Stucture-activity relationship(SAR) studies. · For the relative quantities of N-glycans, the differences were observed in the contents of afucose and high mannose glycans. Althogh the afucosylated glycan is related to Fc effector functions, Fc effector functions are not related to the biological activities of bevacizumab. Also, the relative contents of high mannose for Onbivzi were higher than referene product, there was no meaningful difference in PK profile in nonclinical and Phase I study. Therefore the difference observed in N-glycan profiles was not considered significant. Comparative forced degradation studies including heat stress, exposure to akaline/acidic condition, oxidation and photostress demonstrated similar degradation profiles for Onbevzi and Avastin. Overall, based on the totality of evidence with respect to all quality characteristics and global clinical studies, the biosimilarity of Onbevzi to Avastin was concluded.
MAH	**Mechanism of action**
	Onbevzi(Bevacizumab) is a recombinant humanized monoclonal antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) resulting in inhibition of endothelial cell proliferation, angiogenesis, and VEGF-induced vascular

	permeability in tumor vasculatures.
MAH	**Nonclinical data. *In vitro* studies**
	Potency assays : HUVEC anti-proliferation, VEGF neutralization, VEGFR phosphorylation inhibition, HUVEC anti-migration, ADCC, CDC Binding assays : VEGF-A (165, 121, 189) binding, VEGF-A specificity, FcRn binding, Fc gamma Receptor (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb) binding, C1q binding
MAH	**Nonclinical data. *In vivo* studies**
	***In vivo* pharmacological study** Anti-tumor efficacy studies in COLO 205 and NCI-H358 xenograft mice. **Pharmacokinetics** Multiple dose pharmacokinetics (PK)/toxicokinetics (TK) were evaluated as part of the 4-week repeat-dose toxicity study in cynomolgus monkeys **Toxicity Study (including TK)** A 4-week repeat-dose toxicity study using cynomolgus monkeys
NRA	**Nonclinical data assessment outcome**
	1. *In vitro* studies All *in vitro* PD studies demonstrated the similarity between Onbevzi and Avastin. **2. *In vivo* studies** In vivo pharmacological studies showed similar pharmacodynamics properties between Onbevzi and Avastin treated group. Pharmacokinetic studies showed similar PK profiles between two groups. In a 4-week repeat-dose toxicity study using cynomolgus monkeys, all animals treated Onbevzi or US Avastin were well tolerated at a dose level of 50 mg/kg and there were no differences in toxicity profile between two groups.

	CLINICAL STUDIES **- include relevant study data from the following (not all may be required) which have been included to demonstrate biosimilarity.** • **Pharmacokinetic (PK)** • **Pharmacodynamic (PD)** • **Efficacy** • **Safety** • **Immunogenicity**
MAH	**Clinical data. PK studies**
	Study Number : SB8-G11-NHV • Summary of design : a randomized, double-blind, three-arm, parallel group, single-dose study in healthy male volunteers

	• Randomized subjects (N=114): 38 healthy male subjects in each group -SB8(Onbevzi), EU sourced Avastin, US sourced Avastin) • Objective and primary endpoints : Demonstration of equivalence PK in terms of AUC_{inf}, AUC_{last}, C_{max} between Onbevzi and Avastin in healthy male volunteers after single dose injection. • Dose used: 3 mg/kg • Length of the study : 16 weeks
NRA	**Clinical data. PK data assessment outcome**
	The primary PK results: The 90% Confidence Interval(CI) of the geometric least squares means(LSMeans) ratios of Onbevzi to EU/US Avastin for the PK parameters (AUC_{inf}, AUC_{last} and C_{max}) were comparable between the Onbevzi and EU/US Avastin treatment groups. Onbevzi and EU Avastin showed comparability between the two products as the 90% CIs of the geometric mean ratios for AUC_{inf}, AUC_{last} and C_{max} were 0.880, 0.886 and 0.996, respectively, and these were all within the acceptance range of 80-125%. Onbevzi and US Avastin showed comparability between the two products as the 90% CIs of geometric mean ratios for AUC_{inf}, AUC_{last} and C_{max} were 0.885, 0.891, 1.012, 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
MAH	**Clinical data. Efficacy studies**
	Study Number: SB8-G31-NSCLC • Summary of design: A randomized, double-blind, parallel group, multicenter Phase III study to compare the efficacy, safety, PK and immunogenicity between Onbevzi and EU Avastin in patients with metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC). Eligible patients were randomized in a 1:1 ratio to receive either Onbevzi or EU Avastin (15 mg/kg administered by IV infusion on Day 1 of every 3-week cycle) concurrently with PC chemotherapy (paclitaxel 200 mg/mg^2 and carboplatin AUC 6 by IV infusion on Day 1 of every 3-week cycle) for at least 4 cycles and up to 6 cycles of the induction treatment period. If subjects showed response to treatment, defined as Complete Response (CR)/Partial Response (PR)/stable disease after completion of the induction treatment period of combination chemotherapy with Onbevzi or Avastin, they received Onbevzi or Avastin maintenance therapy as per randomisation until documentation of disease progression(PD), unacceptable toxicity, death, or End of Study(EOS), whichever occurred first. (Randomized patients (N=763): 379 patients in Onbevzi treatment group and 384 patients in EU Avastin treatment group)

	• Objective and primary endpoint: Demonstration of comparable clinical efficacy between Onbevzi and EU Avastin in terms of best overall response rate(ORR) by 24 weeks of chemotherapy in patients with metastatic or recurrent non-squamous NSCLC. • Secondary objective: Evaluation of comparable efficacy between Onbevzi and EU Avastin in terms of Pregression-free survival (PFS), Overall Survival (OS), and Duration of Response(DOR). • Dose used: 15 mg/kg every 3 weeks
NRA	**Clinical data. Efficacy data assessment outcome**

The difference in best ORR was analyzed for the primary analysis. Equivalence was declared when two-sided 95% CI for the difference in best ORR between treatments was entirely contained within the equivalence margin of [-12.5%, 12.5%]. The 95% CIs of the difference in best ORR was estimated in the Per-protocol Set (PPS). In addition, the difference in best ORR was repeated in the Full Analysis Set (FAS) as supportive analyses. In the PPS, the proportion of patients with best ORR were 50.1%(169/337) in Onbevzi treatment group and 44.8% (147/328) in EU Avasin treatment group. The 95% CI of the difference was [-2.2%, 12.9%], which was not contained within the pre-defined equivalence margin [-12.5%, 12.5%]. As the supportive analysis, the difference in the best ORR in the FAS was 4.8%, and the 95% CI of the difference was [-2.3%, 11.9%], which was contained within the pre-defined equivalence margin of [-12.5%, 12.5%]

Analysis set	Treatment (N)	Best ORR N(%)	Adjusted Difference	95% CI
PPS	Onbevzi (N=337)	169 (50.1%)	5.3%	[-2.2%, 12.9%]
	Abastin (N=328)	147 (44.8%)		
FAS	Onbevzi (N=379)	181 (47.6%)	4.8%	[-2.3%, 11.9%]
	Avastin (N=383)	164 (42.8%)		

To explore the robustness of the primary efficacy results, the analysis for the ratio of best ORR was performed in the FAS and PPS. Equivalence was declared when the two-sided 90% CI for the ratio of best ORR between treatment is entirely contained within the equivalence marin of [0.737, 1.357]. The proportion of patients with the best ORR in the Onbevzi and Avastin treatment groups for FAS were 47.6% and 42.8%, respectively. The ratio of best ORR in the FAS was 1.11, and the 90% CI of the ratio was [0.975, 1.269], which was entirely contained within the pre-defined equivalence margin of [0.737, 1.357]. The ratio of best ORR in the PPS was 1.12, and the 90% CI of the ratio was [0.978, 1.280], which was contained within the pre-defined equivalence marin.

Analysis set	Treatment (N)	Best ORR N(%)	Adjusted Ratio	90% CI
FAS	Onbevzi (N=379)	181 (47.6%)	1.11	[0.975, 1.269]

	Avastin (N=383)	164 (42.8%)		
PPS	Onbevzi (N=337)	169 (50.1%)	1.12	[0.978, 1.280]
	Avastin (N=328)	147 (44.8%)		

Although the 95% CI for the difference in the best ORR in the PPS was slightly not within the equivalence margin, the 95% CI for the difference in the best ORR in the FAS and the 90% CI for the ratio in the best ORR in the PPS and FAS were entirely contained within the equivalence margin. In addition, further efficacy endpoints as PFS, OS and DOR between Onbevzi and Avastin treatment groups were similar. Moreover, from the ad-hoc analysis performed as the quantitative measure of tumor response, the means of the maximum percentage change from baseline in tumor burden during the induction treatment period were comparable between Onbevzi and EU Avastin treatment groups, indicating no difference in the treatment effect between the two treatment groups. Therefore, it was concluded that the observed difference was not clinically significant.

MAH

Clinical data. Safety/ Immunogenicity studies

Safety and immunogenicity data were collected from all clinical studies: SB8-G11-NHV and SB8-G31-NSCLC.

NRA

Clinical data. Safety/ Immunogenicity data assessment outcome

Safety.
The overall safety profiles were similar between Onbevzi and Avastin treatment groups.

Immunogenicity.
The overall immunogenicity profiles were similar between the Onbevzi and Avastin treatment groups.

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.
- Period: 2021.03.11. ~ 2025.03.10

NRA

Post-authorization risk measures: assessment outcome.

Post-marketing surveillance study (re-examination study) plan was considered to be acceptable. A sufficient number of subjects was planned for re-examination study of Onbevzi (over 250 subjects)

MAH	**Availability of additional relevant information in the local language/ link**	Not applicable

PART C - REVIEWER CONCLUSIONS

NRA	**Conclusions on biosimilarity, approval**

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

Quality

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

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

Nonclinical

No major differences in nonclinical data were observed for Onbevzi compared to the reference biotherapeutic product Avastin.

Clinical Studies

The Phase I and Phase III studies to demonstrate biosimilarity conducted in healthy volunteers and NSCLC patients provided robust evidence that there are no clinically meaningful differences between Onbevzi and the reference biotherapeutic product Avastin.

Safety: The Adeverse drug reactions (ADRs) observed with Onbevzi were in the similar range as the ADRs observed with the reference biotherapeutic product Avastin.

Immunogenicity: The proportion of patients who developed ADA with Onbevzi was generally similar to the reference biotherapeutic product Avastin.

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

Risk Management

The risk management plan was considered to be acceptable.

Overall Conclusion

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