EU Risk Management Plan for Byooviz (Ranibizumab)

RMP version to be assessed as part of this application:

RMP Version number: 3.1

Data lock point for this RMP: Feb 07, 2024

Date of final sign off: Apr 05, 2024

Rationale for submitting an updated RMP: Updated in response to European Medicines Agency (EMA) validation issue comments regarding reverting back any change in SB11 EU RMP v3.0 not related to SB11 PFS addition unless clarified the rationale in the response

Summary of significant changes in this RMP:

1) Part II, Module SIII:
   - Removal of patients data phrase clarification for Phase III (SB11-G31-AMD)
2) Part II, Module SV:
   - Removal of post-authorization exposure information as the cumulative post-marketing exposure was not changed to a degree where the considerations on the risk evaluation need also to be updated
3) Part II, Module SIV
   - Removal of additional explanation for exposure data for special populations included or not in clinical trial development programmes
4) Part II, Module SVII:
   - Revert back to previous approved wordings used in SB11 EU RMP v2.1

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 2.1

Approved with procedure: EMEA/H/C/005545/IB/0005

Date of approval (opinion date): Nov 10, 2022

EU QPPV name: John Hart

EU QPPV signature: [redacted]

Date of signature: APR 8, 2024

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LIST OF ABBREVIATIONS

AMD	Age-related macular degeneration
ATC	The Anatomical Therapeutic Chemical Classification
CI	Confidence Interval
CNV	Choroidal neovascularization
DME	Diabetic macular oedema
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
HUVEC	Human Umbilical Vein Endothelial cells
IFU	Instructions for use
INN	International Non-proprietary Names
IOP	Intraocular pressure
ITV	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
PDR	Proliferative diabetic retinopathy
PDT	Photodynamic therapy
PFS	Pre-filled syringe
PL	Package leaflet
PM	Pathologic myopia
PSUR	Periodic Safety Update Report
PT	Preferred term
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
ROP	Retinopathy of prematurity
RRD	Rhegmatogenous retinal detachment
RVO	Retinal vein occlusion

SmPC	Summary of Product Characteristics
TEAE	Treatment Emergent Adverse Event
VEGF	Vascular endothelial growth factor
VEGF-A	Vascular endothelial growth factor A

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(International Non-proprietary Names (INN) or common name)**	Ranibizumab
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical Classification (ATC) Code)	Pharmacotherapeutic group: Ophthalmologicals, anti-neovascularization agents (ATC code: S01LA04)
Marketing Authorization Applicant	Samsung Bioepis NL B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Byooviz (company code: SB11)
Marketing authorization procedure	Centralised
Brief description of the product	Chemical class: Ranibizumab is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant deoxyribonucleic acid (DNA) technology.
	Summary of mode of action:

Table Part I.1 – Product Overview

	Ranibizumab is targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularization, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration (AMD), pathologic myopia (PM) and choroidal neovascularization (CNV) or to visual impairment caused by either diabetic macular oedema (DME) or macular oedema secondary to retinal vein occlusion (RVO).
	Important information about its composition: Byooviz is a biosimilar medicinal product to Lucentis containing the active ingredient ranibizumab. Byooviz is produced by recombinant DNA technology in *Escherichia coli* cells. One ml solution contains 10 mg ranibizumab. Each vial contains 2.3 mg of ranibizumab in 0.23 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab. One ml solution contains 10 mg ranibizumab. One pre-filled syringe contains 0.165 ml, equivalent to 1.65 mg ranibizumab. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab. Excipients are α,α-trehalose dihydrate; histidine hydrochloride, monohydrate; histidine; polysorbate 20; water for injections.
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	Current (if applicable): Byooviz is indicated in adults for: • The treatment of neovascular (wet) AMD • The treatment of visual impairment due to DME • The treatment of proliferative diabetic retinopathy (PDR) • The treatment of visual impairment due to macular oedema secondary to RVO (branch RVO or central RVO) • The treatment of visual impairment due to CNV

Table Part I.1 – Product Overview

	Proposed: N/A
Dosage in the EEA	Current (if applicable): Byooviz must be administered by a qualified ophthalmologist experienced in intravitreal injections. Posology The recommended dose for Byooviz is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. The interval between two doses injected into the same eye should be at least four weeks. Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME, PDR and RVO, initially, three or more consecutive, monthly injections may be needed. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters. If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Byooviz should be discontinued. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD and may be extended by up to one month at a time for DME. For PDR and RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly. The treatment of visual impairment due to CNV should be determined individually per patient based on disease activity. Some patients may only need one injection during the first 12 months; others may need more frequent treatment, including a monthly injection. For CNV secondary to

Table Part I.1 – Product Overview

	PM, many patients may only need one or two injections during the first year. *Ranibizumab and laser photocoagulation in DME and in macular oedema secondary to BRVO* There is some experience of ranibizumab administered concomitantly with laser photocoagulation. When given on the same day, ranibizumab should be administered at least 30 minutes after laser photocoagulation. Ranibizumab can be administered in patients who have received previous laser photocoagulation. *Ranibizumab and verteporfin photodynamic therapy (PDT) in CNV secondary to PM* There is no experience of concomitant administration of ranibizumab and verteporfin.
	Proposed: N/A
Pharmaceutical form(s) and strengths	Current (if applicable): 10 mg/ml solution for injection. Clear, colourless to pale yellow aqueous solution. One ml contains 10 mg ranibizumab. Each vial contains 2.3 mg of ranibizumab in 0.23 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab.
	Proposed (if applicable): 10 mg/ml solution for injection. Clear, colourless to pale yellow aqueous solution. One ml contains 10 mg ranibizumab. Each vial contains 2.3 mg of ranibizumab in 0.23 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab. One ml contains 10 mg ranibizumab. One pre-filled syringe contains 0.165 ml, equivalent to 1.65 mg ranibizumab. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable for a biosimilar.

Part II: Module SII - Non-clinical part of the safety specification

A series of *in vitro* studies including binding and cell-based assays, followed by an *in vivo* repeated dose toxicity study were performed to demonstrate similarity between Byooviz and Lucentis.

Key safety findings	Relevance to human usage
***In vitro* VEGF binding assay** The relative binding activities of Byooviz and Lucentis were analysed using enzyme-linked immunosorbent assay. The results showed that there was no significant difference between Byooviz and Lucentis in VEGF binding activity.	No relevance. No significant differences were detected compared to Lucentis.
***In vitro* potency assay (VEGF neutralization assay)** The VEGF neutralization potency of Byooviz and Lucentis were analysed using a VEGFR-2-dependent reporter gene system with the HEK293-NFAT-VEGFR2-Luc cell line. The results showed that there was no significant difference between Byooviz and Lucentis in neutralization potency.	No relevance. No significant differences were detected compared to Lucentis.
***In vitro* potency assay (Human Umbilical Vein Endothelial Cells (HUVEC) anti-proliferation assay)** The inhibitory activities of Byooviz and Lucentis on the human VEGF-A 165 were analysed using the HUVEC anti-proliferation assay by quantifying the intensity of fluorescence dye relative to the number of live cells. The result showed that there was no significant difference between Byooviz and Lucentis in HUVEC anti-proliferation potency.	No relevance. No significant differences were detected compared to Lucentis.

Toxicity

An *in vivo* repeated dose toxicity study using cynomolgus monkeys was conducted to demonstrate similarity in *in vivo* toxicological profiles between Byooviz and US Lucentis.

The other toxicity studies regarding reproductive and developmental toxicology, genotoxicity, and carcinogenicity were not performed for Byooviz in line with the EMA guideline "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)" [1] and “Guideline on similar

biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev.1)" [2].

Key safety findings	Relevance to human usage
***In vivo* repeated dose toxicity study in cynomolgus monkeys** A 4-week repeated dose toxicity study was performed to demonstrate similarity in *in vivo* toxicological profiles between Byooviz and US Lucentis in female cynomolgus monkeys. Byooviz and US Lucentis were well tolerated at a dose level of bilateral 0.5 mg/eye once every two weeks for 4 weeks, without toxicologically significant changes, which is consistent with the results of non-clinical studies of Lucentis performed by the originator.	No significant differences were detected compared to Lucentis. Therefore, findings from the reference product can be referred. In the reference product's studies, bilateral intravitreal administration of ranibizumab to cynomolgus monkeys results in dose-dependent ocular inflammatory effects, and a transient increase in post-dose intraocular pressure (IOP) was observed following intravitreal injections, irrespective of dose. Intraocular inflammation and transient increases in IOP are identified risks following intravitreal administration of ranibizumab. These events are followed in the RMP and will also be followed in the periodic safety update report (PSUR). These are also included in the SmPC Section 4.4 Special warnings and precautions for use.
Reproductive/developmental toxicity, genotoxicity, carcinogenicity As per "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)" [1] and "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev.1)" [2], studies were not conducted as Byooviz is a biosimilar product.	The systemic exposure to ranibizumab is low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/foetotoxic. The reference product's studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryo-foetal development. As the embryo-foetal development investigations were performed in healthy pregnant animals, and diseases may modify the permeability of the placenta towards a Fab fragment, ranibizumab should be used with caution in women of childbearing potential in general, and during pregnancy, in particular. In the SmPC Section 4.6 Fertility, pregnancy and lactation, it is stated that women of childbearing potential should use effective contraception during treatment and that for women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at

Key safety findings	Relevance to human usage
	least 3 months after the last dose of ranibizumab before conceiving a child.

Safety Pharmacology

As per "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)" [1] and "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev.1)" [2], safety pharmacology studies are not required for Byooviz.

Safety pharmacology endpoints were measured in the *in vivo* repeated dose toxicity study in cynomolgus monkeys. There were no treatment-related effects on the electrocardiography parameters, respiration rates and body temperature in all animals treated with Byooviz or US Lucentis during the dosing period.

Part II: Module SIII - Clinical trial exposure

Within the clinical development programme, the safety and tolerability of Byooviz have been studied in phase III randomised, double-masked, parallel group, multicentre study with innovator Lucentis in subjects with neovascular AMD. In this study, patients were randomly allocated in 1:1 ratio to receive either 0.5 mg Byooviz or 0.5 mg Lucentis in study eye. The study drug was administered via intravitreal route every 4 weeks up to Week 48 while the assessment was done on Week 52. A total of 704 patients were randomised (350 subjects in Byooviz and 354 subjects in Lucentis). The patients were evaluated for efficacy, safety, immunogenicity, pharmacokinetic, and quality of life endpoint.

Table SIII.1: Duration of exposure

Cumulative for all indications (person time)		
Duration of exposure	**Subjects**	**Byooviz exposure Person time (Years)**
<29 Days	350	26.68
29 to <57 Days	348	26.54
57 to <85 Days	346	26.32
85 to <113 Days	342	26.15
113 to <141 Days	341	25.94
141 to <169 Days	337	25.50
169 to <197 Days	330	25.14
197 to <225 Days	326	24.73
225 to <253 Days	322	24.41
253 to <281 Days	318	24.23
281 to <309 Days	314	23.83
309 to <337 Days	309	22.93
≥ 337 Days	213	2.25
Total	**350**	**304.63**

Table SIII.2: Age group and gender

Age group	**Subjects**		**Byooviz exposure Person time (Years)**	
	Male	**Female**	**Male**	**Female**
≥ 50 to < 65 years	24	18	21.22	14.36
≥ 65 to < 75 years	55	75	48.12	64.93
≥ 75 years	70	108	60.75	95.26
Total	**149**	**201**	**130.09**	**174.55**

Table SIII.3: Ethnic origin

Race origin	**Subjects**	**Byooviz exposure Person time (Years)**
Asian	51	44.24
Native Hawaiian or Other Pacific Islander	1	0.31
White	296	258.25

Race origin	Subjects	Byooviz exposure Person time (Years)
Other	2	1.84
Total	**350**	**304.63**

Byooviz has been also studied in an open-label, single group, single-dose clinical study to evaluate the usability of the pre-filled syringe (PFS) of Byooviz in subjects with Neovascular Age-Related Macular Degeneration (AMD) or Macular Oedema Secondary to Retinal Vein Occlusion (RVO). A total of 34 subjects were screened and enrolled in the study. All of the enrolled 34 (100.0%) subjects received Byooviz via PFS and completed the Day 7 visit. The mean age was 74.1 years (range: 59-88 years), and all subjects were white. The majority of subjects had neovascular AMD (94.1%) as a main indication.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria described below are based on the Phase III study SB11-G31-AMD:

Previous participation in clinical studies of ocular or systemic investigational products to treat neovascular AMD; Previous participation in any studies of ocular or systemic investigational products to treat ocular or systemic disease other than neovascular AMD within 90 days; Any previous intravitreal anti-VEGF treatment to treat neovascular AMD in either eye; Any previous systemic anti-VEGF treatment within 90 days.

Reason for exclusion	Would have affected efficacy endpoints and safety outcomes.
Is it considered to be included as missing information?	No
Rationale	Aim of studies to study ranibizumab in previously untreated eyes/patients.

Active or recent intraocular, extraocular and periocular inflammation or infection in either eye; History of idiopathic or autoimmune uveitis in either eye.

Reason for exclusion	There is a risk of worsening of an ongoing inflammatory process, or masking inflammation due to another cause. In addition, active intraocular inflammation may be associated with an increased IOP; administering an intraocular injection when there is ongoing inflammation is contraindicated.
Is it considered to be included as missing information?	No
Rationale	Active severe intraocular inflammation and active or suspected ocular or periocular infections are contraindications.

Presence of macular hole in the study eye; History of full-thickness macular hole in the study eye; Any concurrent macular abnormality other than AMD in the study eye.

Reason for exclusion	A patient's macular hole may cause a decline in VA, an important endpoint for safety and efficacy of an intervention for intraocular use. Therefore, the presence of a macular hole could confound efficacy outcomes.
Is it considered to be included as missing information?	No
Rationale	Patients with stage 3 or 4 macular hole included in precautions and warnings for use.

Any intravitreal injection of corticosteroid or intravitreal corticosteroid implant in the study eye within 180 days; Topical ocular corticosteroids administered for ⩾ 30 consecutive days in the study eye within 90 days; Prior treatment with pan-retinal photocoagulation in the study eye; Prior treatment involving macula with photodynamic therapy with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment in the study eye; Current use of systemic medications known to be toxic to the lens, retina or optic nerve; Any systemic treatment or therapy to treat neovascular AMD within 30 days.

Reason for exclusion	Precautionary measure. Use of these agents could interfere with interpretation of the clinical outcomes.
Is it considered to be included as missing information?	No
Rationale	Aim of studies to investigate ranibizumab in previously untreated eyes/patients.

Sub- or intra-retinal haemorrhage that comprises more than 50% of the entire lesion in the study eye, or presence of subfoveal blood equal to or more than one disc area in size; Presence of retinal pigment epithelial tears or rips involving the macula in the study eye; Presence of CNV in either eye due to other causes; Current vitreous haemorrhage in the study eye.

Reason for exclusion	Large subretinal haemorrhage can confound the assessment of the extent and size of the neovascular lesion that needs treatment.
Is it considered to be included as missing information?	No
Rationale	Not to include patient with disease features that would confound or make the results difficult to interpret.

Scar, fibrosis, or atrophy involving the centre of the fovea in the study eye; Aphakia or absence of the posterior capsule in the study eye; Presence of scleromalacia in either eye; Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters.

Reason for exclusion	These anatomic characteristics are representative of pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.
Is it considered to be included as missing information?	No
Rationale	Exclude patient with preexisting pathology from late stage disease where ranibizumab is unlikely to have an effect

History of vitrectomy surgery in the study eye; History of trabeculectomy or other filtration surgery in the study eye; History of submacular surgery or other surgical intervention for AMD in the study eye; Any other intraocular surgery (including cataract surgery) or periocular surgery in the study eye within 90 days (except for lid

surgery, which may not have taken place within 30 days); History of corneal transplantation surgery in the study eye.

Reason for exclusion	Vitreoretinal surgery is associated with the removal of the vitreous gel; thus, it may influence the pharmacodynamics of an intraocular pharmacological treatment. Precautionary measure due to limited data in patients with vitrectomized eyes.
Is it considered to be included as missing information?	No
Rationale	To not introduce confounding factors for interpretation of study results.

History or clinical evidence of diabetic retinopathy or DME in either eye.

Reason for exclusion	Poor glycemic control is correlated with worsening diabetic retinopathy and may confound the results.
Is it considered to be included as missing information?	No
Rationale	In a clinical trial setting exclude patients with poor control of common diseases/condition that may impact overall health and their ability to meet the requirements for study visits and assessments.

History of retinal detachment in the study eye.

Reason for exclusion	Precautionary measure.
Is it considered to be included as missing information?	No
Rationale	To not introduce confounding factors for interpretation of study results.

Any concurrent ocular condition in the study eye which could either increase the risk to the subject safety or which otherwise may interfere with evaluation of efficacy or safety.

Reason for exclusion	Precautionary measure.
Is it considered to be included as missing information?	No
Rationale	To not introduce confounding factors for interpretation of study results.

Uncontrolled ocular hypertension in the study eye; Advanced glaucoma or optic neuropathy in the study eye.

Reason for exclusion	Precautionary measure. Increased IOP and uncontrolled glaucoma is a general contraindication to any invasive intraocular procedure due to known possible associated complications.
Is it considered to be included as missing information?	No

Rationale	Injection of additional volume to the vitreous in patients with increased IOP or uncontrolled glaucoma should generally be avoided to prevent consequences of additional raised IOP including a temporary increase associated with the procedure.

Stroke, transient ischaemic attacks, or myocardial infarction within 90 days.

Reason for exclusion	Precautionary measure based on effects which have been identified following intravitreal administration of VEGF inhibitors.
Is it considered to be included as missing information?	No
Rationale	Precautionary measure in clinical trial setting for patients with a recent event of cerebrovascular accident or myocardial infarction.

History of recurrent significant infections and/or current treatment for active systemic infection.

Reason for exclusion	A systemic infection could spread into the eye through hematogenous circulation, and confound study results. Also, the presence of systemic infection put the patient at higher risk for infection related to the intraocular injection.
Is it considered to be included as missing information?	No
Rationale	Precaution in a clinical trial setting.

Known allergic reactions and/or hypersensitivity to ranibizumab; History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of ranibizumab; History of allergy to the fluorescein sodium for injection in angiography of myopia.

Reason for exclusion	Hypersensitivity to ranibizumab would potentially elicit a severe reaction. Although allergic reactions such as rash, urticaria, pruritus and erythema have been seen following treatment with ranibizumab, there are a number of concurrently administered agents or conditions during the injection procedure which may be the cause of a hypersensitivity reaction.
Is it considered to be included as missing information?	No
Rationale	Standard safety precaution.

Pregnant or lactating woman

Reason for exclusion	Teratogenic and embryofoetal toxicity potential of ranibizumab have been reported due to its mechanism of

Pregnant or lactating woman

	action. On this basis, it may cause foetal harm if administered during pregnancy.
Is it considered to be included as missing information?	No
Rationale	Ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child. It is unknown whether ranibizumab is excreted in human milk. Breast-feeding is not recommended during the use of ranibizumab.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure, and the reactions that occur in other claimed indications.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1 presents an overview of special populations in the pre-authorization clinical development program.

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program

Type of special population	Exposure
Population with relevant different ethnic origin	In phase III clinical trial, the majority of population were White (296 subjects), followed by Asian (51 subjects), Native Hawaiian or Other Pacific Islander (1 subject), and Other (2 subjects). The data is presented in Table SIII.3.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Paediatric population	Children and adolescents under the age of 18 years were not included in the clinical development program.
Elderly population	Subjects ≥ 65 years of age were included in the clinical development program. See details at Table SIII.2.

Part II: Module SV - Post-authorization experience

SV.1 Post-authorization exposure

Not applicable.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no anticipated potential for illegal use of Byooviz given the mechanism of action, as ranibizumab does not have potential for e.g. recreational use or facilitated assault.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The risks are aligned with those of the reference product. In addition, the potential risk of paediatric off-label use is addressed as below.

Potential paediatric off-label use for treatment of retinopathy of prematurity (ROP)

It is acknowledged that there is a potential for off-label use for Byooviz in preterm infants for treatment of ROP with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease as this indication has been approved for the reference product Lucentis.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The proposed Byooviz summary of product characteristics (SmPC) adequately covers the appropriate information for this potential risk. The SmPC Section 4.2 Posology and method of administration states for the paediatric population "The safety and efficacy of Byooviz in children and adolescents below 18 years of age have not been established. Available data in adolescent patients aged 12 to 17 years with visual impairment due to CNV are described but no recommendation on a posology can be made". Additionally, Section 2 of the package leaflet (PL) states "Children and adolescents (below 18 years of age): The use of Byooviz in children and adolescents has not been established and is therefore not recommended".

In addition, the routine risk minimization measure of having Byooviz under the legal status of restricted medical prescription-only medicine concurs, together with the product information, to minimize the risk of off-label use, and the risk will be monitored via routine pharmacovigilance.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Based on the EMA guide on similar biological medicinal products, the RMP should take into account the risks associated with the use of the reference product. The following risks are the safety concerns of both Byooviz and the reference product, Lucentis.

Important identified risks	Risk-benefit impact
Infectious endophthalmitis	Intravitreal injections, including those with ranibizumab, have been associated with endophthalmitis. Infectious endophthalmitis can possibly lead to a loss of vision and in sometimes even to the loss of the eye itself.
Intraocular inflammation	Intravitreal injections, including those with ranibizumab, have been associated with intraocular inflammation. Intraocular inflammation can possibly

Important identified risks	Risk-benefit impact
	lead to a loss of vision and in sometimes even to the loss of the eye itself.
Retinal detachment and retinal tear	Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision.
Intraocular pressure increase	Following an intravitreal injection of ranibizumab, a transient increase in IOP may be anticipated. The injected volume of ranibizumab may lead to an increase in IOP. Ranibizumab should not be administered in the event of an IOP of ≥30 mmHg.

Missing information	Risk-benefit impact
Visudyne (verteporfin-PDT) given in combination with ranibizumab (PM)	Data from two studies (MONT BLANC, BPD952A2308 and DENALI, BPD952A2309) conducted post approval confirmed the efficacy of ranibizumab but did not demonstrate additional effect of the combined administration of Visudyne (verteporfin-PDT) and ranibizumab compared to ranibizumab monotherapy. As such, the safety and efficacy of Visudyne (verteporfin-PDT) given in combination with ranibizumab has not been established and is considered as missing information.
Long term effects on the progression of the condition CNV (other than nAMD)	The long-term safety profile of ranibizumab observed in the 24-month extension study is consistent with the known ranibizumab safety profile. The clinical safety and efficacy of ranibizumab in patients with visual impairment due to CNV in PM and other than secondary to PM and wet AMD have been assessed based on the 12-month data of the double-masked, controlled pivotal study F2301 (RADIANCE) and the double-masked, sham-controlled pivotal study G2301 (MINERVA). Overall, ranibizumab treatment was well tolerated. However, long term (>12 months) effect on the progression of the condition CNV has not been established. Hence, this is considered as missing information.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There were no new safety concerns found from the last version to the data lock point.–

SVII.3 Details of important identified risks, important potential risks, and missing information

Ranibizumab binds with high affinity to the receptor binding site of the VEGF-A isoforms (e.g. $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$). The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors VEGFR-1 and VEGFR-2 on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation, all of which are thought to contribute to the progression of the neovascular form of AMD as well as other claimed indications of ranibizumab. It is also theoretically possible that in other parts of the body, VEGF processes (in particular, endothelial cell proliferation, migration, survival, cell-cell communication, and differentiation) may also be inhibited. However, based on analysis of population pharmacokinetics and disappearance of ranibizumab from serum for patients with neovascular AMD treated with the 0.5 mg dose, serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal ranibizumab concentrations. Serum concentrations in a limited number of DME patients indicate that a slightly higher systemic exposure cannot be excluded compared to those observed in neovascular AMD patients.

Details of the important identified risks, important potential risks and missing information of Byooviz are provided in the following sections.

For each risk presented in this section, the clinical trial database was searched for specified events using search terms and/or stems for that risk based on the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. (Refer to Annex 7 for the specific adverse event terms and/or stems used for risks analysis)

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Infectious endophthalmitis

Potential mechanisms:

Intravitreal injections, including those with ranibizumab, have been associated with endophthalmitis. Proper aseptic injection techniques must always be used when administering ranibizumab.

Evidence source(s) and strength of evidence:

Evidence has been derived from information on the reference product (RMP summary and SmPC; information in the public domain) and the conducted Byooviz Phase III study.

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterization of the risk:

- Frequency with 95% Confidence Interval (CI)

Subject incidence and exposure-adjusted rate of infectious endophthalmitis treatment emergent adverse events (TEAEs) from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	2 (0.571)	0.069-2.049	304.632	2	0.657	0.080-2.372
Lucentis	354	0	0	0	0	0	0

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Number and frequency of infectious endophthalmitis TEAEs from the Phase III Study

MedDRA Preferred Term (PT)	Byooviz N=350	Lucentis N=354
	n	n
Endophthalmitis	2	0
Total	**2**	**0**

N=Total subjects; n=No. of subjects with events.

- Seriousness/outcome

Subject incidence and exposure-adjusted rate of infectious endophthalmitis TEAEs that were serious from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	2 (0.571)	0.069-2.049	304.632	2	0.657	0.080-2.372
Lucentis	354	0	0	0	0	0	0

[a] Subject incidence = (N1/N) × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Of the two subjects experienced serious events with Byooviz, the outcome was recovered/resolved and recovered/resolved with sequelae for each one event.

- Severity

Subject incidence and exposure-adjusted rate of infectious endophthalmitis TEAEs that were severe from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	1 (0.289)	0.007-1.582	304.632	1	0.328	0.008-1.829
Lucentis	354	0	0	0	0	0	0

[a] Subject incidence = (N1/N) × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Background incidence

A retrospective, longitudinal case-control study using a Medicare database of 40,903 injections found an endophthalmitis rate of 0.09% per injection after intravitreal injections of anti-VEGF agents [3]. The rate of endophthalmitis per injection is low, with reported rates varying from 0.025% to 0.2% [4,5,6]. The range of developing endophthalmitis symptoms (eye pain, vitritis, decreased vision, etc.) varied between 1-39 days after injection. The positive cultured occurred up to 60% [4]. Gram-positive bacteria accounts for >95% of culture-positive cases. Coagulase-negative staphylococci accounted for 60% of cases and viridans streptococci 25% [7,8]. Visual outcomes are poor in cases caused by streptococci.

Risk factors and risk groups:

To minimize the occurrence of endophthalmitis, guidance is provided in SmPC on how to administer an intravitreal injection and to inform and educate physicians and patients on prevention and management of this event.

Byooviz is contraindicated in patients with active or suspected ocular or periocular infections or in patients with active severe intraocular inflammation.

Preventability:

To minimize the occurrence of endophthalmitis, guidance is provided in SmPC on how to administer an intravitreal injection with proper aseptic technique and to inform and educate physicians and patients on prevention and management of this event. Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Adult patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Impact on the risk-benefit balance of the product:

Intravitreal injections, including those with ranibizumab, have been associated with endophthalmitis. Infectious endophthalmitis can possibly lead to a loss of vision and in sometimes even to the loss of the eye itself. Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact:

No impact on public health is expected.

Important Identified Risk: Intraocular inflammation

Potential mechanisms:

Intravitreal injections, including those with ranibizumab, have been associated with intraocular inflammation. Proper aseptic injection techniques must always be used when administering ranibizumab. The potential mechanism remains unclear however, immune-related response have been suspected [9].

Evidence source(s) and strength of evidence:

Evidence has been derived from information on the reference product (RMP summary and SmPC; information in the public domain) and the conducted Byooviz Phase III study.

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterization of the risk:

- Frequency with 95% CI

Subject incidence and exposure-adjusted rate of intraocular inflammation TEAEs from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	10 (2.857)	1.378-5.191	304.632	13	4.267	2.272-7.297
Lucentis	354	8 (2.260)	0.981-4.404	313.243	9	2.873	1.314-5.454

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Number and frequency of intraocular inflammation TEAEs from the Phase III Study

MedDRA PT	Byooviz N=350	Lucentis N=354
	n	n
Endophthalmitis	2	0
Episcleritis	0	1
Eye allergy	1	0
Eye irritation	2	2
Iridocyclitis	3	1
Macular oedema	1	2
Ocular hyperaemia	0	1
Retinal oedema	1	1
Uveitis	1	0
Vitritis	1	0
Total	**12**	**8**

N=Total subjects; n=No. of subjects with events

- Seriousness/outcome

Subject incidence and exposure-adjusted rate of intraocular inflammation TEAEs that were serious from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	6 (1.714)	0.632-3.694	304.632	6	1.970	0.723-4.287

Subject incidence and exposure-adjusted rate of intraocular inflammation TEAEs that were serious from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Lucentis	354	1 (0.282)	0.007-1.564	313.243	1	0.319	0.008-1.779

[a] Subject incidence = (N1/N) × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Of the 13 events of intraocular inflammation in Byooviz group, 11 events were recovered/resolved, and 2 events were recovered/resolved with sequelae. Of the 9 events of Intraocular inflammation in Lucentis group, all 9 events were recovered/resolved.

- Severity

Subject incidence and exposure-adjusted rate of intraocular inflammation TEAEs that were severe from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	4 (1.143)	0.312-2.900	304.632	4	1.313	0.358-3.362
Lucentis	354	0	0	0	0	0	0

[a] Subject incidence = (N1/N) × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Background incidence

The incidence varied between 0.033% and 2.9% for sterile endophthalmitis – an acute intraocular inflammation without infection and resolved without antibiotic treatment [10]. The MARINA study [9] and HARBOR study [11] reported the rate of intraocular inflammation 2.6% and 0.4% respectively after ranibizumab injections. The onset varied up to one week after injection of anti-VEGF treatment.

Risk factors and risk groups:

Proper injection techniques must always be used when administering ranibizumab.

Byooviz is contraindicated in patients with active or suspected ocular or periocular infections or in patients with active severe intraocular inflammation.

Preventability:

Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Adult patients should be instructed to report any symptoms suggestive of an intraocular inflammation without delay.

Impact on the risk-benefit balance of the product:

Inflammation following intravitreal anti-VEGF injections can cause a reduction in acuity [12].

Intraocular inflammation can possibly lead to a loss of vision and sometimes even to the loss of the eye itself. Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact:

No impact on public health is expected.

Important Identified Risk: Retinal detachment and retinal tear

Potential mechanisms:

Rhegmatogenous retinal detachment (RRD) occurs when subretinal fluid accumulates between the neurosensory retina and the retinal pigment epithelium [13].

Traction retinal detachment occurs when scar tissue or other abnormal tissue grows on the surface of the retina, pulling the retina away from the layer beneath it. This does not necessarily cause a specific tear or break in the retina. In patients with advanced stages of ROP, retinal detachment develops when neovascularization progresses and proliferous fibrous and vascular tissue lead to traction over the ridge.

Exudative retinal detachment occurs when blood or fluid from the choroid flows into the space under the retina and separates the retina from the layer beneath it. The detachment does not involve tears in the retina or traction from the vitreous. Exudative retinal detachment is most often a complication of other diseases including macular degeneration, eye tumors, inflammation in the choroid or the retina, or severe high blood pressure.

Evidence source(s) and strength of evidence:

Evidence has been derived from information on the reference product (RMP summary and SmPC; information in the public domain) and the conducted Byooviz Phase III study.

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterization of the risk:

- Frequency with 95% CI

Subject incidence and exposure-adjusted rate of retinal detachment and retinal tear TEAEs from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	5 (1.429)	0.465-3.302	304.632	5	1.641	0.533-3.830
Lucentis	354	9 (2.542)	1.169-4.771	313.243	9	2.873	1.314-5.454

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Number and frequency of retinal detachment and retinal tear TEAEs from the Phase III Study

Subject incidence and exposure-adjusted rate of retinal detachment and retinal tear TEAEs from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI

MedDRA PT	Byooviz N=350	Lucentis N=354
	n	n
Detachment of macular retinal pigment epithelium	0	1
Detachment of retinal pigment epithelium	0	2
Retinal haemorrhage	3	4
Retinal pigment epithelial tear	2	2
Total	**5**	**9**

N=Total subjects; n=No. of subjects with events

- Seriousness/outcome

Subject incidence and exposure-adjusted rate of retinal detachment and retinal tear TEAEs that were serious from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	2 (0.571)	0.069-2.049	304.632	2	0.657	0.080-2.372
Lucentis	354	1 (0.282)	0.007-1.564	313.243	1	0.319	0.008-1.779

[a] Subject incidence = (N1/N) × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Of the 5 events of retinal detachment and retinal tear reported in Byooviz group, 3 events were not recovered/not resolved, 1 event was recovered/resolved, and 1 event was recovering/resolving. Of the 9 events of retinal detachment and retinal tear in Lucentis group, 3 events were not recovered/not resolved, 3 events were recovering/resolving, 2 events were recovered/resolved, and 1 event was unknown.

- Severity

Subject incidence and exposure-adjusted rate of retinal detachment and retinal tear TEAEs that were severe from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	1 (0.286)	0.007-1.582	304.632	1	0.328	0.008-1.829
Lucentis	354	1 (0.282)	0.007-1.564	313.243	1	0.319	0.008-1.779

[a] Subject incidence = (N1/N) × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Background incidence

RRD after intravitreal injection of anti-VEGF medications was reported to be 0.013% (1 RRD per 7532 intravitreal injections) and 0.19% (1 RRD per 530 patients). A retinal tear was found located in the quadrant of the injection site (within 1.5 clock hours of the injection) in 15 of 24 patients (62.5%; P < 0.0001) [14].

RRD annual incidence in United Kingdom was reported to be 12.05 per 100,000 population (95% CI, 11.35–12.70). The age-specific incidence increased to a peak in both sexes in the 60- to 69-year age group. RRD was significantly more frequent in males than in females (14.70 vs. 8.75 per 100,000; P < 0.001) [15].

The RRD annual incidence reported in Korea was 10.39 cases per 100,000 person-years (95% CI, 10.26–10.52). The incidence in men (11.32 cases per 100,000 person-years; 95% CI: 11.13–11.51) was significantly higher than that in women (9.47 cases per 100,000 person-years; 95% CI: 9.29–9.64) (p<0.001). The age-specific RRD incidence pattern in Korea followed a bimodal distribution [16].

Risk factors and risk groups:

The following conditions might increase the risk for retinal detachment: previous retinal detachment or retinal tear, eye tumors, inflammation in the choroid or the retina, eye injury, or severe high blood pressure.

Preventability:

Caution should be exercised in patients with risk factors of large and/or high pigment epithelial retinal detachment for retinal pigment epithelial tears, as in most cases a retinal detachment cannot be prevented. Treatment should be discontinued in subjects with RRD or stage 3 or 4 macular holes. In ROP patients, retinal detachment is associated with advanced stages of the disease and can be prevented by treatment.

Impact on the risk-benefit balance of the product:

Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision. Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact:

No impact on public health is expected.

Important Identified Risk: Intraocular pressure increase

Potential mechanisms:

Injection of ranibizumab into vitreous cavity increases the intraocular volume by adding fluid, which can induce an increase in IOP and can vary according to globe size, injected volume, scleral thickness, and scleral rigidity [17,18].

Several theoretical mechanisms of an inflammatory response, a direct toxic effect of anti-VEGF agents to the trabecular meshwork, injury to the trabecular meshwork from injection of a high volume of fluid, or a mechanical blockade of the trabecular meshwork by protein aggregates or contaminant particles have been postulated for IOP increase [19].

Evidence source(s) and strength of evidence:

Evidence has been derived from information on the reference product (RMP summary and SmPC; information in the public domain) and the conducted Byooviz Phase III study.

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterization of the risk:

- Frequency with 95% CI

Subject incidence and exposure-adjusted rate of IOP increase TEAEs from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	23 (6.571)	4.211-9.697	304.632	40	13.131	9.381-17.880
Lucentis	354	26 (7.345)	4.854-10.577	313.243	67	21.389	16.576-27.163

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Number and frequency of IOP increase TEAEs from the Phase III Study

MedDRA PT	Byooviz N=350	Lucentis N=354
	n	n
Intraocular pressure increased	23	26
Total	**23**	**26**

N=Total subjects; n=No. of subjects with event

- Seriousness/outcome

There were no serious TEAEs reported.
Of the 40 events reported for IOP increase in Byooviz group, 37 events were recovered/resolved, 2 events were not recovered/not resolved, and 1 event was recovering/resolving. Of the 67 events reported for IOP increase in Lucentis group, 66 events were recovered/resolved, and 1 event was recovering/resolving.

- Severity

Subject incidence and exposure-adjusted rate of IOP increase TEAEs that were severe from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Byooviz	350	1 (0.286)	0.007-1.582	304.632	1	0.328	0.008-1.829
Lucentis	354	0	0	0	0	0	0

Subject incidence and exposure-adjusted rate of IOP increase TEAEs that were severe from the Phase III Study

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI

[a] Subject incidence = (N1/N) × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Background incidence

The incidence of sustained elevation of IOP in patients with neovascular AMD varied from 3.45% to 11.6% [20]. There were 3.1% of eyes receiving ranibizumab injections that experienced increased IOP [21].

Risk factors and risk groups:

Pre-existing high IOP is also a risk factor; ranibizumab should not be administered in the event of an IOP of ≥30 mmHg.

Preventability:

Therapy should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of increase of IOP ≥30 mmHg. Both IOP and the perfusion of the optic nerve head must be monitored and managed appropriately. Adult patients are advised to call their ophthalmologist if they have eye pain or vision loss or other signs or symptoms that may indicate acute increase of IOP following an injection.

Impact on the risk-benefit balance of the product:

The IOP elevation is common with drug treatment, it is unknown whether repeated IOP spikes may cause damage in predisposed eyes [22]. There have been evidence for visual field defect or significant optic nerve damage [23]. Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact:

No impact on public health is expected.

SVII.3.2. Presentation of the missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infectious endophthalmitis Intraocular inflammation Retinal detachment and retinal tear Intraocular pressure increase

Part III: Pharmacovigilance Plan (including post-authorization safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns

Specific AE follow-up questionnaire will be used to collect further data to help further characterize and/or closely monitor the safety concern specified below:

- Infectious endophthalmitis

The questionnaire is provided in Annex 4.

Other forms of routine pharmacovigilance activities for safety concerns

Follow up of case reports: The minimum desired case information for ranibizumab includes the brand name and batch number of the suspect product. Additional efforts must be made to collect this information in accordance with GVP VI.

III.2 Additional pharmacovigilance activities

There are no ongoing/planned additional pharmacovigilance activities.

In particular, it is considered that, for biosimilars, the additional pharmacovigilance activity of a paediatric investigation plan is not applicable, provided also that ranibizumab is not approved for use in patients under the age of 18 years.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

Part IV: Plans for post-authorization efficacy studies

Table Part IV.1: Planned and on-going post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Infectious endophthalmitis	Routine risk communication: SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6. PL Sections 2, 3, 4. Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for proper aseptic injection techniques, monitoring of patients during the week following the injection to permit early treatment if an infection occurs, and instructing patients to report any symptoms suggestive of endophthalmitis without delay are given in SmPC Section 4.4. Step-by-step instructions for preparing Byooviz for intravitreal administration are provided in SmPC Section 6.6. Other routine risk minimization measures beyond the Product Information: Pack size: One vial or one PFS for single use only. Legal status: Restricted medical prescription-only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Intraocular inflammation	Routine risk communication: SmPC Sections 4.3, 4.4. PL Sections 2, 4. Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for proper aseptic injection techniques, monitoring of patients during the week following the injection, and

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
	instructing patients to report any symptoms suggestive of intraocular inflammation without delay are given in SmPC Section 4.4. Step-by-step instructions for preparing Byooviz for intravitreal administration are provided in SmPC Section 6.6. Other routine risk minimization measures beyond the Product Information: Pack size: One vial or one PFS for single use only. Legal status: Restricted medical prescription-only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Retinal detachment and retinal tear	Routine risk communication: SmPC Sections 4.4, 4.8. PL Sections 2, 4. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Pack size: One vial or one PFS for single use only. Legal status: Restricted medical prescription-only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Intraocular pressure increase	Routine risk communication: SmPC Sections 4.4, 4.8, 4.9. PL Sections 2, 4. Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation to monitor and manage both IOP and the perfusion of the optic nerve head appropriately is provided in SmPC Section 4.4. Recommendation to withhold ranibizumab in the event of an IOP of ≥30 mmHg is given in SmPC Section 4.4. Other routine risk minimization measures beyond the Product Information: .

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
	Pack size: One vial or one PFS for single use only. Legal status: Restricted medical prescription-only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.

V.2. Additional Risk Minimization Measures

<Educational plan for adult patients>

Objectives:

To ensure that patients are adequately informed about the potential to develop IOP increase, intraocular inflammation, retinal detachment and retinal tear, and infectious endophthalmitis after an intravitreal injection of ranibizumab, patient information booklets (also available in spoken form in audio format) are developed. The booklets are provided to the physician for distribution to the patient after Byooviz is prescribed to them.

Rationale for the additional risk minimization activity:

This particular additional risk minimization measure is aligned with that of reference product.

The patient information booklets aim to provide adequate patient education on key signs and symptoms of potential adverse reactions and when to seek urgent attention from their physician, ensuring rapid identification and treatment of these events.

Key signs and symptoms of the following identified risks are covered in the patient information booklet:

Infectious endophthalmitis

- Infectious endophthalmitis is a serious ocular condition, often caused by an intraocular infection, and can potentially lead to blindness.
- Patients need to contact their clinical immediately if they develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in the patient's vision, or increased sensitivity to light.

Intraocular inflammation

- Intraocular inflammation can cause eye pain, worsening eye redness, blurred vision, an increased number of small particles in the patient's vision, or increased sensitivity to light.

Retinal detachment and retinal tear

- Warning signs may include symptoms such as increased eye discomfort, light flashes, and blurred or decreased vision.

Intraocular pressure increase

- Increases in IOP within 60 minutes of injection of ranibizumab are very common. They may be asymptomatic, or could cause eye pain and decreased vision.

In addition, the booklets contain follow-up recommendations for adequate care after the injection, including recommendations to contact the physician in case of additional questions.

Target audience and planned distribution path:

The patient educational materials are provided to all ophthalmology clinics where Byooviz is expected to be used in adult patients for distribution to the patients receiving Byooviz.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable.

<Removal of additional risk minimization activities>

Not applicable.

V.3 Summary of risk minimization measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infectious endophthalmitis	<Routine risk minimization measures> SmPC Sections 4.2, 4.3, 4.4, 4.8 and 6.6; PL Sections 2, 3, 4. Pack size: One vial or one PFS for single use only. Restricted medical-prescription-only medication <Additional risk minimization measures> Educational plan for adult patients	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> Specific AE follow-up questionnaire <Additional pharmacovigilance activities> None
Intraocular inflammation	<Routine risk minimization measures> SmPC Sections 4.3, 4.4; PL Sections 2, 4. Pack size: One vial or one PFS for single use only. Restricted medical prescription-only medication <Additional risk minimization measures> Educational plan for adult patients	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Retinal detachment and retinal tear	<Routine risk minimization measures> SmPC Sections 4.4, 4.8; PL Sections 2, 4. Pack size: One vial or one PFS for single use only. Restricted medical prescription-only medication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
	<Additional risk minimization measures> Educational plan for adult patients.	
Intraocular pressure increase	<Routine risk minimization measures> SmPC Sections 4.4, 4.8, 4.9; PL Sections 2, 4. Pack size: One vial or one PFS for single use only. Restricted medical prescription-only medication <Additional risk minimization measures> Educational plan for adult patients.	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None

Part VI: Summary of the risk management plan

Summary of risk management plan for Byooviz (ranibizumab)

This is a summary of the risk management plan (RMP) for Byooviz. The RMP details important risks of Byooviz, how these risks can be minimized, and how more information will be obtained about Byooviz's risks and uncertainties (missing information).

Byooviz's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Byooviz should be used.

This summary of the RMP for Byooviz should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Byooviz's RMP.

I. The medicine and what it is used for

Byooviz is authorized in adults for neovascular (wet) age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), proliferative diabetic retinopathy (PDR, visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), and visual impairment due to choroidal neovascularization (CNV). It contains ranibizumab as the active substance. Byooviz is a solution for injection and must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Further information about the evaluation of ranibizumab's benefits can be found in ranibizumab's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/byooviz

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Byooviz, together with measures to minimize such risks and the proposed studies for learning more about Byooviz's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Byooviz, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Byooviz is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Byooviz are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Byooviz. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Infectious endophthalmitis Intraocular inflammation Retinal detachment and retinal tear Intraocular pressure increase

II.B Summary of important risks

Important identified risk: Infectious endophthalmitis	
Evidence for linking the risk to the medicine	Evidence has been derived from information on the reference product (RMP summary and SmPC; information in the public domain) and the conducted Byooviz Phase III study.
Risk factors and risk groups	To minimize the occurrence of endophthalmitis guidance is provided in SmPC on how to administer an intravitreal injection and to inform and educate physicians and patients on prevention and management of this event. Byooviz is contraindicated in patients with active or suspected ocular or periocular infections or in patients with active severe intraocular inflammation.
Risk minimization measures	<Routine risk minimization measures> SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6. PL Sections 2, 3, 4. Pack size: One vial or one PFS for single use only. Restricted medical prescription-only medication

Important identified risk: Infectious endophthalmitis	
	<Additional risk minimization measures> Educational plan for adult patients

Important identified risk: Intraocular inflammation	
Evidence for linking the risk to the medicine	Evidence has been derived from information on the reference product (RMP summary and SmPC; information in the public domain) and the conducted Byooviz Phase III study.
Risk factors and risk groups	Proper aseptic injection techniques must always be used when administering ranibizumab. Byooviz is contraindicated in patients with active or suspected ocular or periocular infections or in patients with active severe intraocular inflammation.
Risk minimization measures	<Routine risk minimization measures> SmPC Sections 4.3, 4.4. PL Sections 2, 4. Pack size: One vial or one PFS for single use only. Restricted medical prescription-only medication <Additional risk minimization measures> Educational plan for adult patients

Important identified risk: Retinal detachment and retinal tear	
Evidence for linking the risk to the medicine	Evidence has been derived from information on the reference product (RMP summary and SmPC; information in the public domain) and the conducted Byooviz Phase III study.
Risk factors and risk groups	The following conditions might increase the risk for retinal detachment: previous retinal detachment or retinal tear, eye tumors, inflammation in the choroid or the retina, eye injury, or severe high blood pressure.
Risk minimization measures	<Routine risk minimization measures> SmPC Section 4.4, 4.8. PL Sections 2, 4. Pack size: One vial or one PFS for single use only. Restricted medical prescription-only medication <Additional risk minimization measures>

Important identified risk: Retinal detachment and retinal tear	
	Educational plan for adult patients

Important identified risk: Intraocular pressure increase	
Evidence for linking the risk to the medicine	Evidence has been derived from information on the reference product (RMP summary and SmPC; information in the public domain) and the conducted Byooviz Phase III study.
Risk factors and risk groups	Pre-existing high IOP; ranibizumab should not be administered in the event of an IOP of ≥30 mmHg.
Risk minimization measures	<Routine risk minimization measures> SmPC Sections 4.4, 4.8, 4.9. PL Section 2, 4. Pack size: One vial or one PFS for single use only. Restricted medical prescription-only medication <Additional risk minimization measures> Educational plan for adult patients

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Byooviz.

II.C.2 Other studies in post-authorization development plan

There are no studies required for Byooviz.

Annex 4 - Specific adverse drug reaction follow-up forms

Follow-up forms: Infectious endophthalmitis

Questionnaire: Infectious Endophthalmitis

In addition to collecting routine information for this AE, please ensure the following additional information is provided and/or confirmed.

A. Patient Information

Initials/Identifiers: Date of birth: M M M D D Y Y Y Y

Sex: ☐ Male ☐ Female Product/Manufacturer/Lot#:

B. Event Description

Date of last ranibizumab injection before event onset: M M M D D Y Y Y Y

Number of ranibizumab injections received before event onset:

Eye(s) affected: ☐ Right eye ☐ Left eye ☐ Both

Was the event in the injected eye? ☐ Yes ☐ No ☐ Unknown

Did the patient have eye pain as a presenting symptom? ☐ Yes ☐ No ☐ Unknown

Did the patient have any other presenting symptom(s)? ☐ Yes ☐ No ☐ Unknown

- If yes, please describe:

Did the patient receive prophylactic topical antibiotics prior to injection? ☐ Yes ☐ No ☐ Unknown

- If yes, for how many days?

Did the patient receive post injection antibiotics? ☐ Yes ☐ No ☐ Unknown

- If yes, for how many days?

Was full aseptic technique used when injection was administered? (e.g., use of sterile gloves, drape, eye speculum, povidone iodine flush) ☐ Yes ☐ No ☐ Unknown

- If no, please describe what was used:

Was a culture done? ☐ Yes ☐ No ☐ Unknown

- If yes, what were the results?

Any other relevant examination or laboratory data?

Any other relevant information?

C. Relevant medical history (concurrent and pre-existing conditions)

Did the patient receive prior laser therapy? ☐ Yes ☐ No ☐ Unknown

- If yes, please provide the following information.

  Date of last treatment: M M M D D Y Y Y Y

  Which eye(s) was treated: ☐ Right eye ☐ Left eye ☐ Both

Any medications administered via intravitreal injection previous to AE? ☐ Yes ☐ No ☐ Unknown

Questionnaire: Infectious Endophthalmitis

C. Relevant medical history (concurrent and pre-existing conditions)

- If yes, please describe including which eye(s) was treated:

Prior history of endophthalmitis? ☐ Yes ☐ No ☐ Unknown

- If yes, please describe including date of occurrence and affected eye:

Prior history of periocular infection? ☐ Yes ☐ No ☐ Unknown

- If yes, please describe including date of occurrence, affected eye, therapeutic management, and outcome (ongoing or resolved):

Prior eye surgery or trauma to affected eye(s)? ☐ Yes ☐ No ☐ Unknown

- If yes, please describe including date of occurrence and affected eye:

Is the patient immunocompromised? ☐ Yes ☐ No ☐ Unknown

- If yes, please describe:

D. Additional Comments

Signature(s)

Reporter's name: _____ Signature: _____ Date: _____

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Draft key messages of the additional risk minimization measures

The patient information pack:

The patient information booklets provide information on the key signs and symptoms of potential adverse reactions, ensuring rapid identification and treatment of these events. Patient information booklets are provided to all ophthalmology clinics where Byooviz is expected to be used for treatment of adult patients.

The patient information pack should be provided in both the form of patient information booklets and an audio file that contain following key elements:

- Patient information leaflet
- How to prepare for Byooviz treatment
- What are the steps following treatment with Byooviz
- Key signs and symptoms of serious adverse events including increased IOP, intraocular inflammation, retinal detachment and retinal tear, and infectious endophthalmitis
- When to seek urgent attention from the health care provider

Details of proposed educational program for adult patients:

To ensure that patients are adequately informed about the potential adverse events of Byooviz, patient information booklets (also available in spoken form) are provided to the physician for distribution to the patients after Byooviz is prescribed to them.

The booklets aim to provide adequate patient education on the following:

- What is nAMD, CNV, PDR with or without DME, and RVO
- How Byooviz works, what to expect from Byooviz treatment, and how Byooviz is administered
- What the key signs and symptoms of serious adverse events including increased IOP, intraocular inflammation, retinal detachment and retinal tear, and infectious endophthalmitis are
- When to seek urgent attention from the health care provider

The following are the key safety messages to be communicated to allow early diagnosis and appropriate treatment:

- It is important that patients monitor any changes in the condition of their eye and their overall well-being in the week following injection with Byooviz.
- Patients need to contact their clinic immediately if they develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision, or increased sensitivity to light.

In addition, the booklets contain follow-up recommendations for adequate care after the injection, including recommendations to contact the physician in case of additional questions.