CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761202Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	761202
Received Date	September 17, 2020
BsUFA Goal Date	September 17, 2021
Division/Office	Division of Ophthalmology
Review Completion Date	See DARRTS stamped date
Product Code Name	SB11
Proposed Nonproprietary Name[1]	ranibizumab-nuna
Proposed Proprietary Name[1]	Byooviz
Pharmacologic Class	vascular endothelial growth factor (VEGF) inhibitor
Applicant	Samsung Bioepis Co., Ltd.
Applicant Proposed Indication(s)	Indicated for the treatment of patients with: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Myopic Choroidal Neovascularization (mCNV)
Regulatory Action	Approval

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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Reviewers of Biosimilar Multidisciplinary Evaluation and Review

Regulatory Project Manager	Lois Almoza
Nonclinical Pharmacology/Toxicology Reviewer(s)	María I. Rivera, PhD
Nonclinical Pharmacology/Toxicology Team Leader(s)	Lori E. Kotch, PhD
Clinical Pharmacology Reviewer(s)	Amit A. Somani, PhD
Clinical Pharmacology Team Leader(s)	Ping Ji, PhD
Clinical Reviewer(s)	Lucious Lim, M.D.
Clinical Team Leader(s)	William M. Boyd, M.D.
Clinical Statistics Reviewer(s)	Yushuf Sharker, PhD
Clinical Statistics Team Leader(s)	Greg Soon, PhD
Cross-Discipline Team Leader(s) (CDTL(s))	William M. Boyd, M.D.
Designated Signatory Authority	Wiley A. Chambers, M.D.

Additional Reviewers of Application

OBP	
OPRO RBPM	Anh-Thy Ly
OBP Team Leader (ATL)	Willie Wilson
OBP Reviewer -Drug Product -Drug Substance - Immunogenicity - Comparative Analytical Assessment	Jens Fricke
OBP Biosimilar Policy (included for 351k applications)	Marlene Schultz-DePalo and Joel Welch
OBP Labeling Reviewer	Vicky Borders-Hemphill
OPMA	
OPMA Facility Team Leader	Zhong Li
OPMA Micro Team Leader for Drug Substance and Drug Product	Max Van Tassell
OPMA Primary Drug Substance Micro and Facility Reviewer	Lindsey Brown
OPMA Primary Drug Product Micro and Facility Reviewer	Wendy Tan
OPDP	James Dvorsky
OSI	
Reviewer	Ling Yang
Team Leader	Min Lu

Branch Chief	Kassa Ayalew
OSE/DEPI	Natasha Pratt
OSE/DMEPA	Nasim Roosta/Valerie Vaughan
OSE PM	Oyinlola Fashina
OSE/DRM	Jacqueline Sheppard/Ingrid Chapman
OSE/DPV	Rachna Kapoor
OSE/DRISK	N/A
DPMH	N/A
Other	N/A

OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGE	Special Government Employee
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events

Signatures

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/Approved
Nonclinical Reviewer			4, 13.3
	Signature: Maria I. Rivera -S Digitally signed by Maria I. Rivera -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300159002, cn=Maria I. Rivera -S Date: 2021.09.15 16:39:18 -04'00'		
Nonclinical Team Leader			4, 13.3
	Signature: Mukesh Summan -S Digitally signed by Mukesh Summan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mukesh Summan -S, 0.9.2342.19200300.100.1.1=2000337340 Date: 2021.09.15 21:39:00 -04'00'		
Clinical Pharmacology Reviewer	Amit A. Somani	CDER/OTS/DIIP	5, 13.4
	Signature: Amit A. Somani -S Digitally signed by Amit A. Somani -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amit A. Somani -S, 0.9.2342.19200300.100.1.1=2002153064 Date: 2021.09.15 15:08:08 -04'00'		
Clinical Pharmacology Team Leader			5, 13.4
	Signature: Ping Ji Digitally signed by Ping Ji DN: cn=Ping Ji, o=FDA, ou=FDA, email=ping.ji@fda.hhs.goc, c=US Date: 2021.09.15 17:06:34 -04'00'		
Clinical Reviewer			2, 7, 8, 10, 13.2, 13.5
	Signature: William M. Boyd -S Digitally signed by William M. Boyd -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300139743, cn=William M. Boyd -S Date: 2021.09.16 12:52:08 -04'00'		
Clinical Team Leader			2, 7, 8, 10, 13.2, 13.5
	Signature: William M. Boyd -S Digitally signed by William M. Boyd -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300139743, cn=William M. Boyd -S Date: 2021.09.16 12:52:54 -04'00'		
Clinical Statistics Reviewer	Yushuf Sharker	CDER/OTS/OB	6

	Signature: M A Yushuf Sharker -S (Affiliate) Digitally signed by M A Yushuf Sharker -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002702312, cn=M A Yushuf Sharker -S (Affiliate) Date: 2021.09.16 08:57:29 -04'00'		
Clinical Statistics Team Leader	Guoxing Soon	CDER/OTS/OB/DB4	6
	Signature: Guoxing Soon -S Digitally signed by Guoxing Soon -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Guoxing Soon -S, 0.9.2342.19200300.100.1.1=1300124920 Date: 2021.09.16 09:20:02 -04'00'		
Associate Director for Labeling (Optional)			7
	Signature: Derek Alberding -S Digitally signed by Derek Alberding -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001577879, cn=Derek Alberding -S Date: 2021.09.16 13:04:27 -04'00'		
Cross-Discipline Team Leader			1, 3, 6.6, 9, 11
	Signature: William M. Boyd -S Digitally signed by William M. Boyd -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300139743, cn=William M. Boyd -S Date: 2021.09.16 13:21:53 -04'00'		
Designated Signatory Authority (Division Director)			N/A
	Signature: Wiley A. Chambers -S Digitally signed by Wiley A. Chambers -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300042908, cn=Wiley A. Chambers -S Date: 2021.09.16 13:26:44 -04'00'		

Executive Summary

1.1 Product Introduction

SB11 (ranibizumab-nuna; Byooviz) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use that has been developed as a proposed biosimilar to US-licensed Lucentis. Ranibizumab-nuna binds to the receptor binding sites of Vascular Endothelial Growth Factor-A (VEGF-A) isoforms, including the proteolytically cleaved VEGF-A 110 isoform. The binding of ranibizumab to VEGF-A reduces the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2).

The Applicant is seeking licensure for the 0.5 mg (10 mg/mL) strength in a single-dose vial for the following indications which are the same as those previously approved for US-licensed Lucentis[2]:

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)

For neovascular (wet) age-related macular degeneration (AMD), Byooviz 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days). For macular edema following retinal vein occlusion (RVO), Byooviz 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days). For myopic choroidal neovascularization (mCNV), Byooviz 0.5 mg (0.05 mL) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to three months. These dosing regimen are the same as approved for US-licensed Lucentis.

1.2 Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

1.3 Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

This BLA contains sufficient data and information to demonstrate that SB11 and US-licensed Lucentis utilize the same mechanism of action (MOA) to the extent known for the proposed neovascular (wet) age-related macular degeneration (AMD), macular

[2] U.S. Prescribing Information, US-licensed Lucentis, Accessed August 26, 2021 from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125156s117lbl.pdf

edema following retinal vein occlusion (RVO), and myopic choroidal neovascularization (mCNV) indications. SB11 binds to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to contribute to retinal neovascularization and retinal leakage. The binding of SB11 to VEGF-A reduces the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2).

To support the demonstration that SB11 is highly similar to US-licensed Lucentis, Samsung performed a comparative analytical assessment of SB11 and US-licensed Lucentis. The comparative analytical assessment data provided support the conclusion that SB11 is highly similar to US-licensed Lucentis. SB11 has the same mechanism(s) of action as that of U.S.-licensed Lucentis.

US-licensed Lucentis is licensed in 0.3mg (6mg/mL) and 0.5mg (10mg/mL) strengths, in single-dose vial and single-dose pre-filled syringe. Samsung is seeking licensure for the 0.5mg (10mg/mL) strength in a single-dose vial. The route of administration (ROA), dosage form, and the strength of the proposed product are the same as those of the US-licensed reference product.

The condition(s) of use for which the applicant is seeking licensure have been previously approved for US-licensed Lucentis.

1.4 Inspection of Manufacturing Facilities

The following facilities were inspected and found to be in compliance with cGMPs:

(b) (4)

1.5 Scientific Justification for Use of a Non-US-licensed Comparator Product

Not applicable.

1.6 Biosimilarity Assessment

Table 1: Summary and Assessment of Biosimilarity

Comparative Analytical Studies[3]	
Summary of Evidence	• SB11 is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components • SB11 0.5 mg (10 mg/mL) in a single-dose vial is the same strength as that of US-licensed Lucentis • The dosage form and route of administration is also the same as that of US-licensed Lucentis
Assessment of Residual Uncertainties	• There are no residual uncertainties from a product quality perspective.
Animal/Nonclinical Studies	
Summary of Evidence	• A 4-week repeat-dose toxicity study comparing SB11 and US-Lucentis in cynomolgus monkeys was submitted. • The comparative analytical data was adequate to support initiation of the proposed comparative clinical study. The repeat-dose toxicity study data did not preclude the demonstration of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties.

[3]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter of therein for additional information regarding comparative analytical data.

Clinical	
Clinical Pharmacology Studies	
Summary of Evidence	• Systemic exposure of SB11 and US-licensed Lucentis was evaluated in the a subset of patients with neovascular AMD in the comparative clinical study SB11-G31-AMD as one of the secondary endpoints. Comparable systemic exposures between SB11 and US-licensed Lucentis based on descriptive analysis supports a demonstration of no clinically meaningful differences between SB11 and US-licensed Lucentis. • Comparable incidence of ADA/NAb formation between SB11 and US-licensed Lucentis in patients with neovascular AMD supports a demonstration of no clinically meaningful differences.
Assessment of Residual Uncertainties	• There are no residual uncertainties from a clinical pharmacology perspective.
Clinical Studies	
Summary of Evidence	• In Study SB11-G31-AMD, there were no meaningful differences in terms of efficacy or safety between SB11 and US-licensed Lucentis. The data from this study support a demonstration of no clinically meaningful differences between SB11 and US-licensed Lucentis. • In Study SB11-G31-AMD, the contralateral eye was concurrently treated with US-licensed Lucentis in individuals with bilateral disease. This contralateral administration exposed individuals to both SB11 and US-licensed Lucentis concurrently. There were no meaningful differences in terms of efficacy or safety in either eye. The data from this study support a demonstration of no clinically meaningful differences between SB11 and US-licensed Lucentis.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or clinical statistical perspectives.

Extrapolation	
Summary of Evidence	• DO has determined that the Applicant has provided adequate scientific justification and agrees with the applicant's justification for extrapolation to the other indications listed in the US-licensed Lucentis package insert being sought for licensure based on: 1) the mechanism of action of ranibizumab, including the structure and drug-target interactions in each condition is consistent across all approved indications. For each of the indications being sought for licensure, effective treatment can be expected by binding to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, and myopic choroidal neovascularization by reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation; and 2) the analysis of the known safety and immunogenicity profiles of ranibizumab across each of the indications being sought is consistent and there are no known differences in expected toxicities for each indication. • This justification supports licensure of SB11 as a biosimilar for the following indications for which US-licensed Lucentis has been previously approved: o Macular edema following retinal vein occlusion o Myopic choroidal neovascularization
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the scientific justification for extrapolation.

1.7 Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that SB11 is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between SB11 and US-licensed Lucentis in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that SB11 is biosimilar to US-licensed Lucentis for each of the following indications for which US-licensed Lucentis has been previously approved and for which the Applicant is seeking licensure of SB11: [4]

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)

Author:
William M. Boyd, M.D.
Deputy Division Director

1. Introduction and Regulatory Background

2.1 Summary of Presubmission Regulatory History Related to Submission

Pre-IND (130331) meetings were held on June 10, 2016, and November 7, 2016. The Original IND was submitted and received on July 7, 2017. BPD Type 2 meetings/teleconferences were held on August 21, 2018, March 5, 2019, and February 24, 2020. A BPD Type 4 (pre-BLA) meeting was held on July 20, 2020.

[4]The proposed SB11 labeling states: BYOOVIZ (ranibizumab-nuna) is biosimilar to Lucentis (ranibizumab injection).

2.2 Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

Table 2: Animal Studies Submitted

Study Title	Study Number	Species	Number Per Treatment Arm	Study Duration	Route of administration/Dose
Animal Studies					
4-Week repeat-dose toxicity study of SB11	(b) (4) 327-007	Cynomolgus Monkey	4	1 month	Intravitreal; 0.5 mg/eye once every 2 weeks (total of 3 administrations)

Table 3: Relevant Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
Comparative Clinical Study(ies)					
Study SB11-G31-AMD	NCT03150589	Comparative safety, efficacy, PK, and immunogenicity	Randomized, double-masked, parallel-group, multicenter (US and international study sites)	Subjects with nAMD	SB11 or US-licensed Lucentis administered at a dose of 0.5 mg to the study eye every 4 weeks up to Week 48

Authors:

Lucious Lim
Medical Officer

William M. Boyd, M.D.
Deputy Director

2. Summary of Conclusions of Other Review Disciplines

3.1 Office of Pharmaceutical Quality (OPQ)

Ranibizumab-nuna binds to the receptor binding site of human alternatively spliced Vascular Endothelial Growth Factor-A (VEGF-A) isoforms, including the proteolytically cleaved VEGF-A 110 isoform. The binding of ranibizumab to VEGF-A reduces the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells resulting in the reduction of endothelial cell proliferation, vascular leakage and new blood vessel formation. Ranibizumab-nuna drug product is manufactured to have the same strength, dosage form, and route of administration as the 10 mg/mL strength of US-licensed Lucentis in single-dose vial. It also has the same formulation and presentation as US-licensed Lucentis. Byooviz is a sterile, preservative-free, clear to slightly opalescent and colorless to pale yellow solution for intravitreal injection supplied in single-dose glass vials containing ranibizumab-nuna at 10 mg/mL.

Manufacture of the proposed product is well-controlled and leads to a product that is safe, pure, and potent. To support the demonstration that SB11 is highly similar to US-licensed Lucentis, Samsung performed a comparative analytical assessment of SB11 and US-licensed Lucentis. As part of the comparative analytical assessment, the molecular attributes of ranibizumab were collectively assigned to appropriate assessment categories and a sufficient number of lots of each product were evaluated. A comprehensive array of analytical methods was used to support a demonstration that the products are highly similar. Each method was demonstrated to be suitable to detect and/or quantitate potential differences in critical quality attributes between SB11 and US-licensed Lucentis. SB11 is highly similar to US-licensed Lucentis notwithstanding minor differences in clinically inactive components.

Based on the comparative analytical assessment and manufacturing data, the proposed presentation of SB11 has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-licensed Lucentis (10 mg/mL). Each SB11 0.5 mg carton will contain a single-dose, 2-mL glass vial with a blue cap designed to deliver 0.05 mL of 10 mg/mL drug product solution.

3.2 Division of Medication Error Prevention and Analysis (DMEPA)

The Applicant's proposed nonproprietary name, ranibizumab-nuna, was found to be conditionally acceptable by the Office of Medication Error Prevention and Risk Management in a letter to the applicant dated 7/11/2021. The proposed proprietary name for ranibizumab-nuna is conditionally approved as Byooviz. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded the name was acceptable in a letter to the applicant dated 12/15/2020. DMEPA completed a labeling review of the original applicant-submitted prescribing

information, container labels, and carton labeling on 7/1/2021.

3.3 Office of Study Integrity and Surveillance (OSIS)

Not applicable.

3.4 Office of Scientific Investigations (OSI)

Three clinical investigators (CIs) for Study SB11-G31-AMD: Drs. Sunil Patel (Site 2812), James Luu (Site 2816) and Atul Jain (Site 2821) were selected for clinical inspections. These sites were selected based on the number of subjects enrolled in the study. The inspections verified that the sponsor, Samsung Bioepsis Co., Ltd. (Samsung) submitted clinical data consistent with the source records at the CI sites. Based on the results of these inspections, Study SB11-G31-AMD is considered to have been conducted adequately, and the data generated by the sponsor appear acceptable in support of the application.

Author:
William M. Boyd, M.D.
Deputy Division Director

3. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1 Nonclinical Executive Summary and Recommendation

At the IND stage, the Applicant conducted a 4-week comparative ocular toxicology study in cynomolgus monkeys without seeking guidance from the FDA. The Applicant explained the study was conducted in support of country specific regulatory requirements outside the United States. In previous communications with the Applicant (pre-IND stage), it was agreed that *in vivo* PK and PD studies may be necessary only if there is lack of sufficient comparative analytical data. If *in vivo* studies were deemed necessary, DPT-ORPURM recommended a single-dose rabbit ocular PK/tolerability study comparing SB11 and US-licensed Lucentis.

The results of the 4-week repeated dose study in monkeys showed that SB11 and US-licensed Lucentis were well tolerated following bilateral administration of 0.5 mg/eye once every two weeks for 4 weeks (total of 3 administrations). There were no ocular or systemic toxicologically significant findings. Justification for dose selection/frequency, endpoint selection/methods, animal number, and study duration were not provided. ERG analysis was insufficient, and no assurance was provided that histopathologic sections included a section through the macula.

The Product Quality review team concluded that there was sufficient comparative analytic data (i.e., structural and functional characterization) between SB11 and US-licensed Lucentis to support safety, and did not identify any impurity issues that warrant additional studies. Therefore, the 4-week comparative ocular toxicology study was not needed to initiate the proposed comparative clinical study. The study data do not preclude a demonstration of biosimilarity between SB11 and US-licensed Lucentis and did not raise new safety questions.

4.1.1 Nonclinical Residual Uncertainties Assessment

Based on the conclusion from the Product Quality team of sufficient comparative analytical data, there were no nonclinical residual uncertainties.

4.2 Product Information

Product Formulation

SB11 Drug Product is a clear to slightly opalescent, colorless to pale yellow, sterile and preservative-free solution and presented as a single-dose vial for intravitreal injection. One single-dose vial contains SB11 drug substance, and the following excipients: α,α-trehalose dihydrate, histidine, histidine hydrochloride monohydrate, and polysorbate 20, at a target pH of 5.5. The composition of SB11 DP is shown in the following table.

Table 4: Composition of SB11 Drug Product

Component	Nominal Quantity/Vial	Function	Quality Standard
SB11 DS	2.3 mg	Active substance	In-house[a]
α,α-trehalose dihydrate	23 mg	(b) (4)	Ph. Eur., USP/NF, JP
Histidine	0.081 mg		Ph. Eur., USP, JP
Histidine Hydrochloride, monohydrate	0.375 mg		Ph. Eur., BP, JP
Polysorbate 20	0.023 mg		Ph. Eur., JPE, NF
Water for injection	*q.s.*		Ph. Eur., USP

[a] Specification of SB11 DS is provided in CTD Section 3.2.S.4.1.

SB11 and US-licensed Lucentis have the same formulation, as shown in the following table. The excipients in SB11 are the same and present in the same levels as the excipients in US-licensed Lucentis.

Table 5: Formulation Comparison between US-licensed Lucentis and SB11

Category	Component	Lucentis		SB11 DP	
		Concentration	Nominal Quantity/Via[a]	Concentration	Nominal Quantity/Vial
Active substance	protein	10 mg/mL	2.3 mg	10 mg/mL	2.3 mg
(b) (4)	Histidine	10 mM	Histidine 0.074 mg	10 mM	Histidine 0.081 mg[b]
			Histidine hydrochloride, monohydrate 0.382 mg		Histidine hydrochloride, monohydrate 0.375 mg[b]
	α,α-trehalose dihydrate	10%	23 mg	10%	23 mg
	Polysorbate 20	0.01%	0.023 mg	0.01%	0.023 mg
pH		5.5		5.5	

[a] Retrieved from drug label information of Lucentis in DailyMed.

[b] The ratio of the pair acid/base in the buffering agent was calculated from the Henderson-Hasselbalch equation. Calculation data is based on pKa for Histidine (6.04), target pH (5.5) and pair acid/base molecular weight (Histidine hydrochloride monohydrate: 209.63 g/mol, Histidine: 155.15 g/mol).

No impurities of concern were identified.

Authors:

María I Rivera, PhD
Pharmacology/Toxicology reviewer

Lori E. Kotch, PhD
Pharmacology/Toxicology Supervisor

4. Clinical Pharmacology Evaluation and Recommendations

5.1 Clinical Pharmacology Executive Summary and Recommendation

Table 6: Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
PK similarity	• Systemic exposure of SB11 and US-licensed Lucentis evaluated in the a subset of subjects with neovascular AMD in study SB11-G31-AMD were comparable based on descriptive analysis which supports a demonstration of no clinically meaningful differences between SB11 and US-licensed Lucentis.
PD similarity, if applicable	• Not applicable.
Immunogenicity assessment	• Comparable incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb) formation between SB11 and US-licensed Lucentis in subjects with neovascular AMD supports a demonstration of no clinically meaningful differences between SB11 and US-licensed Lucentis.

5.1.1 Clinical Pharmacology Residual Uncertainties Assessment

There are no clinical pharmacology residual uncertainties regarding the PK and immunogenicity assessment for SB11 and US-licensed Lucentis.

5.2 Clinical Pharmacology Studies to Support the Use of a Non-US-licensed Comparator Product

Not applicable.

5.3 Human Pharmacokinetic and Pharmacodynamic Studies

A PK similarity study using traditional PK endpoints, such as AUC and C_{max}, in healthy subjects is not considered to be feasible for the following reasons: 1) ranibizumab is administered by intravitreal (IVT) injection directly into the eye to treat diseases that are localized to the eye and the systemic exposures following IVT injection is low (i.e., negligible) and variable, and 2) the conduct of a PK study in healthy subjects is considered unethical due to the invasiveness of IVT injections. Therefore, a PK

sub-study within the comparative clinical study was recommended to provide PK data in support of no clinically meaningful differences in systemic safety. The objective of the PK sub-study was to descriptively compare the peak serum study drug concentrations.

Clinical Pharmacology Study Design Features and Endpoints

The PK profiles of SB11 and US-licensed Lucentis were descriptively evaluated within a subgroup of neovascular AMD patients as part of the comparative clinical study (Study SB11-G31-AMD). The PK data were pre-specified to be analyzed qualitatively. Analyses included:

a. Systemic exposure measured pre-dose (trough serum concentration [Ctrough]) and 24-72 hours post-dose (close to maximum serum concentration [Cmax]) in a subpopulation of patients from both treatment groups
b. Incidence of anti-drug antibodies (ADAs) to SB11 and US-licensed Lucentis
c. Incidence of neutralizing antibodies (NAbs) to SB11 and US-licensed Lucentis

Of the 705 subjects enrolled, 25 [7.1%] subjects in the SB11 and 29 [8.2%] subjects in the US-licensed Lucentis treatment groups were included in PK Analysis Set.

Bioanalytical PK method and performance

A validated electrochemiluminescent (ECL) assay of Meso Scale Discovery (MSD) platform was used for measurement of study drug in serum samples of the patients with neovascular AMD in study SB11-G31-AMD. The lower and upper quantification limits for plasma study drug concentrations were 600 pg/mL and 16000 pg/mL, respectively.

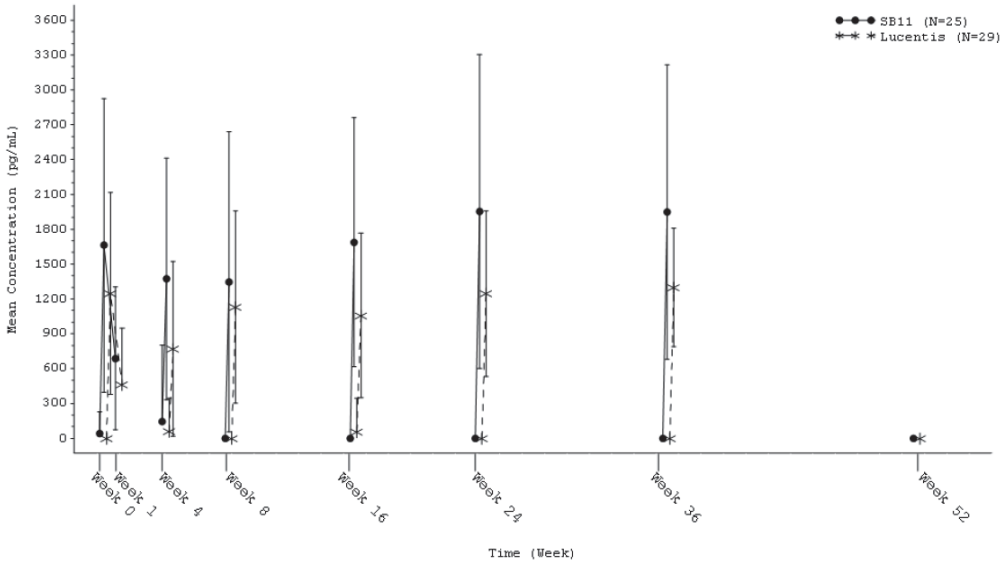
PK of SB11 and US-licensed Lucentis in patients with neovascular AMD (Study SB11-G31-AMD)

In Study SB11-G31-AMD, selected sites invited subjects to participate in PK sampling until approximately 50 subjects had been enrolled in the PK Analysis Set. Blood samples for PK assessments were collected prior to IVT injection and 24-72 hours following the IVT injection at Week 0 (Day 1), Week 4, Week 8, Week 16, Week 24, and Week 36. Blood samples were also collected at any time during the visit at Week 1 and Week 52 (EOS Visit) or Early Termination Visit.

The arithmetic mean (± standard deviation [SD]) serum concentration profiles by treatment in the two subgroups are presented in Figure 1. The descriptive PK results for the subgroups are provided in Table 7. As expected, the pre-dose concentrations of SB11 and US-licensed Lucentis were non-quantifiable in the majority of subjects at all visits. Over all the post-dose PK sampling time-points, the arithmetic mean concentrations ranged from 1346.5 pg/mL to 1952.2 pg/mL for SB11 and from 771.2 pg/mL to 1298.0 pg/mL for US-licensed Lucentis. The systemic concentrations are an indicator of the extent of systemic VEGF activity. Therefore, it is important to note that these post-dose concentrations are all below the concentration range of ranibizumab (11-27 ng/mL) that is necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an *in vitro* cellular proliferation assay. The observed variability (CV%) is

high for all the post-dose concentrations, ranging between 63.61% and 96.03% for SB11 and between 39.39% and 97.73% for US-licensed Lucentis. Given the low concentrations observed in both treatment groups, the numerically higher mean concentrations of SB11 as compared to US-licensed Lucentis are not considered clinically meaningful and unlikely to have any implications on systemic safety.

Figure 1: Mean Concentration versus Time for SB11 and US-licensed Lucentis



Source: Section 5.3.5.1 Final CSR, Study SB11-G31-AMD, Figure 11-7, Figure 14.2-5.1

Table 7: Pharmacokinetic Results (Pharmacokinetic Analysis Set)

Study SB11-G31=AMD Serum Concentration (pg/mL), Mean

Scheduled Time	Timpoint	SB11 (n=25)	US-licensed Lucentis (n=29)
Week 0 Baseline	Pre-dose	41.2	0.0
	Post-dose	1660.9	1246.9
Week 1	N/A	687.3	462.5
Week 4	Pre-dose	143.8	57.2
	Post-dose	1371.7	771.2
Week 8	Pre-dose	0	0
	Post-dose	1346.5	1130.2
Week 16	Pre-dose	0	56.5
	Post-dose	1688.1	1057.0
Week 24	Pre-dose	0	0
	Post-dose	1952.2	1245.8
Week 36	Pre-dose	0	0
	Post-dose	1947.0	1298.0
Week 52	N/A	0	0

N/A=not applicable. Pre-dose=before intravitreal injection.

Source: Section 5.3.5.1 Final CSR, SB11-G31-AMD, Table 14.2-7.1

PD similarity assessment

Not applicable.

5.4 Clinical Immunogenicity Studies

Design Features of the Clinical Immunogenicity Assessment

Immunogenicity (ADA and Nab) was evaluated in Study SB11-G31-AMD as one of the secondary endpoints. Refer to Sections 5.3 and 6.2 for design features of Study SB11-G31-AMD.

Immunogenicity Endpoints

Serum samples collected for immunogenicity assessment were first tested for ADA. Samples confirmed as positive for ADA were further tested for NAb.

Immunogenicity Assay's Capability of Detecting the ADA in the Presence of Proposed Product, Reference Product, and Any Other Comparator Product (as applicable) in the Study Samples

The Applicant developed binding and neutralizing antibody assays that are suitable for detecting ADA and NAb in the presence of expected levels of SB11 and US-licensed Lucentis.

Adequacy of the Sampling Plan to Capture Baseline, Early Onset, and Dynamic Profile (Transient or Persistent) of ADA Formation

The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation. Blood sampling for immunogenicity assessment were collected prior to IVT injection of SB11 or US-licensed Lucentis at Week 0 (Day 1), Week 4, Week 8, Week 16, Week 24, and Week 36. Blood sampling for immunogenicity was also collected at any time during the visit at Week 1 and Week 52 (EOS visit) or ET visit.

Comparison of Incidence of ADA and NAb

The formation of ADA and NAb was similar between the SB11 and US-licensed Lucentis treatment groups in Study SB11-G31-AMD. Table 8 summarizes the incidence of ADA and NAb by treatment group and time points in Study SB11-G31-AMD. The incidence of an ADA positive response was generally low and comparable across treatments at each immunogenicity assessment timepoint for the two treatment groups. The majority of detected ADAs in the SB11 and US-licensed Lucentis treatment groups were non-neutralizing up to Week 52. The incidence of NAb between the SB11 and US-licensed Lucentis treatment groups were also comparable at each timepoint.

Table 8: Incidence of Anti-drug Antibody (ADA) and Neutralizing Antibodies (NAb) by Visit (Safety Set, Study SB11-G31-AMD)

Timepoint	SB 11	Lucentis	SB 11	Lucentis	SB 11	Lucentis	SB 11	Lucentis
	ADA Positive	ADA Positive	ADA Negative	ADA Negative	NAb Positive	NAb Positive	NAb Negative	NAb Negative
Week 0 (BL)	7/343 (2%)	4/348 (1%)	336/343 (98%)	344/348 (99%)	1/7	0/4	6/7	4/4
Week 1	9/334 (3%)	3/325 (1%)	325/334 (97%)	322/325 (99%)	0/9	1/3	9/9	2/3
Week 4	8/318 (3%)	5/321 (2%)	310/318 (97%)	316/321 (98%)	2/8	1/5	6/8	4/5
Week 8	8/312 (3%)	7/311 (2%)	304/312 (97%)	304/311 (98%)	1/8	1/7	7/8	6/7
Week 16	4/301 (1%)	4/297 (1%)	297/301 (99%)	293/297 (99%)	1/4	0/4	3/4	4/4
Week 24	7/294 (2%)	2/290 (1%)	287/294 (98%)	288/290 (99%)	0/7	1/2	7/7	1/2
Week 36	8/270 (3%)	5/274 (2%)	262/270 (97%)	269/274 (98%)	2/8	0/5	6/8	5/5
Week 52	9/257 (4%)	12/267 (4%)	248/257 (96%)	255/267 (96%)	1/9	0/12	8/9	12/12

ADA=anti-drug antibody; BL=baseline; NAb=neutralizing antibody
Source: Section 5.3.5.1 Final CSR, Study SB11-G31-AMD, Table 12-12, Table 14.3-3.1

Comparison of ADA Titers

The distribution of ADA titers is comparable between the SB11 and US-licensed Lucentis treatment groups as seen in Table 9. There was no specific trend indicating the difference in the distribution of ADA titers between the SB11 and US-licensed Lucentis treatment groups.

Table 9: Incidence of Anti-drug Antibody (ADA) by Titer, Visit, and Treatment Group (Safety Set, Study SB11-G31-AMD)

		<50	50	100	200	400	800	3200
Week 0	SB11	0	3	3	1			
	Lucentis	1	2	1				
Week 1	SB11	1	4	2	1	1		
	Lucentis	0	0	2	1			
Week 4	SB11	3	0	3	0	2		
	Lucentis	1	3	0	0	1		
Week 8	SB11	0	4	3	1			
	Lucentis	3	2	1	0			
Week 16	SB11	0	1	2	1			
	Lucentis	1	1	1	1			
Week 24	SB11	0	3	1	2	1		
	Lucentis	0	0	1	1			
Week 36	SB11	0	1	3	1	1	1	1
	Lucentis	0	1	4				
Week 52	SB11	1	3	3	0	1	0	1
	Lucentis	2	6	3	1			

Source: Section 5.3.5.1 Final CSR, Study SB11-G31-AMD, Table 14.3-3.2

Comparison of Immunogenicity Impact on PK

Among 54 subjects who were included in the PK Analysis set, only 3 subjects had positive ADA results (2 subjects in SB11 group at Week 52, and 1 subject in US-licensed Lucentis group at Week 36) and therefore it is not possible to correlate blood levels and antibody rates. Based on the low level of positivity, there are no safety concerns related to antibody formation.

Comparison of Immunogenicity Impact on Efficacy

The number of ADA-positive subjects was small (< 3%) and equally divided between treatment arms at Week 8. Comparable low incidence of anti-drug antibody (ADA) formation and only single neutralizing antibody (NAb) formation in each group supports a demonstration of no clinically meaningful differences between SB11 and US-licensed Lucentis.

Comparison of Immunogenicity Impact on Safety

The comparison of immunogenicity impact on safety was evaluated based on the assessment of the overall, ocular, and non-ocular treatment-emergent adverse events (TEAE) by overall anti-drug antibody result up to end of study (Week 52) (Table 10). Overall, ocular and non-ocular TEAEs at Week 52 in patient with overall ADA positive status up to Week 52 were comparable between the SB11 and US-licensed Lucentis treatment groups.

Table 10: Treatment-emergent Adverse Events by Overall Anti-drug Antibody (ADA) Result up to Week 52 (Safety Set, Study SB11-G31-AMD)

	SB11			US-licensed Lucentis		
	n/n'	(%)	E	n/n'	(%)	E
	Overall TEAE					
Overall ADA positive	11 / 14	(78.6)	29	13 / 18	(72.2)	29
Overall ADA negative	225/ 312	(72.1)	824	223 / 308	(72.4)	818
Inconclusive	2/ 4	(50.0)	1	1 / 1	(100.0)	1
	Ocular TEAE (Study Eye)					
Overall ADA positive	5 / 14	(35.7)	11	4 / 18	(22.2)	9
Overall ADA negative	95 / 312	(30.4)	177	95 / 308	(30.8)	206
Inconclusive	1 / 4	(25.0)	1	1 / 1	(100.0)	1
	Ocular TEAE (Fellow eye)					
Overall ADA positive	2 / 14	(14.3)	2	2 /18	(11.1)	4
Overall ADA negative	79 / 312	(25.3)	101	69 / 308	(22.4)	106
Inconclusive	2 / 4	(50.0)	3	0 / 0	(0.0)	0
	Non-Ocular TEAE					
Overall ADA positive	8/14	(57.1)	16	9/18	(50)	16
Overall ADA negative	173/312	(55.4)	546	181/308	(57.1)	1052
Inconclusive	1/4	(25.0)	4	0/1	(0)	4

ADA = anti-drug antibody; E = frequency of events; N = total number of subjects in the Safety Set; n = number of subjects with event; n' = number of subjects with overall ADA result up to End of Treatment; TEAE = treatment-emergent adverse event
Percentages were based on n'.
Overall ADA results were determined as positive for a patient with treatment-induced or treatment-boosted ADA, where treatment-induced ADA indicates at least 1 positive result after pre-dose of Week 0 for subjects with negative ADA at pre-dose of Week 0, and treatment-boosted ADA indicates at least 1 positive result with higher titer level compared with pre-dose of Week 0 after pre-dose of Week 0 for subjects with positive ADA at pre-dose of Week 0.
Overall ADA result was defined as negative for a patient without positive ADA until Week 52.
Overall ADA result was defined as inconclusive for a patient with positive ADA at Week 0 and without positive result with higher titer level observed after pre-dose of Week 0 up to Week 52.

Source: Section 5.3.5.1 Final CSR, Study SB11-G31-AMD, Table 14.3.1-1.4.1, Table 14.3.1-1.4.2, Table 14.3.1-1.4.3, Table 14.3.1-1.4.4

Authors:
Amit A. Somani, PhD
Clinical Pharmacology Reviewer

Ping Ji, PhD
Biosimilar Scientific lead

5. Statistical and Clinical Evaluation and Recommendations

6.1 Statistical and Clinical Executive Summary and Recommendation

The application includes a randomized, double-masked, parallel group, multicenter comparative clinical study of SB11 to US-licensed Lucentis among subjects with nAMD. The study evaluated efficacy by comparing the primary endpoint of change in best corrected distance visual acuity (BCVA) from baseline to Week 8 between SB11 and US-licensed Lucentis. The results of the comparative efficacy analysis would support that there are no meaningful differences between SB11 and US-licensed Lucentis if the two-sided 90% confidence interval (CI) of the difference of least square means of the primary endpoint between arms was within the pre-defined equivalence margin of [−3 letters, 3 letters]. The data from Study SB11-G31-AMD contained in this submission compared 0.5 mg (10 mg/mL) of each product administered by intravitreal injection once a month (approximately 28 days) in patients with age-related macular degeneration. Study SB11-G31-AMD demonstrated comparable efficacy between groups with respect to the change in best-corrected visual acuity (BCVA) from baseline to Week 8.

6.1.1 Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses.

6.2 Review of Comparative Clinical Studies with Statistical Endpoints

The application includes a single comparative clinical study (SB11-G31-AMD) to support a demonstration of no clinically meaningful differences.

6.2.1 Study SB11-G31-AMD

This was a randomized, double-masked, parallel group, multicenter study to evaluate the comparative efficacy, safety, and immunogenicity of SB11 compared with US-licensed Lucentis in subjects with neovascular age-related macular degeneration (AMD). A PK sub-study was included to descriptively compare the peak serum study drug concentrations.

Subjects who met all inclusion/exclusion criteria were randomized in a 1:1 ratio to receive 0.5 mg of either SB11 or US-licensed Lucentis via intravitreal injection every 4 weeks (approximately every 28 days) up to Week 48. The last assessment was done at Week 52. The primary comparative efficacy analysis was assessed at Week 8. The safety analyses were assessed through Week 52.

Data and Analysis Quality

Randomization

Randomized treatment assignments of the study were verified based on the submitted the randomization method, scheme, and codes of the study.

Masking

Subjects, Investigators, and the other study personnel were masked to the treatment assignments throughout the study period.

Amendments

Protocol amendments are listed according the date as follows:

- March 03, 2017 The first version of the protocol approved
- September 01, 2017 Protocol amendment
- March 14, 2018 Study starts

The protocol amendment modified the inclusion and exclusion criteria, study design, secondary and exploratory endpoints, statistical methods, and analysis sets definitions.

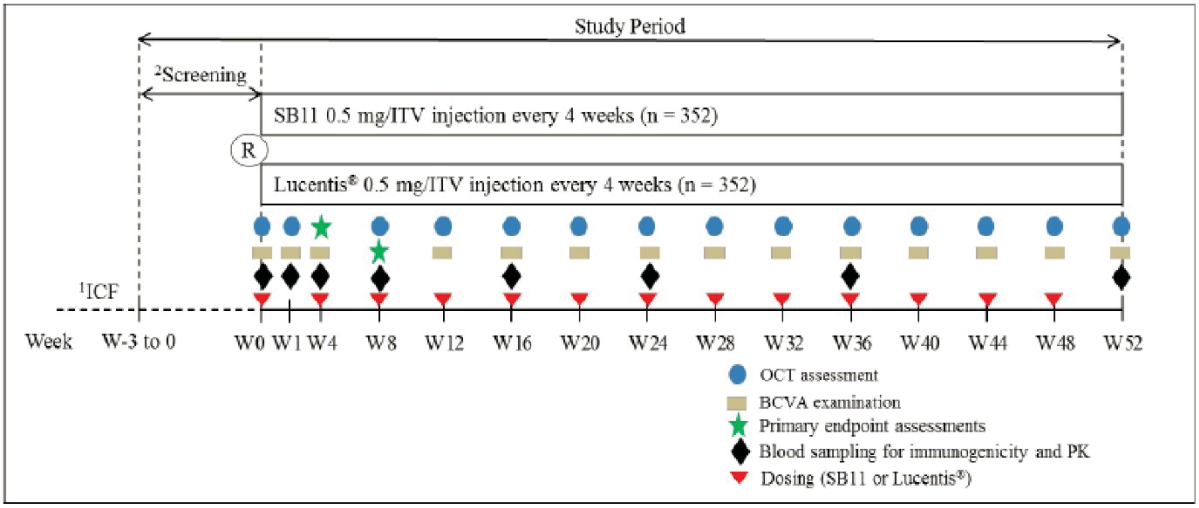
An SAP was included with the first version of the protocol. Later, The Applicant submitted the final Statistical Analysis Plan (SAP) for Study SB11-G31-AMD. Dates pertaining to the SAP are as follows:

- March 03, 2017 The primary SAP for the study with the protocol version 1.0 (Submitted to FDA on July 17, 2017)
- September 01, 2017 Protocol amendment 1 (Submitted to FDA on December 14, 2017)
- March 14, 2018 Study starts
- December 09, 2019 Study completes
- January 29, 2020 SAP amendment.
- February 03, 2020 Database lock
- March 3, 2020 Conduct statistical analyses
- May 7, 2020 The efficacy data discussed in the Data Safety and Monitoring Board (DSMB) meeting

The estimand and the primary statistical methods remain unchanged in the amendments. The quality of the submitted data and analysis were acceptable. There are no concerns regarding the data quality and integrity for this clinical study.

Study Design and Endpoints

Figure 2: Schematic of the study design



Source: Complete Study Report (pp 20)

- *BCVA, Best corrected visual acuity; ICF, Informed consent form; ITV, Intravitreal; n, Number of subjects; OCT, Optical coherence tomography; PK, Pharmacokinetics; R, Randomization; W, Week.*
- *[1] Written informed consent was obtained from the subject prior to any study related procedures.*
- *[2] Screening was done within 21 days prior to randomization.*

In the figure above, there are two primary endpoint evaluation indications (the green stars). The Week 4 assessment corresponds to the primary endpoint evaluation time for the European Medicines Agency (EMA) and the Week 8 assessment corresponds the evaluation time for the FDA. The figure does not include the BCVA examination at Week 8 however, there was an assessment in BCVA at Week 8 for the primary efficacy endpoint for FDA.

Eligibility Criteria

The inclusion criteria include:

- Subjects of Age ≥ 50
- Newly diagnosed active sub foveal CNV lesion secondary to Age Related Macular Degeneration (AMD) in the study eye and the area of CNV must occupy at least 50% of the total lesion
- Total lesion area ≤ 9.0 disc areas (DA) in size
- BCVA of 20/40 to 20/200 (letter score of 73 to 34) using Early Treatment Diabetic Retinopathy Study (ETDRS) chart prior to randomization.

The exclusion criteria include:

- Sub- or intra-retinal hemorrhage that comprises more than 50% of the entire lesion in the study eye
- Presence of sub foveal blood equal to or more than one DA in size
- Scar, fibrosis, or atrophy involving the center of the fovea in the study eye
- Presence of CNV in either eye due to other causes

- Presence of retinal pigment epithelial tears or rips involving the macula in the study eye
- Presence of macular hole at any stage in the study eye.

The study enrolled subjects who met all the inclusion criteria and none of the exclusion criteria.

Study eye
Only one eye that met the eligibility criteria was considered as the study eye. For subjects who had both eyes eligible, the eye with the worst visual acuity (VA) was selected as the study eye. If both eyes had equal VA, the study eye was selected at the Investigator's discretion.

List of Investigators
There were 75 study center(s) in the following countries: Czech Republic (7), Germany (10), Hungary (10), India (6), Poland (7), Russia (5), South Korea (7), United Kingdom (4), USA (19).

Safety Assessments
Adverse events, clinical laboratory test, physical examination, vital signs, full ophthalmic examinations (slit-lamp biomicroscopy, IOP measurements, and fundus examinations).

Statistical Methodologies

Primary endpoints measurement
The primary endpoint was the change in best corrected distance (4 meters) visual acuity (BCVA) at Week 8 from the Baseline.

Sample size
The study assumed the following for the sample size calculation:
- The means difference between the study groups = 0.5 letters
- Pooled standard deviation = 12.5 letters
- A two-sided 5% level of significance (EU recommended significance level)
- Loss to follow up at Week 8 of 5%
- Power 80% and
- Equivalence margin of [−3 letters, 3 letters] (FDA recommended margin)

With the assumptions, a sample of size 352 subjects per study group (704 subjects in total) was required to assess the equivalence. The study finally enrolled 705 subjects with 351 subjects in SB11 group and 354 in the US-licensed Lucentis group.

The FDA does not expect a two-sided 5% level of significance. The FDA expects a two-sided 10% level of significance.

Analysis populations

The primary efficacy analysis was performed on Full Analysis Set (FAS). The FAS included all randomized subjects who received the study drug. Subjects who did not qualify for randomization and were inadvertently randomized into the study never received any investigational product and excluded from the FAS.

Sensitivity analyses were conducted on the Per Protocol set for BCVA (PPS-BCVA), which included all FAS subjects who had received the first two investigational product doses and completed the procedures at Week 8 without any major protocol deviations. Major protocol deviations were defined prior to unmasking the treatment group assignment.

Safety was evaluated on the safety analysis set that included all subjects who received at least one investigational product during the study period.

Efficacy Analysis

The primary endpoint was analyzed using an Analysis of Covariance (ANCOVA) model. The model included the Baseline BCVA level as continuous, and the region and treatment group as factor covariates. Comparable was declared if the two-sided 90% confidence interval (CI) of the difference of least square means of the outcomes between groups was within the pre-defined [−3 letters, 3 letters] equivalence margin. Discontinuation from the investigational product or from the study due to intercurrent events were treated as missing and imputed for the primary efficacy analysis.

Missing Data Methods

Missing values at Week 8 could be from those who dropped out of the study or those who did not drop out but missed the Week 8 visit. The study assumed that subjects who had missing values were similar to subjects who completed the study in that treatment group (missing-at-random [MAR]). A preliminary step was taken to transform data to be monotonically missing, i.e., an observation of a variable at time *j* is missing implies the variable is missing for all times $k \geq j$. The Applicant used regression method to impute the missing observations under those assumptions.

The Applicant provided the codes for the missing value imputations. From the code, the algorithm for missing imputation method was as follows:

Step 1: Include data until Week 8 (Visit 5)
Step 2: Impute missing values to get a monotone pattern using MCMC multivariate normal for both groups and modify the imputed values using the BCVA rules.
Step 3: Impute missing values by monotone regression method. In the regression method, a regression model is fitted for outcome variables Y_t for time $t = Week\ 8$. The outcome variables before time t and the study groups were considered as covariates. Based on the fitted regression model, a new regression model is simulated from the posterior predictive distribution of the

parameters and is used to impute the missing values for each variable[5]. Imputation method was completed by modifying the imputed missing values using the BCVA rule

Step 4: Repeat the process 1000 times that generate 1000 replications of missing imputations

The Multiple Imputation procedure generates 1000 replications of imputed data sets and thus 1000 replication of the statistics of interest for efficacy assessment. The final inference for efficacy was made based on the pooled estimate of those 1000 replications of statistics.

The study evaluated the sensitivity of inferences from the primary analysis by conducting different imputation methods and analysis populations as follows:

1. Impute missing observations by last observation carry forward (LOCF) approach for FAS
2. Impute missing observations by multiple imputation by regression method under missing-not-at-random (MI-MNAR) assumption for FAS. In the MI-MNAR approach, subjects who dropped out due to any AE, the 20% worsening was implied for the mean difference. For BCVA components at week 8: Imputed value = previous imputed value − (previous imputed value × 0.2).
3. Primary analysis ignoring missing subjects (based on available cases) in FAS Using the PPS-BCVA analysis set for primary analysis

In addition, we evaluated the distribution of missing to see if the two treatment groups behaved similarly.

Interim analysis and statistical corrections:

The Interim analysis was conducted by the Data Safety and Monitoring Board (DSMB). The DSMB consisted of external experts who reviewed the safety and tolerability data at the pre-specified time interval. The randomization code was broken for the first time for the interim analysis on October 21, 2019, when all subjects completed the procedure of Week 24. An independent unmasked statistician conducted the interim data analysis and communicated to the DSMB directly. The Investigators and the subjects were masked over the study period. The Applicant did not consider any Type I error correction due to interim analysis because the analysis was conducted after all subjects had completed the comparative efficacy endpoint.

[5] The MI Procedure (sas.com)

Planned sub-group analyses
The applicant planned sub-group analyses to evaluate the change from Baseline in BCVA at Week 8 from the Baseline for the FAS by the following prognostic factors at Baseline:

- Overall Anti-Drug Antibody (ADA) result up to Week 8
- Lesion type (Positive, Negative, Inconclusive)
- Total lesion area (≤4DA vs. >4DA)
- Country of residence

The study was not expected to be powered for analysis of these subgroups and these subgroup analyses were not expected by the FDA.

In addition to the potential prognostic factors, the statistical reviewer conducted additional analysis to evaluate the change in BCVA at Week 8 from the Baseline for the FAS for the following demographic sub-groups: age, gender, race.

Efficacy Analyses
The primary comparative efficacy analysis was performed for the FAS with the change from baseline of BCVA at Week 8 using an analysis of covariance model with the baseline BCVA as a covariate, region (or pooled centers) and treatment group as factors. Equivalence was defined as a two-sided 90% Confidence Interval (CI) of the difference in mean changes from baseline at Week 8, lying within a 3 letter margin.

Safety Analyses
All reported terms for AEs (ocular and systemic) were to be coded using Medical Dictionary for Regulatory Activities (MedDRA). For all AE and SAE tables, subjects were counted once for each preferred term and each system organ class.

Changes in vital signs and clinical laboratory parameters were summarized descriptively by treatment group and visit. All safety analyses were performed using the SAF.

Subject Disposition

The study screened 1095 subjects of which 705 subjects were randomized into two groups: 351 in SB11 and 353 in US-licensed Lucentis. The FAS included 100% of subjects from SB11 group and 99.7% of subjects from US-licensed Lucentis group. There was 1 subject who did not qualify for randomization that was inadvertently randomized into the study but never received any investigational product and was excluded from the FAS.

Table 11. Subjects disposition and analysis sets by treatment groups

	SB11 n (%)	Lucentis n (%)	Overall n (%)
Screened			1095
Screen Failure			390
Reason for screen failure			
Does not meet eligibility criteria			353 (90.5)
Consent withdrawal			25 (6.4)
Loss to follow up			2 (0.5)
Other			10 (2.6)
Randomized	351 (100)	354 (100)	
Full Analysis Set	351 (100)	353 (99.7)	
Excluded from FAS[a]	0 (0.0)	1 (0.3)	
Per Protocol Analysis Set (BCVA)	336 (95.7)	333 (94.1)	
Safety Analysis Set	351 (100)	353 (99.7)	
Subjects completed Week 8 (Visit 5)	346 (98.5)	348 (98.3)	
Subjects missing at Week 8 (Visit 5)	5 (1.5)	5 (1.3)	
Reasons for missing at Week 8			
Withdrawal by subjects	1 (0.3)	1 (0.3)	
Adverse event	0 (0.0)	1 (0.3)	
Protocol deviation	1 (0.3)	1 (0.3)	
Missing (Continued to participate)[b]	3 (0.8)	2 (0.6)	
Subjects completed Week 24 (Visit 9)	335 (95.4)	337 (95.2)	
Subjects discontinued before Week 24	16 (4.6)	17 (4.8)	
Reasons for investigational product discontinuation			
Withdrawal by subjects	5 (1.4)	5 (1.4)	
Adverse event	4 (1.1)	4 (1.1)	
Protocol deviation	3 (0.9)	2 (0.6)	
Death	1 (0.3)	2 (0.6)	
Others	0 (0.0)	1 (0.3)	
Subjects completed Week 52 (Visit 16)	307 (87.5)	327 (92.4)	
Subjects discontinued before Week 52	44 (12.5)	27 (7.6)	
Reasons for investigational product discontinuation			
Withdrawal by subjects	16 (4.6)	9 (2.5)	
Adverse event	7 (2.0)	6 (1.7)	
Protocol deviation	4 (1.1)	3 (0.8)	
Death	2 (0.6)	3 (0.8)	
Investigational product non-compliance	9 (2.6)	1 (0.3)	
Others	3 (0.9)	2 (0.6)	

Source: Statistical reviewer's analysis.

[a] *The subject did not qualify for randomization and were inadvertently randomized into the study never received any investigational product and excluded from the FAS*

[b] *These subjects had missing data only at the Week 8 (Visit 5) Evaluation, but they continued to participate in the study until the last visits.*

Reviewer's Comments: *The groups are similar. No concerns are raised from the number of subjects in the dataset.*

Protocol Deviations

The statistical reviewer can reproduce the reported summary of protocol deviations (PD) in the Complete Study Report (CSR)

Table 12. Summary of protocol deviations by treatment group.

	SB11 N = 351 n (%)	Lucentis N = 354 n (%)
All protocol deviations	**248 (70.7)**	**264 (74.6)**
At least one major protocol deviation	**131 (37.3)**	**142 (40.1)**
Study procedure[a]	89 (25.4)	104 (29.4)
Investigational product compliance[a]	39 (11.1)	33 (9.3)
Others [a]	3 (0.9)	5 (1.4)
Excluded from PPS-BCVA	**13 (3.7)**	**18 (5.1)**
Exclusion criteria	3 (0.9)	4 (1.1)
Investigational product compliance	2 (0.6)	1 (0.3)
Inclusion criteria	0 (0.0)	1 (0.3)
Study procedure	8 (2.3)	12 (3.4)
Withdrawal criteria	2 (0.6)	0 (0.0)
Others	**127 (36.2)**	**131 (37.0)**
Concomitant medication criteria	1 (0.3)	1 (0.3)
Investigational product compliance	44 (12.5)	41 (11.6)
Study procedure	96 (27.4)	105 (29.7)
Withdrawal criteria	2 (0.6)	1 (0.3)
With at least one minor protocol deviation	218 (62.1)	225 (63.6)
Investigational product compliance	1 (0.3)	1 (0.3)
Study procedure	218 (62.1)	225 (63.6)

Source: Reviewer's analysis

[a] A single subject may have multiple major PDs and the frequency is based on the first major PD of a subject.

- BCVA, best corrected visual acuity; CST, Central subfield thickness; IP, Investigational product; N, Total number of subjects; n, Number of subjects; PPS-BCVA, Per-protocol set for BCVA;.

Reviewer's Comments: *The groups are similar. No concerns are raised from the number of subjects in the dataset.*

Table 13: Number (%) of Subjects in the Analysis Sets

Number of Subjects	SB11 n (%)	Lucentis n (%)
Full Analysis Set	354 (100.0)	353 (99.7)
Per-Protocol Set for BCVA	336 (95.7)	333 (94.1)
Safety Analysis Set	350 (99.7)	354 (100.0)

Source: Study SB11-G31-AMD CSR, Table 11-1
BCVA – Best Corrected Visual Acuity
Percentages were based on the number of subjects in the Randomized Set

Reviewer's Comments: *The groups are similar. No concerns are raised from the number of subjects in the dataset.*

Table 14: Disposition

Number of Subjects	SB11 n (%)	Lucentis n (%)	Total n (%)
Screened			1,095
Screening failures			390
Reason for screening failures			
Does not meet eligibility criteria			353 (90.5)
Consent withdrawal			25 (6.4)
Lost to follow-up			2 (0.5)
Other			10 (2.6)
Randomized*	351 (100.0)	354 (100.0)	
Completed at Week 24*	335 (95.4)	337 (95.2)	
Main reason for investigational product discontinuation			
Consent withdrawal by subject	5 (1.4)	5 (1.4)	
Adverse event	4 (1.1)	4 (1.1)	
Protocol deviations	3 (0.9)	2 (0.6)	
Lost to follow-up	1 (0.3)	2 (0.6)	
Investigational product non-compliance	2 (0.6)	1 (0.3)	
Death	2 (0.6)	3 (0.8)	
Other	3 (0.9)	2 (0.6)	
Completed at Week 52*	307 (87.5)	327 (92.4)	
Main reasons for investigational product discontinuation			
Consent withdrawal by subject	16 (4.6)	9 (2.5)	
Adverse event	7 (2.0)	6 (1.7)	
Protocol deviations	4 (1.1)	3 (0.8)	
Lost to follow-up	3 (0.9)	3 (0.8)	

Number of Subjects	SB11 n (%)	Lucentis n (%)	Total n (%)
Investigational product non-compliance	9 (2.6)	1 (0.3)	
Death	2 (0.6)	3 (0.8)	
Other	3 (0.9)	2 (0.6)	

Source: Study SB11-G31-AMD CSR, Table 10-1
IP – Investigational products, n – Number
*Percentages were based on the number of randomized subjects

Reviewer's Comments: *The groups are similar. No concerns are raised from the number of subjects in the dataset.*

Table 15: Summary of Protocol Deviations by Treatment Group (Randomized Set)

Type of Deviation	SB11 N=351 n (%)	Lucentis N=354 n (%)
Any protocol deviations	248 (70.7)	264 (74.6)
With at least one major protocol deviation	131 (37.3)	142 (40.1)
Excluded from PPS-BCVA	13 (3.7)	18 (5.1)
Exclusion criteria	3 (0.9)	4 (1.1)
Investigational product compliance	2 (0.6)	1 (0.3)
Inclusion criteria	3 (1.0)	7 (2.2)
Study procedure	3 (1.0)	9 (2.9)
Withdrawal criteria	1 (0.3)	5 (1.6)
Others	127 (36.2)	131 (37.0)
Concomitant medication criteria	1 (0.3)	1 (0.3)
Investigational product compliance	44 (12.5)	41 (11.6)
Study procedure	96 (27.4)	105 (29.7)
Withdrawal criteria	2 (0.6)	1 (0.3)
With at least one minor protocol deviation	218 (62.1)	225 (63.6)
Investigational product compliance	1 (0.3)	1 (0.3)
Study procedure	218 (62.1)	225 (63.6)

Source: Study SB11-G31-AMD CSR, Table 10-2
BCVA – Best Corrected Visual Acuity; IP – Investigational products; N – Total number of subjects; n – Number of subjects; PPS-BCVA – Per-protocol set for BCVA
Percentages were based on the number of subjects in the Randomized Set

Reviewer's Comments: *The groups are similar. No concerns are raised from the protocol deviations.*

Demographics and Baseline Characteristics

Table 16. Demographic characteristics by treatment groups for the randomized set

	SB11 N = 351	Lucentis N = 354
Age (years)		
Mean	74.4	73.8
SD	8.00	8.92
Median	75.0	75.0
Min, Max	51, 96	51, 94
Gender, n (%)		
Male	149 (42.5)	153 (43.2)
Female	202 (57.5)	201 (56.8)
Race, n (%)		
White	297 (84.6)	300 (84.7)
Asian	51 (14.5)	52 (14.7)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0.0)
Other	2 (0.6)	2 (0.6)
Ethnicity, n (%)		
Other	320 (91.2)	319 (90.1)
Mixed Ethnicity	14 (4.0)	20 (5.6)
Indian (Indian Subcontinent)	10 (2.8)	11 (3.1)
Hispanic or Latino	6 (1.7)	4 (1.1)
Japanese	1 (0.3)	0 (0.0)
Country, n (%)		
Czech Republic	82 (23.4)	77 (21.8)
Hungary	71 (20.2)	71 (20.1)
US	55 (15.7)	58 (16.4)
Poland	47 (13.4)	49 (13.8)
Korea	40 (11.4)	40 (11.3)
Russia	21 (6.0)	21 (5.9)
Germany	14 (4.0)	17 (4.8)
United Kingdom	11 (3.1)	10 (2.8)
India	10 (2.8)	11 (3.1)
Region, n (%)		
EU	214 (61.0)	214 (60.5)
US	55 (15.7)	58 (16.4)
Others	82 (23.4)	82 (23.2)
Weight (kg)		
n	351	353
Mean	75.95	75.95

	SB11 N = 351	Lucentis N = 354
SD	16.27	16.67
Median	75.00	75.00
Min, Max	43.9, 143.3	40.7, 149.6
Height (cm)		
n	351	353
Mean	164.90	165.40
SD	9.899	9.457
Median	165.00	165.60
Min, Max	132.1, 196.0	140.0, 198.1
BMI (kg/m^2)		
n	351	353
Mean	27.80	27.65
SD	4.740	5.151
Median	27.30	26.90
Min, Max	16.2, 45.6	18.0, 54.3

- Source: Reviewer's analysis. The table corresponds to the table 11-2 of the complete study report
- BMI, Body mass index; EU, European Union; N, Total number of subjects; n, Number of subjects; SD, Standard deviation; US, United States.

Reviewer's Comments: *The groups are similar. No concerns are raised from the baseline characteristics.*

Table 17: Baseline Ocular Characteristics by Treatment group (Randomized Set)

Baseline Characteristic	SB11 N=351	Lucentis N=354
BCVA, number of ETDRS letters		
Mean (SD)	58.7 (10.42)	57.9 (10.82)
Median	60.0	59.0
Min, Max	34, 73	33, 73
CST, µm		
Mean	403.55	411.65
SD	113.806	121.307
Median	390.00	396.00
Min, Max	166.0, 843.0	143.0, 830.0
CPT, µm		
Mean	312.91	324.68
SD	135.142	142.142
Median	282.50	294.75

Baseline Characteristic	SB11 N=351	Lucentis N=354
Min, Max	89.5, 908.0	26.5, 847.5
CRLT, µm		
Mean	348.38	360.08
SD	137.133	143.915
Median	319.00	329.25
Min, Max	112.5, 975.5	42.0, 887.0
Total lesion area (mm^2)		
Mean	8.212	8.326
SD	4.9763	5.4720
Median	7.510	7.345
Min, Max	0.03, 21.40	0.00, 22.66
Area of CNV (mm^2)		
Mean	7.988	8.135
SD	4.8455	5.3760
Median	7.390	7.175
Min, Max	0.00, 21.40	0.00, 22.66
Lesion type, n (%)		
No CNV	0 (0.0)	1 (0.3)
Classic CNV	28 (8.0)	27 (7.6)
Classic and Occult	115 (32.8)	124 (35.0)
Occult	208 (59.3)	202 (57.1)
Disciform scar	0 (0.0)	0 (0.0)
Years since first diagnosis of neovascular AMD		
Mean	0.21	0.13
SD	0.557	0.411
Median	0.10	0.10
Min, Max	0.0, 4.5	0.0, 7.0
IOP (mmHg)		
Mean	15.28	15.16
SD	2.754	2.665
Median	15.00	15.00
Min, Max	8.0, 22.0	7.0, 24.0

Source: Study SB11-G31-AMD CSR, Tables 11-3
AMD – Age-related macular degeneration; BCVA – Best Corrected Visual Acuity; CNV – Choroidal neovascularization; CPT – Central point thickness; CRLT – Central retinal lesion thickness; CST – Central subfield thickness;

Reviewer's Comments: *The groups are similar. No concerns are raised from the baseline characteristics.*

Analysis of Primary Clinical Endpoint(s)

The equivalence of SB11 to US-licensed Lucentis to treat subjects with nAMD was evaluated based on the endpoint of the change in BCVA at Week 8 from the Baseline. The Applicant discussed the endpoint with FDA and obtained FDA agreement with their proposal prior to the study start. The equivalence in BCVA was declared if the 2-sided 90% confidence interval (CI) of the difference in least squares (LS) mean change from the Baseline to Week 8 between study groups lies within the [−3 letters, 3 letters] margin . The primary analyses by the statistical reviewer are reported in the following table. **A difference between groups was not demonstrated in any analysis.**

Table 18: Analysis of change from the Baseline in best corrected visual acuity at week 8 for different analysis populations and different missing imputation methods

Analysis Population	Imputation Method	Treatment Groups	Mean (SE)	LS Mean (SE)	Difference (SB11 − Lucentis)	
					Mean (SE)	90% CI
FAS[a]	MI-MAR	SB11 (N = 351)	6.5 (0.44)	6.18 (0.52)	−0.80 (0.62)	-1.83, 0.22
		Lucentis (N = 353)	7.3 (0.44)	6.99 (5.1)		
FAS Available set	NA	SB11 (N = 351)	6.5 (0.45)	6.26 (0.51)	−0.82 (0.62)	−1.85, 0.20
		Lucentis (N = 353)	7.4 (0.44)	7.08 (0.51)		
PPS-BCVA	NA	SB11 (N = 336)	6.6 (0.45)	6.39 (0.52)	−0.76 (0.64)	-1.8, 0.29
		Lucentis (N = 333)	7.4 (0.45)	7.15 (5.2)		
FAS	LOCF	SB11 (N = 351)	6.4 (0.45)	6.12 (0.52)	−0.83 (0.63)	-1.86, 0.198
		Lucentis (N = 353)	7.23 (0.44)	6.96 (5.1)		
FAS	MI-MNAR	SB11 (N = 351)	6.16 (0.52)	6.16 (0.52)	−0.77 (0.62)	-1.8, 0.25
		Lucentis (N = 353)	6.93 (0.51)	6.93 (5.1)		

- *[a] Pre-specified primary analysis.*
- *CI, Confidence interval; LOCF, Last observation carry forward; MAR, Missing-at-random; MI, Multiple imputation; MNAR, Missing-not-at-random; N, Total number of subjects; n, Total number of subjects with available data at Week 8; SE, Standard error; LS, Least Square; NA, Not applicable.*
- *Inferential statistics were based on analysis of covariance model with the Baseline BCVA as a covariate and region (country) and treatment as fixed factors.*
- *For analysis of MI-MAR, we used the data provided by the applicant. The dataset had 1000 replications of dataset and each dataset includes the replications of missing imputations along with the non-missing*

observations. We ran the same method that was used in primary analysis for each of the replication of dataset. Subsequently, the pooled means, SE and the 90% CI were computed.

- *For MI-MNAR, we replace the observations of those subjects who was missing due to AE in the MI-MAR dataset. The replacement rule as imputed total BCVA = MAR BCVA - .2* MAR BCVA.*

In the FAS, the LS mean change in BCVA at Week 8 from the Baseline in the SB11 group and US-licensed Lucentis group were 6.18 letters and 6.99 letters respectively. The adjusted treatment difference in change in BCVA was −0.80 and the 90% CI was [−1.83 letters, 0.22 letters]. The CI was inside the [−3 letters, 3 letters] margin , supporting the study groups comparability with respect to efficacy and supporting a demonstration that there are no clinically meaningful differences between SB11 and US-licensed Lucentis.

Potential Effects of Missing Data

There were 5 missing observations in SB11 group and 6 missing observations in the US-licensed Lucentis group at Week 8, the endpoint evaluation time. Among them, there was one subject in the US-licensed Lucentis group who was withdrawn due to adverse events. In the primary analysis the missing observations were imputed using MI-MAR regression method. Sensitivity analysis were conducted using FAS excluding missing observations, PPS-BCVA, FAS with missing imputed by LOCF, and FSA with MNAR regression method. Missing efficacy data were handled according to the procedures pre-specified in the protocol. Primary efficacy study results were not significantly impacted by missing data.

The comparability observed in the primary analysis is robust against these different imputation methods, thus supporting a demonstration of no clinically meaningful differences between SB11 and US-licensed Lucentis.

6.3 Review of Safety Data

6.3.1 Methods

Categorization of Adverse Events

Safety of SB11 and US-licensed Lucentis in Study SB11-G31-AMD was comparatively assessed by monitoring treatment-emergent adverse events (TEAEs, ocular/non-ocular), serious adverse events (SAEs, ocular/non-ocular), adverse events of special interest (AESI), clinical laboratory evaluations, ophthalmic assessments, and as well as immunogenicity which is an important safety aspect of therapeutic proteins.

6.3.2 Major Safety Results

Deaths

Table 19: Deaths by Week 52

Country/ Center/ Patient Number	Age/ Sex	Cause of Death	Start Date (Study Day)/ Death Date (Study Day)
Study SB11-G31-AMD			
SB11			
USA/ 2816/ (b) (6)	73 M	COPD worsening	(b) (6) (142)/ (b) (6) (158)
USA/ 2822/	68 F	Cause unknown	(310)/ (310)
Lucentis			
CZE/ 0403/ (b) (6)	79 M	Infection of unknown etiology	(b) (6) (125)/ (b) (6) (188)
POL/ 1001/	82 M	Pneumonia	(226)/ 247)
POL/ 1002/	79 F	Cause unknown	(141)/ (b) (6) (218)
USA/ 2822	87 F	Cause unknown	(164)/ (b) (6) (164)

Source: Study SB11-G31-AMD CSR, Section 14.3.4

Reviewer's Comment: *The deaths which occurred during the study in which the cause of death was known are consistent with the age and past medical history of the subjects enrolled. There were no significant differences between groups. No concerns are raised by the comparison.*

Table 20: Treatment Emergent Adverse Events in ≥ 2% (Safety Set) Week 52

System Organ Class Preferred term	Study SB11-G31-AMD	
	SB11 N = 350 n (%) Events	Lucentis N = 354 n (%) Events
Any adverse event	**255 (72.9) 910**	**256 (72.3) 897**
Eye disorders	**135 (38.6) 247**	**130 (36.7) 247**
Neovascular age-related macular degeneration	25 (7.1) 25	23 (6.5) 23
Visual acuity reduced	23 (6.6) 30	23 (6.5) 32
Conjunctival hemorrhage	19 (5.4) 23	19 (5.4) 21
Cataract	13 (3.7) 16	7 (2.0) 11
Macular degeneration	10 (2.9) 11	9 (2.5) 9
Vitreous detachment	8 (2.3) 11	6 (1.7) 7
Posterior capsular opacification	7 (2.0) 12	3 (0.8) 3
Visual impairment	6 (1.7) 6	14 (4.0) 16
Dry eye	5 (1.4) 8	8 (2.3) 13
Ocular hypertension	3 (0.9) 6	8 (2.3) 16
Vitreous floaters	3 (0.9) 3	9 (2.5) 9
Gastrointestinal disorders	**34 (9.7) 46**	**29 (8.2) 45**
Constipation	9 (2.6) 9	0 (0.0) 0
Diarrhea	3 (0.9) 6	8 (2.3) 8
Infections and infestations	**114 (32.6) 174**	**98 (27.7) 142**
Nasopharyngitis	37 (10.6) 42	35 (9.9) 40
Influenza	15 (4.3) 15	11 (3.1) 11
Urinary tract infection	14 (4.0) 21	8 (2.3) 11
Bronchitis	13 (3.7) 13	6 (1.7) 8
Upper respiratory tract infection	9 (2.6) 10	3 (0.8) 3
Injury, poisoning and procedural complications	**35 (10.0) 49**	**32 (9.0) 44**
Fall	8 (2.3) 9	8 (2.3) 8
Investigations	**47 (13.4) 89**	**46 (13.0) 131**
Intraocular pressure increased	24 (6.9) 47	29 (8.2) 77
Blood Pressure increased	4 (1.1) 4	9 (2.5) 11
Musculoskeletal and connective tissue disorders	**35 (10.0) 54**	**38 (10.7) 55**
Back pain	12 (3.4) 12	8 (2.3) 8
Arthralgia	6 (1.7) 7	7 (2.0) 7
Nervous system disorders	**31 (8.9) 42**	**29 (8.2) 36**
Headache	14 (4.0) 16	10 (2.8) 10
Dizziness	66 (1.7) 6	7 (2.0) 8
Renal and urinary disorders	**18 (5.1) 24**	**13 (3.7) 17**
Hematuria	7 (2.0) 8	2 (0.6) 2
Respiratory, thoracic and mediastinal disorders	**25 (7.1) 28**	**17 (4.8) 19**

System Organ Class Preferred term	Study SB11-G31-AMD	
	SB11 N = 350 n (%) Events	Lucentis N = 354 n (%) Events
Cough	5 (1.4) 6	8 (2.3) 8
Vascular disorders	**28 (8.0) 32**	**32 (9.0) 45**

Source: Module 2.7.4, Study SB11-G31-AMD, Table 9

Reviewer's Comment: *The overall ocular adverse event rates were similar between SB11 and US-licensed Lucentis. No concerns are raised from the comparison.*

Dropouts and/or Discontinuations

Table 21: Adverse Events Leading to Study Discontinuation (Safety Set) – Week 52

System Organ Class Preferred term	Study SB11-G31-AMD	
	SB11 N = 350 n (%) Events	Lucentis N = 354 n (%) Events
Any adverse event leading to discontinuation	**9 (2.6) 12**	**5 (1.4) 8**
Cataract	1 (0.3) 1	0 (0.0) 0
Iridocyclitis	1 (0.3) 1	0 (0.0) 0
Macular hole	1 (0.3) 1	0 (0.0) 0
Macular edema	1 (0.3) 1	0 (0.0) 0
Retinal hemorrhage	1 (0.3) 1	1 (0.3) 1
Retinal pigment epithelial tear	1 (0.3) 1	0 (0.0) 0
Subretinal fluid	1 (0.3) 1	1 (0.3) 1
Visual acuity reduced	1 (0.3) 1	0 (0.0) 0
Macular degeneration	0 (0.0) 0	1 (0.3) 1
Macular fibrosis	0 (0.0) 0	1 (0.3) 1
Retinal degeneration	0 (0.0) 0	1 (0.3) 2
Endophthalmitis	1 (0.3) 1	0 (0.0) 0
Pathological fracture	0 (0.0) 0	1 (0.3) 1
Plasma cell myeloma	0 (0.0) 0	1 (0.3) 1
Cerebral circulatory failure	1 (0.3) 1	0 (0.0) 0
Cerebral hemorrhage	1 (0.3) 1	0 (0.0) 0
Speech disorders	1 (0.3) 1	0 (0.0) 0

Source: Module 2.7.4, Study SB11-G31-AMD, Table 17

Reviewer's Comment: *There were no significant differences between groups. No concerns are raised by the comparison.*

6.3.3 Additional Safety Evaluations

Table 22: Ocular Serious Adverse Events (Safety Set) – Week 52

System Organ Class Preferred term	Study SB11-G31-AMD	
	SB11 N = 350 n (%) Events	Lucentis N = 354 n (%) Events
Any ocular SAE	**10 (2.9) 14**	**8 (2.3) 8**
Eye disorders	**8 (2.3) 12**	**8 (2.3) 8**
Cataract	2 (0.6) 2	0 (0.0) 0
Visual acuity reduced	2 (0.6) 3	1 (0.3) 1
Iridocyclitis	1 (0.3) 1	0 (0.0) 0
Macular edema	1 (0.3) 1	1 (0.3) 1
Retinal hemorrhage	1 (0.3) 1	1 (0.3) 1
Retinal pigment epithelial tear	1 (0.3) 1	0 (0.0) 0
Sub-retinal fluid	1 (0.3) 1	1 (0.3) 1
Uveitis	1 (0.3) 1	0 (0.0) 0
Vitritis	1 (0.3) 1	0 (0.0) 0
Cataract subcapsular	0 (0.0) 0	1 (0.3) 1
Macular degeneration	0 (0.0) 0	2 (0.6) 2
Retinal artery occlusion	0 (0.0) 0	1 (0.3) 1
Infections and infestations	**2 (0.6) 2**	**0 (0.0) 0**
Endophthalmitis	2 (0.6) 2	0 (0.0) 0

Source: Module 2.7.4, Study SB11-G31-AMD, Table 14

Reviewer's Comment: *Ocular serious adverse events occurred in less than 3% of subjects in both treatment groups. The reported rates in each group were similar. No concerns are raised from the comparison.*

Table 23: Non-ocular Serious Adverse Events (Safety Set) – Week 52

System Organ Class Preferred term	Study SB11-G31-AMD	
	SB11 N = 350 n (%) Events	Lucentis N = 354 n (%) Events
Any non-ocular SAE	**41 (11.7) 52**	**42 (11.9)**
Anemia	1 (0.3) 1	1 (0.3) 1
Atrial fibrillation	4 (1.1) 4	3 (0.8) 3
Cardiac failure congestive	2 (0.6) 2	2 (0.6) 2
Angina pectoris	1 (0.3) 1	1 (0.3) 1
Coronary artery disease	1 (0.3) 1	0 (0.0) 0
Left ventricular failure	1 (0.3) 1	0 (0.0) 0
Myocardial ischemia	1 (0.3) 1	0 (0.0) 0
Angina unstable	0 (0.0) 0	1 (0.3) 1
Bradycardia	0 (0.0) 0	1 (0.3) 1
Vestibular disorder	1 (0.3) 1	0 (0.0) 0
Gastric ulcer hemorrhage	0 (0.0) 0	1 (0.3) 1
Inguinal hernia	0 (0.0) 0	1 (0.3) 1
Intra-abdominal hemorrhage	0 (0.0) 0	1 (0.3) 1
Pancreatitis acute	0 (0.0) 0	2 (0.6) 2
Small intestinal obstruction	0 (0.0) 0	1 (0.3) 1
Bile duct stone	1 (0.3) 1	0 (0.0) 0
Cholelithiasis	1 (0.3) 1	1 (0.3) 1
Cholecystitis	0 (0.0) 0	1 (0.3) 1
Pneumonia	1 (0.3) 1	1 (0.3) 1
Pneumonia bacterial	1 (0.3) 1	0 (0.0) 0
Urinary tract infection	1 (0.3) 1	1 (0.3) 1
Bacterial colitis	0 (0.0) 0	1 (0.3) 1
Cystitis	0 (0.0) 0	2 (0.6) 2
Diverticulitis intestinal hemorrhagic	0 (0.0) 0	1 (0.3) 1
Hepatitis C	0 (0.0) 0	1 (0.3) 1
Infection	0 (0.0) 0	1 (0.3) 1
Meningitis aseptic	0 (0.0) 0	1 (0.3) 1
Pulmonary tuberculosis	0 (0.0) 0	1 (0.3) 1
Sepsis	0 (0.0) 0	1 (0.3) 1
Anemia postoperative	1 (0.3) 1	0 (0.0) 0
Ankle fracture	1 (0.3) 1	0 (0.0) 0
Femoral neck fracture	1 (0.3) 1	2 (0.6) 2
Hand fracture	1 (0.3) 1	0 (0.0) 0
Humerus fracture	1 (0.3) 1	0 (0.0) 0
Pneumothorax traumatic	1 (0.3) 1	0 (0.0) 0

System Organ Class Preferred term	Study SB11-G31-AMD	
	SB11 N = 350 n (%) Events	Lucentis N = 354 n (%) Events
Postoperative ileus	1 (0.3) 1	0 (0.0) 0
Joint dislocation	0 (0.0) 0	1 (0.3) 1
Lower limb fracture	0 (0.0) 0	1 (0.3) 1
Radius fracture	0 (0.0) 0	1 (0.3) 1
Spinal compression fracture	0 (0.0) 0	1 (0.3) 1
Subdural hematoma	0 (0.0) 0	1 (0.3) 1
Upper limb fracture	0 (0.0) 0	1 (0.3) 1
Dehydration	1 (0.3) 1	0 (0.0) 0
Spinal osteoarthritis	1 (0.3) 1	0 (0.0) 0
Arthralgia	0 (0.0) 0	1 (0.3) 1
Back pain	1 (0.1) 1	1 (0.3) 1
Myalgia	0 (0.0) 0	1 (0.3) 1
Neck pain	0 (0.0) 0	1 (0.3) 1
Chronic lymphocytic leukemia	1 (0.3) 1	0 (0.0)
Colon cancer	1 (0.3) 1	0 (0.0)
Endometrial adenocarcinoma	1 (0.3) 1	0 (0.0)
Lung adenocarcinoma	1 (0.3) 1	0 (0.0)
Mantle cell lymphoma	1 (0.3) 1	0 (0.0)
Pancreatic carcinoma	1 (0.3) 1	0 (0.0)
Prostate cancer	1 (0.3) 1	1 (0.3)
Schwannoma	1 (0.3) 1	0 (0.0)
Squamous cell carcinoma of lung	1 (0.1) 1	0 (0.0)
Uterine cancer	1 (0.3) 1	0 (0.0)
Breast cancer female	0 (0.0) 0	1 (0.3)
Plasma cell myeloma	0 (0.0) 0	1 (0.3)
Cerebral circulatory failure	1 (0.3) 1	0 (0.0) 0
Cerebral hemorrhage	1 (0.3) 1	0 (0.0) 0
Syncope	1 (0.3) 1	0 (0.0) 0
Acute kidney injury	3 (0.9) 3	1 (0.3) 1
Renal colic	1 (0.3) 1	0 (0.0) 0
Calculus bladder	0 (0.0) 0	1 (0.3) 1
Nephrolithiasis	0 (0.0) 0	1 (0.3) 1
Renal artery stenosis	0 (0.0) 0	1 (0.3) 1
Urethral stenosis	0 (0.0) 0	1 (0.3) 1
Benign prostatic hyperplasia	0 (0.0) 0	1 (0.3) 1
Metrorrhagia	0 (0.0) 0	1 (0.3) 1
Chronic obstructive pulmonary disease	2 (0.6) 2	0 (0.0) 0

System Organ Class Preferred term	Study SB11-G31-AMD	
	SB11 N = 350 n (%) Events	Lucentis N = 354 n (%) Events
Angioedema	0 (0.0) 0	1 (0.3) 1
Rash	0 (0.0) 0	1 (0.3) 1
Hypertension	3 (0.9) 3	0 (0.0) 0
Aortic aneurysm	1 (0.3) 1	0 (0.0) 0
Iliac artery embolism	1 (0.3) 1	0 (0.0) 0
Peripheral ischemia	1 (0.3) 1	0 (0.0) 0
Hematoma	0 (0.0) 0	1 (0.3) 1

Source: Module 2.7.4, Study SB11-G31-AMD, Table 16

Reviewer's Comment: *The reported rates in each group were similar. No concerns are raised from the comparison.*

6.4 Clinical Conclusions

Study SB11-G31-AMD demonstrated that SB11 is comparable to US-licensed Lucentis with respect to the change in best-corrected visual acuity (BCVA) from baseline to Week 8. The adverse event profile was not significantly different between subjects treated with SB11 and US-licensed Lucentis. No concerns are raised from the comparison.

Authors:

Lucious Lim, MD
Medical Officer

William M. Boyd, M.D.
Deputy Division Director

Yushuf Sharker, PhD
Statistical Reviewer, OB/DBIV

Greg Soon, PhD
Statistical Team Leader, OB/DBIV

6.5 Extrapolation

The Applicant submitted data and information in support of a demonstration that SB11 is highly similar to US-licensed Lucentis notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between SB11 and US-licensed Lucentis in terms of safety, purity and potency.

The Applicant is seeking licensure of SB11 for the following indication(s) for which US-licensed Lucentis has been previously licensed and for which SB11 has not been directly studied: macular edema following retinal vein occlusion (RVO) and myopic choroidal neovascularization (mCNV).

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of SB11 as a biosimilar for each such indication for which licensure is sought and for which US-licensed Lucentis has been previously approved. This Applicant's justification was evaluated and considered adequate, as summarized below.

> The mechanism of action of ranibizumab including the structure and drug-target interactions in each condition is consistent across all approved indications. For each of the indications, effective treatment can be expected by binding to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, and myopic choroidal neovascularization by reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation; and the analysis of the known safety and immunogenicity profiles of ranibizumab across each of the indications is consistent and there are no known differences in expected toxicities for each indication.

Therefore, the totality of the evidence provided by the Applicant supports licensure of SB11 for each of the following indication(s) for which Samsung is seeking licensure of SB11: neovascular (Wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO) and myopic choroidal neovascularization (mCNV).

6.5.1 Division of Ophthalmology

Mechanism of Action

The Applicant provided adequate justification to support that SB11 has the same known and potential mechanisms of action as US-licensed Lucentis for Neovascular (wet) AMD, RVO, and mCNV.

Pharmacokinetics (PK)

Over all the post-dose PK sampling time-points, the arithmetic mean concentrations were below the concentration range of ranibizumab that is necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an *in vitro* cellular proliferation assay. Given the low concentrations observed in both treatment groups, the levels are not considered clinically meaningful and unlikely to have any implications on systemic safety.

Immunogenicity

The incidences of Anti-Drug Antibody (ADA) and Neutralizing Antibodies (Nab) were very low and comparable between SB11 and US-licensed Lucentis treatment groups

across all timepoints up to Week 52 in the comparative clinical study. AMD, RVO and mCNV do not differ in clinical characteristics that would affect immunogenicity. The low incidences do not pose a safety concern for any of the US-licensed Lucentis indications.

Toxicity

AMD, RVO and mCNV do not differ in clinical characteristics that would affect toxicity. The safety profile resulting from the intravitreal administration of a comparable anti-VEGF product would not be expected to differ on the basis of the indication.

Conclusions

The Division of Ophthalmology concludes that the Applicant has provided sufficient scientific justification (based on the mechanism of action, and toxicity profile) for extrapolation of the data and information submitted in the application to support licensure of SB11 for RVO, and mCNV.

Author:
William M. Boyd, M.D.
Deputy Division Director

6. Labeling Recommendations

7.1 Nonproprietary Name

The Applicant's proposed nonproprietary name, ranibizumab-nuna, was found to be conditionally acceptable by the Office of Medication Error Prevention and Risk Management in a letter to the applicant dated 7/11/2021.

7.2 Proprietary Name

The proposed proprietary name for ranibizumab-nuna is conditionally approved as Byooviz. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded the name was acceptable in a letter to the applicant dated 12/15/2020.

7.3 Other Labeling Recommendations

The proposed labeling which follows, submitted to the application on August 13, 2021, is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product. In a September 8, 2021, internal teleconference between the Division of Ophthalmology and DMEPA, DMEPA expressed concern with the current expression of the strength presentation on the carton and container of 0.5 mg. They recommended revision to a strength presentation of 0.5 mg/0.05 mL.

In a review dated September 10, 2021, DMEPA also recommended the following additional labeling revisions be made **PRIOR** to approval:

> A. Include the statement “Discard unused portion” following the single dose vial statement on the back panel of the vial.
>
> B. In the *Dosage Forms and Strengths* section of the Highlights of Prescribing Information and Full Prescribing Information, include the intended dosage in mg units immediately after the dose volume so that the first line reads “Single-dose glass vial designed to provide 0.05 mL (0.5 mg) for intravitreal injection…”

In a review dated September 13, 2021, the Office of Biotechnology Products (OBP) labeling reviewer stated that the prescribing information submitted on August 13, 2021, is **NOT** acceptable due to the lack of the dosage form in required parts and sections of the Prescribing Information. The Division of Ophthalmology does not agree with the conclusions from DMEPA or the OBP labeling reviewer that the labeling submitted by the applicant on August 13, 2021, is unacceptable. SB11 is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use that has been developed as a proposed biosimilar to US-licensed Lucentis. The submitted labeling from August 13, 2021, is consistent with the approved labeling for US-licensed Lucentis. Both DMEPA and the OBP labeling reviewer were in attendance for the September 8, 2021, internal teleconference with the Division of Ophthalmology where these specific issues were discussed. In the meeting, the Signatory Authority decided that SB-11’s labeling, i.e., package insert carton and container labeling, should be consistent with the reference product, US-licensed Lucentis, with regard to the issues raised by DMEPA and OBP.

21 page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 14.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Author:
William M. Boyd, M.D.
Deputy Division Director

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

Author:
William M. Boyd, M.D.
Deputy Division Director

10. Pediatrics

The Pediatric Review Committee (PeRC) discussed this application on August 10, 2020. The labeling for U.S.-licensed Lucentis does not contain pediatric information for the indications for which the applicant is seeking licensure, and PREA requirements were waived for, or inapplicable to, U.S.-licensed Lucentis for those indications. Therefore, the agency has determined that, at this time, no pediatric studies will be required under PREA for this BLA. See QA.I.16, FDA Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act (Rev. 2) (Sept. 2021).

Author:

William M. Boyd, M.D.
Deputy Division Director

Wiley A. Chambers, MD
Division Director

11. REMS and Postmarketing Requirements and Commitments

11.1 Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2 Recommendations for Postmarket Requirements and Commitments

The Office of Pharmaceutical Quality has recommended the following post-marketing commitments and the approval letter will include them:

4108-1

Provide bioburden test method suitability data for in-process samples from at least one additional lot of SB11 drug substance.

The timetable you submitted on July 13, 2021, states that you will conduct this study and submit the Final Report results by December 31, 2021.

4108-2

Perform real-time drug product commercial container closure system leachable studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at regular intervals through the end of shelf life. The study results will be updated annually in the BLA Annual Report. The final results of the study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

The timetable you submitted on July 13, 2021, states that you will conduct this study and submit the Final Report results by December 31, 2024.

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."

Author:
William M. Boyd, M.D.
Deputy Division Director

12. Comments to Applicant

There are no additional comments for the applicant.

13. Division Director Comments

13.1 Division Director (OND – Clinical) Comments

The Review Team is in agreement that the application supports SB11 is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components. SB11 is included in a single-dose vial with sufficient drug product to enable administration of 0.5 mg of the 10mg/mL, the same strength as that of US-licensed Lucentis. The dosage form and route of administration is also the same as that of US-licensed Lucentis. There are no residual uncertainties from a product quality perspective. The Product Quality review team in a review dated September 16, 2021, concluded that there was sufficient comparative analytical data (i.e., structural and functional characterization) between SB11 and US-licensed Lucentis to support a demonstration that SB11 is highly similar to US-licensed Lucentis.

Systemic exposure of SB11 and US-licensed Lucentis was evaluated in the a subset of patients with neovascular AMD in the comparative clinical study SB11-G31-AMD. There were comparable, low systemic exposures of both SB11 and US-licensed Lucentis supporting a demonstration of no clinically meaningful differences between SB11 and

US-licensed Lucentis. There were also comparable, low incidences of ADA/NAb formation in both SB11 and US-licensed Lucentis supporting a demonstration of no clinically meaningful differences.

Study SB11-G31-AMD supported no clinically meaningful differences in efficacy or safety between SB11 and US-licensed Lucentis in patients with AMD. In Study SB11-G31-AMD, patients with bilateral disease were concurrently treated with US-licensed Lucentis in the contralateral eye. For those who were randomized to receive SB11 in the study eye, this contralateral administration exposed individuals to both SB11 and US-licensed Lucentis concurrently. There are no residual uncertainties from the clinical or clinical statistical perspectives regarding a demonstration that SB11 is biosimilar to US-licensed Lucentis.

The Applicant provided adequate scientific justification for extrapolation to the other indications listed in the US-licensed Lucentis package insert being sought for licensure (i.e., RVO and mCNV) based on: 1) the mechanism of action of ranibizumab, including the structure and drug-target interactions in each condition being consistent across all approved indications. For each of the indications being sought for licensure, effective treatment can be expected by binding to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, and myopic choroidal neovascularization by reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation; and 2) the analysis of the known safety and immunogenicity profiles of ranibizumab across each of the indications being sought is consistent and there are no known differences in expected toxicities for each indication being sought. The data in this BLA and this justification supports licensure of SB11 as a biosimilar for the following indications for which US-licensed Lucentis has been previously approved: neovascular (wet) age-related macular degeneration, macular edema following retinal vein occlusion and myopic choroidal neovascularization. There are no residual uncertainties regarding the scientific justification for extrapolation.

Author:
Wiley A. Chambers, M.D.
Division Director

14. Appendices

14.1 Financial Disclosure

Covered Clinical Study: SB11-G31-AMD

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 606		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.2 Nonclinical Appendices

14.2.1 Nonclinical Pharmacology

In Vivo Pharmacology

No studies were conducted.

14.2.2 Nonclinical Pharmacokinetics

No studies were conducted.

14.2.3 General Toxicology

A 4-week repeated dose toxicity study in female cynomolgus monkeys was conducted to demonstrate similarity in *in vivo* toxicological profiles between SB11 and US-licensed Lucentis. The final report for this study was previously reviewed under the initial IND submission (review copied below).

There were no ocular or systemic toxicologically significant findings following bilateral injection of 0.5 mg/eye SB11 or US-licensed Lucentis once every two weeks for 4 weeks (a total of 3 administrations). Therefore, this study did not identify differences in the toxicological profile between SB11 and US-licensed Lucentis.

The study had the following limitation: justifications for dose selection/frequency, endpoint selection/methods, animal number and study duration were not provided. ERG analysis was insufficient, and no assurance was provided that histopathologic sections included a section through the macula/fovea. Given the study limitations, the submitted monkey study alone was not considered sufficient to provide adequate safety support.

The Product Quality review team concluded there was sufficient comparative analytic similarity data (i.e., structural and functional characterization) between SB11 and US-licensed Lucentis to support safety. As such, the 4-week monkey study provides additional *in vivo* support regarding a demonstration of biosimilarity between SB11 and US-licensed Lucentis.

Single-Dose Toxicity/Toxicokinetics

No studies were conducted.

Repeat-Dose Toxicity/Toxicokinetics

Study title: A 4-Week Repeat Dose Toxicity Study of SB11 in Cynomolgus Monkeys

Study no.:	(b) (4) 327-007
Study report location:	DocuBridge Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 21, 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SB11 10 mg/mL, lot # P74602A, 99.9% pure Lucentis 10 mg/mL (US sourced), lot # 3068002

Key Study Findings:

- No test article-related ocular or systemic toxicities were identified following IVT administration of SB11 and US-licensed Lucentis at a dose of 0.5 mg/eye, once every 2 weeks for 4 weeks (a total of 3 administrations). This dosing regimen exceeds the approved recommended dosing frequency of the US-licensed Lucentis (0.5 mg/eye, once monthly).
- There were no significant differences in *in vivo* toxicity profile between SB11 and US-licensed Lucentis; however, justification for dose selection/frequency, endpoint selection/methodology, animal number and study duration were not provided. In the absence of this information, study adequacy cannot be determined.

Methods

Doses:	0 (vehicle), 500 µg/eye SB 11, 500 µg/eye US-licensed Lucentis
Frequency of dosing:	Once every 2 weeks for 4 weeks (a total of 3 times)
Route of administration:	Intravitreal (IVT) injection to both eyes
Dose volume:	50 µL/eye
Formulation/Vehicle:	SB11 formulation buffer [10 mM histidine/HCl, 10% (w/v) trehalose, 0.01% polysorbate 20 (pH 5.5)]
Species/Strain:	Cynomolgus monkeys (*Macaca fascicularis)*
Number/Sex/Group:	4 females/group
Age:	3 years old
Weight:	2.56 to 3.24 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None with an impact in the interpretation of the study
Dosing solution analyses:	The date of manufacture of SB11 Drug Product 10 mg/mL was 12-7-2016 and the expiry date was 6-6-2017. The Drug Product stability covers the dosing period duration (1-11-2017 to 2-9-2017).

Observations and Results

Parameters	**Major findings**
Mortality:	Observed twice daily. There were no mortalities.
Clinical signs:	Observed twice daily. None was considered test article related.
Body weights:	Measured weekly. No SB11- or US-licensed Lucentis-related effects were observed.
Feed consumption:	Measured daily. No SB11- or US-licensed Lucentis-related effects were observed.
Ophthalmoscopy:	Slit lamp and indirect ophthalmoscopy measured prestudy and on Days 2, 8, 22, 29, and 30. No SB11 or US-licensed Lucentis-related effects were observed.
Intraocular pressure (IOP):	Measured prestudy, and on Days 1, 15, and 29 before dosing and 6 hours after dosing. No SB11 or US-licensed Lucentis-related effects were observed.
Electroretinography (ERG):	Measured prestudy and on Day 30. No SB11 or US-licensed Lucentis-related effects were observed. However, ERG evaluation was considered insufficient because there was no indication of light adaptation and only one luminescence intensity was used.
Electrocardiography (ECG):	Measured prestudy, Days 8 and 22 by standard leads I, II, and III. No SB11 or US-licensed Lucentis-related effects in heart rate, and PR, QRS, QT, and QTc intervals

Respiratory rate and body temperature:	Measured on Days 8 and 22. No SB11 or US-licensed Lucentis-related effects were observed.
Hematology and clinical chemistry:	Measured prestudy and on Day 31. No SB11 or US-licensed Lucentis-related effects were observed.
Gross pathology:	Conducted on Day 30. No SB11 or US-licensed Lucentis-related findings were observed.
Organ weights:	Conducted in lungs, submandibular glands, liver, heart, kidneys, ovaries, uterus, brain, spleen, thymus, pituitary, thyroids/parathyroids, adrenals. Absolute and relative (to body weight) uterus weights were statistically significantly lower in both SB11 and US-licensed Lucentis treated groups compared to controls (absolute mean values ± SD of 3.65 ± 0.85, 4.38 ± 0.46, and 5.0 ± 0.98 g, respectively; relative mean values of 1.328 ± 0.324, 1.553 ± 0.221, and 2.053 ± 0.181 g/kg respectively). There was no microscopic correlate. The change was not considered toxicologically relevant.
Histopathology:	Tissues evaluated: eyeball, lacrimal glands, optic nerve, standard battery of systemic tissues. No SB11 or US-licensed Lucentis-related findings were observed. It is not clear whether macula/fovea was assessed.
TK:	Not evaluated

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/s/

WILEY A CHAMBERS
09/17/2021 05:48:43 PM

WILLIAM M BOYD
09/17/2021 05:57:56 PM