EU Risk Management Plan
for

Rimmyrah 10 mg/ml solution for injection

RMP version to be assessed as part of this application:	
RMP Version number	0.2
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Summary of significant changes in this RMP	Not applicable
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QPPV name*	Prashanth Belathur
QPPV signature	The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

*QPPV name will not be redacted in case of an access to document request; see HMA/ EMA Guidance document on the identification if commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Ranibizumab
Pharmacotherapeutic group(s) (ATC Code)	Ophthalmologicals, antineovascularisation agents. (ATC code: S01LA04)
Marketing Authorisation Applicant	QILU PHARMA SPAIN S.L.
Medicinal products to which this RMP refers	One (01)
Invented name(s) in the European Economic Area (EEA)	Rimmyrah 10 mg/ml solution for injection
Marketing authorisation procedure	Centralized Procedure
Brief description of the product	**Ranibizumab** Ophthalmologicals, antineovascularisation agents **Chemical Name**: Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFab V2 γ1-chain), disulfide with human-mouse monoclonal rhuFab V2 κ-chain **Empirical Formula:** $C_{2158}H_{3282}N_{562}O_{681}S_{12}$ **Molecular Weight:** 48379.97 g/mol **Structural Formula:** >Light Chain DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC >Heavy Chain EVQLVESGGGLVQPGGSLRLSCAASGYDFTHYGMNWVRQAPGKGLEWVGWINTYTGEPTY AADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPYYYGTSHWYFDVWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHL Green highlight: Cysteine

	Blue font: CDR (Complementarity-Determining Region) Red linkage: Disulfide bond
	Summary of mode of action: Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), 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 neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO in adults.
	Important information about product composition: 1 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 to adult patients. *Ranibizumab is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology. <u>List of excipients</u>: Trehalose dihydrate Histidine hydrochloride, monohydrate Histidine Polysorbate 20 (E432) Water for injections
Hyperlink to the Product Information	Refer to Module-1, Section-1.3.1-spclabelpl
Indication(s) in the EEA	Rimmyrah is indicated in adults for: • The treatment of neovascular (wet) age-related macular degeneration (AMD) • The treatment of visual impairment due to diabetic macular oedema (DME) • The treatment of proliferative diabetic retinopathy (PDR)

	• The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) • The treatment of visual impairment due to choroidal neovascularisation (CNV) •
	Proposed: Not Applicable.
Dosage in the EEA	**Current:** Rimmyrah must be administered by a qualified ophthalmologist experienced in intravitreal injections. <u>Posology</u> <u>Adults</u> The recommended dose for Rimmyrah in adults 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 in adults 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, Rimmyrah 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 pathologic myopia (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 in CNV secondary to PM* There is no experience of concomitant administration of ranibizumab and verteporfin. Method of administration Single-use vial for intravitreal use only. Since the volume contained in the vial (0.23 ml) is greater than the recommended dose (0.05 ml for adults), a portion of the volume contained in the vial must be discarded prior to administration. Rimmyrah should be inspected visually for particulate matter and discoloration prior to administration.
	Proposed: Not Applicable.
Pharmaceutical form(s) and strengths	**Current:** 10 mg/ml solution for injection
	Proposed: Not Applicable.
Is the product subjected to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

Module SI - Epidemiology of the Indication(s) and Target Population(s)

Since this is a biosimilar product, this section is not applicable.

Module SII - Non-Clinical Part of the Safety Specification

To support the safety comparability via ITV administration of QL1205 and Lucentis®, the following non-clinical safety studies were conducted. QL1205 is a monoclonal antibody Fab fragment, which is a biological product. According to relevant guidelines, genotoxicity, carcinogenicity, and reproductive toxicity tests were not separately conducted.

Overview of Toxicology Studies

Study type	**Species/Strain**	**Route of administration**	**Duration**	**Dose (mg/eye)**
Single-dose toxicity	Rhesus monkey	*itv/iv*	Single dose	1.94, 0.5 (ITV) 1(IV)
Repeat-dose toxicity (accompanied by toxicokinetics, immunogenicity, immunotoxicity, and safety pharmacology)	Rhesus monkey	*itv*	Q2W Total 4 times	0, 0.5, 0.5 (Lucentis®), 1.94 (QL1205)
Hemolysis study	Red blood cells of rabbit	*in vitro*	/	10 mg/mL
Local tolerance	Japanese white rabbit	*Eye instillation*	QW Total 4 times	0, 0.5

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
Toxicity	
Single-dose toxicity **Single Intravitreal Injection and Intravenous Injection Toxicity Studies in Rhesus Monkeys (non-GLP)** In this study, two rhesus monkeys (1 male and 1 female) were randomly divided into two groups: QL1205 low dose group (0.5 mg/eye) and QL1205 high dose group (1.94 mg/eye). This study was carried out in two phases. Phase 1: The high dose was given by ITV of 60 μL/eye with the maximum concentration of 32.3 mg/mL QL1205 as the administration concentration, and the final dose was 1.94 mg/eye;	There were no abnormalities seen with QL1205 in single-dose toxicity studies; hence, no relevance for human use could be found.

the low dose was given by ITV at the concentration of 10 mg/mL, 50 μL/eye, and the final dose was 0.5 mg/eye. Phase 2: The QL1205 low dose group and high dose group were both given an intravenous injection of 10 mg/mL concentration of QL1205 injection according to the dose of 1 mg/animal. After each phase of administration, the animals were observed once a day for 14 days, to observe the possible acute toxicity effect. The results showed that all rhesus monkeys were generally in good condition, with normal autonomic activity and clean hair. No obvious abnormal reactions were observed in local eyes, and no other toxic reactions related to the test article were observed. Ophthalmic examination showed no abnormality, and no other general toxic reaction was observed. In summary, no abnormalities in ophthalmologic examination or general toxicity were found in rhesus monkeys after single ITV administration of QL1205 to both eyes at 0.5 mg/eye and 2 mg/eye or IV administration of QL1205 at 1 mg/animal. *Repeat-Dose Toxicity* **6-Week Intravitreal Injection Toxicity Study with QL1205 in Rhesus Monkeys with a 4-week Recovery (GLP)** A total of 24 rhesus monkeys (female: male = 1:1) were used in this study and randomly divided into four groups according to sex: excipient control group, Lucentis® group (0.5 mg/eye), QL1205 low (0.5 mg/eye) and high (1.94 mg/eye) dose groups, with six animals in each group. The administration volume was 60 μL in the excipient control group and QL1205 high dose group, and 50 μL in the Lucentis® group and QL1205 low dose group. All groups received intravitreal injection of blank excipient, Lucentis®, or QL1205 at different concentrations every 2 weeks for four consecutive doses, and a 4-week recovery period was set to evaluate the reversibility, persistence, or possible delayed toxicity. The results showed that no drug-related ocular toxicity was observed in the test animals of each group. No abnormal changes were observed in the	No significant difference in systemic exposure was observed between QL1205 and Lucentis® at the same dose. The no-observed-adverse-effect-level in this study was 1.94 mg/eye. The clinical dosage of Lucentis® is 0.3 and 0.5 mg/eye, 50 μL/eye, once a month, and the eyeball volume of monkeys is smaller than that of humans, so the dose and volume set in the repeat-dose toxicity study were sufficient to indicate the safety of human clinical trials. The immunological characteristics and toxicokinetic characteristics of QL1205 and Lucentis® were similar.

body weight, body temperature, food consumption, haematology, blood biochemistry, urine, bone marrow, immune indicators, ECG, blood pressure, organ weight and organ coefficient, or histopathological examination of various organs including eyeball and optic nerve of monkeys in each group. The immunological characteristics and toxicokinetic characteristics of QL1205 and Lucentis® were similar. In the repeat-dose study of QL1205, the animals in the control group and QL1205 injection 0.5 mg/eye low dose group had intraocular inflammatory reaction in the right eye, without any abnormal histological change in the left eye. In addition, no significant abnormalities were observed in the ophthalmic examination of monkeys throughout the study at the high dose of QL1205 1.94 mg/eye. Therefore, the intraocular inflammation in the right eye of these monkeys may be due to mechanical injury caused by the intravitreal injection procedure or infection during the procedure. In the literature on marketed products, ocular inflammation was observed in the intravitreal injection group or in the negative control group at a rate similar to that in this study, and it was thought to be related to the injection procedure and not to the drug or solvent given.	
Genotoxicity Studies As a monoclonal antibody Fab fragment, QL1205 is a biological product and is not expected to interact with DNA or other chromosomal substances. According to relevant guidelines, the general genotoxicity test used for drug evaluation is not applicable to biological products. In addition, the systemic exposure of QL1205 is very low, and no special safety concern has been shown in the completed general toxicological study.	Not applicable
Carcinogenicity Studies According to relevant guidelines, the conventional carcinogenicity test method is unsuitable for most biological products; meanwhile, no relevant carcinogenicity study has been submitted for Lucentis® in the FDA and EMA review, so no carcinogenicity-related test has been conducted for QL1205.	Not applicable

Reproductive and Development Toxicity Studies Since the maximum drug concentration in serum is lower than the effective concentration, Lucentis® has been marketed without conducting reproductive toxicity studies. Considering that QL1205 is highly similar to the marketed Lucentis® in the comparative study of structure, function, and general toxicological tests, reproductive toxicity tests have not been conducted for QL1205. According to the package insert of Lucentis®, there is no data on the use of marketed Lucentis® in pregnant women. It is unknown whether the use of this product in pregnant women will cause foetal harm or affect fertility. It is clearly stated in the package insert that it should not be used in pregnant women unless the expected benefits outweigh the potential risks to the foetus.	Not applicable
Other toxicity-related information or data	
Local Tolerance Studies According to the characteristics of QL1205, a repeat-dose eye tolerance study in rabbits was performed to investigate whether it causes irritation to the cornea, iris, and conjunctiva and evaluate its safety in clinical use. The study included control group and QL1205 group with four Japanese white rabbits per group, half male, and half female. A 0.9% sodium chloride injection and 10 mg/mL QL1205 were separately dropped into conjunctival sac of both eyes of rabbits in the control group and QL1205 group at the dose of 50 μL/eye, once a week, for four doses in total. General conditions of the animals were observed daily after administration; ocular observation rating and slit-lamp examination were performed before and at 1 and 24 h after the first, second, and third doses, before and at 1, 2, 4, 24, 48, and 72 h after the last dose; fluorescein sodium staining was performed before and at 1 and 24 h after the first, second, and third doses before, and at 1, 24, and 72 h after the last dose. The results showed no abnormalities in the general condition, slit-lamp examination, observation score, or fluorescein sodium staining examination of rabbits after eye drops of 0.5 mg/eye once a week for a total of four doses. In conclusion, this product was considered to be non-irritating to rabbit eyes.	There were no abnormalities seen with QL1205 in local tolerance studies; hence, no relevance for human use could be found.

Immunotoxicity and Immunogenicity Immunotoxicity and immunogenicity studies were conducted together with repeat-dose toxicity studies in rhesus monkeys to compare QL1205 with Lucentis®. There was no immunotoxicity in rhesus monkeys after ITV administration of QL1205 0.5 mg/eye and 1.94 mg/eye or Lucentis® 0.5 mg/eye injection (the marketed drug) every 2 weeks for four consecutive doses and a 4-week recovery period under the conditions of the study. A low proportion of animals in the Lucentis® injection group and the high dose and low dose QL1205 groups produced anti-drug antibodies with certain neutralizing activities. At the same dose, the immunogenicity of QL1205 was comparable with that of Lucentis® injection.	There was no immunotoxicity seen in this non-clinical study; hence, no relevance for human use could be found. The immunogenicity of QL1205 was comparable with that of Lucentis® injection.
Hemolysis Effect Hemolytic and agglutination effects of QL1205 on rabbit RBCs were investigated by *in vitro* test tube method. After QL1205 was added to tubes 1-5, turbidity was observed at the early phase without any clear red or brown findings. A small amount of precipitated erythrocytes was also observed in the tube bottom. The deposited erythrocytes gradually increased over the time. At 3 hr after the incubation, a large amount of erythrocytes deposited in tubes 1-5, which can be scattered after gentle shake. It had no apparent difference as compared with the negative control of tube 6, suggesting the absence of hemolysis or aggregation. QL1205 did not induce *in vitro* hemolysis or aggregation of rabbit red blood cells.	Both QL1205 and Lucentis® did not induce erythrocyte haemolysis or agglutination; hence, no relevance for human use could be found.

In conclusion, QL1205 showed consistent reaction characteristics with the reference drug Lucentis® in the single-dose toxicity study, repeat-dose toxicity study, and the accompanied safety pharmacology, toxicokinetics, immunogenicity, and immunotoxicity study, with less risk of haemolysis and eye irritation. In combination with the toxicology study data published by Lucentis® and clinical experience and adverse reactions of Lucentis®, it was considered that QL1205 has similar efficacy and safety in clinical trials and clinical application. The dosage, route, frequency, and duration of QL1205 can be determined by referring to the administration of Lucentis® and clinical requirements. In summary, the presented nonclinical development of QL1205 is considered adequate to demonstrate its biosimilarity with the approved and licensed Lucentis® and to support the safe clinical use of QL1205 for the proposed indications.

Module SIII - Clinical Trial Exposure

Phase 1

A randomized, double-blind, two-arm, parallel, positive-controlled Phase 1 clinical trial was conducted to compare the safety, pharmacokinetics, and pharmacodynamics of QL1205and Lucentis® in patients with wet age-related macular degeneration. A total of 48 subjects were randomized (23 in the experimental drug arm and 25 in the control arm). A total of 46 subjects completed the study.

	Experimental group	**Control group**
Drug	QL1205, intravitreal injection	Lucentis®, intravitreal injection
Dose	0.5 mg (0.05 mL), once every 4 weeks, 3 consecutive doses (D1, D29, D57)	0.5 mg (0.05 mL), once every 4 weeks, 3 consecutive doses (D1, D29, D57)
Number of patients	23	25

Phase 3

A clinical development program included a randomized, Phase 3, double-masked, parallel-group, multicenter study to compare efficacy and safety of QL1205versus Lucentis® in subjects with neovascular age-related macular degeneration. Six hundred and sixteen subjects were randomized into two groups.

	Experimental group	**Control group**
Drug	QL1205	Lucentis®
Dose	The recommended dosage is 0.5 mg per dose (equivalent to 0.05 mL of injection volume), once every 4 weeks for 48 weeks.	The recommended dosage is 0.5 mg per dose (equivalent to 0.05 mL of injection volume), once every 4 weeks for 48 weeks
Number of patients enrolled	309	307

Module SIV - Populations Not Studied in Clinical Trials

A randomized, Phase 3, double-masked, parallel-group, multicenter study was conducted to compare efficacy and safety of QL1205 versus Lucentis® in subjects with neovascular age-related macular degeneration. Patient selection was done using inclusion and exclusion criteria. Male or female patients with ≥ 50 years with newly diagnosed, treatment-naive, active subfoveal CNV lesion secondary to AMD, those with BCVA of 34 to 73 (inclusive) were eligible for inclusion in the study.

However, the patients were excluded based on the exclusion criteria presented in table below.

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

Important exclusion criteria

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
Previous ocular treatment/surgery for wAMD in either eye	Ranibizumab is likely to cause ocular inflammation and complications.	No	It is a known precautionary measure as mentioned in the SmPC.
Previous intravitreal treatment/vitreal surgery in either eye			
Any previous intravitreal anti-VEGF treatment (eg, bevacizumab, aflibercept, ranibizumab) in either eye	Caution should be used in patients with these risk factors for retinal pigment epithelial tears	No	Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD and potentially also other forms of CNV, include a large and/or high pigment epithelial retinal detachment.

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
Any previous systemic anti-VEGF treatment	Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors	No	There is a known risk and has been specified as a precautionary measure. Concurrent use of ranibizumab with other anti-VEGF must be avoided.
Sub- or intraretinal hemorrhage involving the fovea in the study eye of 50% or more of the total lesion area assessed by FA and confirmed by the central reading center (before randomization)	Ranibizumab is likely to cause or worsen intraretinal hemorrhage.	No	The higher affinity and thus stronger initial effects of ranibizumab which rapidly penetrates through the retina to reach the choroid may be responsible for the severe side effects.[1]
Subfoveal fibrosis or atrophy in the study eye assessed by FA and confirmed by the central reading center (before randomization)	Ranibizumab is likely to cause or worsen these conditions.	No	Subfoveal fibrosis or atrophic scarring was related to poor visual outcomes after ranibizumab treatment.[2]
Scarring exceeding 50% of total lesion size in the study eye and confirmed by the central reading center (before randomization)			

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
Choroidal neovascularization in either eye due to non-AMD causes assessed by FA and confirmed by the central reading center (before randomization)	It is one of the most vision threatening complications induced by ranibizumab.[3]	No	Cautious use is recommended.
Retinal pigment epithelial tear involving the macula in the study eye as assessed by FA and confirmed by the central reading center (before randomization)	Ranibizumab is likely to cause or worsen retinal pigment epithelial tear.	No	There is a known risk and has been specified as a precautionary measure.
Any concurrent intraocular condition in the study eye (eg, cataract or diabetic retinopathy) that, in the opinion of the investigator, could require treatment during the study period to prevent or treat loss of visual acuity	Ranibizumab is likely to worsen intraocular conditions.	No	There are reports of decrease in retrobulbar blood flow parameters, retinal arteriolar vasoconstriction, and worsening of macular ischemia after intravitreal injection.
Other intraocular surgery (including cataract surgery) or periocular surgery in the study eye within 3 months before randomization, except for eyelid surgery within 30 days before randomization	Intravitreous injections, with ranibizumab, have been associated with iatrogenic traumatic cataract	No	Less frequently reported, but more serious, adverse reactions include iatrogenic traumatic cataract. Cataract formation was observed in some animals after a relatively long period

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
			of intense inflammation.
Corneal transplant in the study eye	Ranibizumab induced corneal revascularization may further affect the cornea and could impact those who underwent transplant.	No	All the ocular events and complications are inter-connected which may harm the overall health of the subjects.
Active or recent (within 28 days before randomization) intraocular, extraocular, and periocular inflammation or infection in either eye, including conjunctivitis, keratitis, scleritis, or endophthalmitis	It is known that these events are likely to be worsened by the use of ranibizumab.	No	These events are common and can cause serious complications adversely affecting the risk benefit balance.
Current vitreous hemorrhage in the study eye	Ranibizumab is likely to cause or worsen hemorrhage.	No	The higher affinity and thus stronger initial effects of ranibizumab which rapidly penetrates through the retina to reach the choroid may be responsible for the severe side effects.

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
History of retinal detachment in the study eye	Caution should be used in patients with these risk factors for retinal pigment epithelial tears	No	Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD and potentially also other forms of CNV, include a large and/or high pigment epithelial retinal detachment.
History of macular hole in the study eye	Ranibizumab has not been studied in patients who have macular hole.	No	It is already a known risk and has been mentioned as a precautionary measure. Ranibizumab should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes
History of idiopathic or autoimmune-associated uveitis in either eye	Every case of uveitis after intravitreal anti-VEGF injection should be considered as suspected endophthalmitis and should administer intravitreal antibiotics whenever there are	No	All the ocular events and complications are inter-connected which may harm the overall health of the subjects

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
	high clinical suspicions.		
Aphakia or absence of the posterior capsule in the study eye, unless it occurred as a result of a Yttrium Aluminium Garnet posterior capsulotomy in association with prior posterior chamber intraocular lens implantation	Condition such as glaucoma may lead to deterioration of the eye lens or it may be removed due to cataract, which may be aggravated by ranibizumab.	No	All the ocular events and complications are inter-connected which may harm the overall health of the subjects.
Presence of advanced glaucoma or optic neuropathy that involves or threatens the central visual field in the study eye	Ranibizumab is known to elevate IOP, thus creating ocular complications.	No	Patients with pre-existing glaucoma have higher rates of IOP elevation compared with those without pre-existing glaucoma. In adults, transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of ranibizumab. Sustained IOP increases have also been identified.
History of glaucoma filtering surgery in the study eye			
Uncontrolled ocular hypertension in the study eye, defined as intraocular pressure ≥ 25 mm Hg despite treatment with anti-glaucoma medication			
Spherical equivalent of the refractive error in the	It can be a repercussion of	No	Cautious use is recommended. It may

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
study eye demonstrating more than 8 diopters of myopia	retinal haemorrhage with or without exudation, caused by use of ranibizumab.		be risky for the subjects.
Contraindication for Lucentis® (hypersensitivity to ranibizumab or to any of the excipients, active or suspected ocular or periocular infection, or active severe intraocular inflammation), or known allergic reactions to any ingredients of QL1205	An increase in severe intraocular inflammation may occur due to treatment of Ranibizumab.	No	There is a potential for immunogenicity with ranibizumab. Since there is a potential for an increased systemic exposure in subjects with DME, an increased risk for developing hypersensitivity in this patient population cannot be excluded.
Current treatment for active systemic infection	Ranibizumab has not been studied in patients who have active systemic infections	No	All the ocular events and complications are inter-connected which may harm the overall health of the subjects.
Subjects with known history of seropositivity for hepatitis B, hepatitis C antibody, HIV antibody, syphilis tests, or any immunodeficiency and/or immunosuppressive disease or active systemic infection. Seropositivity for hepatitis B is defined as (1) positive for hepatitis B surface	There is a potential for immunogenicity with ranibizumab, which in turn may cause inflammation in the body organs	No	All the ocular events and complications are inter-connected which may harm the overall health of the subjects.

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
antigen and (2) positive for hepatitis B virus DNA			
Reasonable suspicion of a disease or condition that might render the subject at high risk of treatment complications or affect interpretation of the study results (as judged by the investigator), such as uncontrolled hypertension (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg), stroke, or myocardial infarction within 6 months before randomization	Intravitreal ranibizumab may lead to persistent hypertension. However, there are limited data on safety in the treatment of DME, macular oedema due to RVO and CNV secondary to PM patients with prior history of stroke or transient ischaemic attacks.	No	Caution should be exercised when treating such patients as it is already mentioned as a precautionary measure in SmPC.
Participation in another clinical trial within the previous 3 months or any previous participation in a clinical trial of anti-angiogenic drugs with receipt of previous study drug within 3 months of signing the ICF for this study	Possible interactions/complications with ranibizumab.	No	Any study involves the use of drugs which may/may not be known to the subject, thus there are chances of interaction with ranibizumab.
Topical ocular corticosteroids administrated for ≥ 30 consecutive days in the	The use of these drugs lead to complications like glaucoma, cataract and delayed wound healing, which may	No	All the ocular events and complications are inter-connected which may harm the overall health of the subjects.

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
study eye within 90 days before randomization	be further aggravated by ranibizumab.		
Any systemic treatment or therapy (including prescribed herbal medication) to treat neovascular AMD within 30 days before randomization, and such treatment or therapy will not be allowed during the study period. However, dietary supplements, vitamins, or minerals will be allowed	Possible interactions/complications with ranibizumab.	No	Any study involves the use of drugs which may/may not be known to the subject, thus there are chances of interaction with ranibizumab.

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

Phase 1 clinical trial: A total of 59 subjects were screened. Among which, 48 subjects were randomized (23 in the experimental arm and 25 in the control arm). A total of 46 subjects completed the study. After treatment, 15 subjects (65.2%) in the experimental arm reported 54 cases of treatment emergent adverse events (TEAE), among which 7 subjects (30.4%) reported 15 cases of ocular TEAEs. 13 subjects (52%) in the control arm reported 36 cases of TEAEs, among which 4 subjects (16%) reported 7 cases of ocular TEAEs. There were no reports of AEs leading to treatment discontinuation. A total of 2 subjects (8.7%) in the experimental arm reported 2 cases of serious adverse events (SAE). One subject developed pancreatic cancer, which led to withdrawal from the study and death and the other subject was hospitalized due to arrhythmia. Subjects in the control arm did not report any SAE. All SAEs were determined by the investigator to be unrelated to the study drug.

Phase 3 clinical trial: A total of 616 subjects exposed to QL1205 (n=309) or Lucentis®(n=307) and the safety information is presented below:

Overall, both QL1205 and Lucentis® treatments were well tolerated in the study population with comparable safety profile. The incidences of TEAEs, TEAEs in the study eye, and serious TEAEs were comparable between QL1205 and Lucentis® treatment group. Incidence of other

significant TEAEs (TEAE leading to IP discontinuation, TEAE of special interest, i.e. COVID-19, Pneumonia, Cerebrovascular accident and Cerebral infarction) were comparable between the QL1205 treatment group and the Lucentis® treatment group.

Most of the TEAEs reported were mild to moderate intensity[1] and the number of TEAEs that was considered to be related to study treatment was comparable between the QL1205 and the Lucentis® treatment groups.

There were 8 death cases reported from the QL1205and Lucentis® treatment groups, due to Gastrointestinal bleed, Multiple organ dysfunction syndrome, Septic shock, etc. which was considered not related to the study treatment or protocol-required procedures.

Clinical laboratory data, vital signs, physical examination, SLE and other safety parameters did not show any significant safety issues that were not expected with QL1205/Lucentis® treatment.

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

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program
Breast-feeding 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
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

[1] Mild: An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities.
Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Severe: An AE that prevents normal everyday activities; treatment or other intervention usually needed.

Type of special population	**Exposure**
Other	Only patient's aged ⩾ 50 years were included in the study. Hence, no paediatric population were included in the clinical development program.

Module SV - Post-Authorisation Experience

Not applicable as the product is not marketed.

Module SVI - Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

The Summary of Product Characteristics and package insert provides detailed information to the prescribers and users on the appropriate use of the Rimmyrah which includes proper method of administration as well as number of doses and dosing. At the dose of clinical recommendation and clinical guidelines, there has been no dependency identified. Further, Rimmyrah is a prescription drug and misuse for illegal purpose is unlikely.

Module SVII - Identified and Potential Risks

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

Important identified risks	• Infectious endophthalmitis • Intraocular inflammation • Retinal detachment and retinal tear • Intraocular pressure increase
Important potential risks	• None
Missing information	• None

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

Risks	**Listed in Section**	**Reason for not including an identified or potential risk in the list of safety concerns in the RMP**
Hypersensitivity to the active substance or to any of the excipients.	Listed under SmPC Section 4.3 'Contraindications'.	These are known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers.
Concomitant use of other anti-VEGF (vascular endothelial growth factor).	Listed under SmPC Section 4.4 'Special warnings and precautions for use'.	This is a known interaction and has been specified as a precautionary measure. Concurrent use of ranibizumab with other anti-VEGF must be avoided.
Accidental Overdose	Listed under SmPC Section 4.9 'Overdose.	These are common adverse effects observed with ranibizumab which may have clinical consequences, even serious. These are considered to be acceptable in relation to the severity of the indication treated.

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

Safety Concerns	**Risk-benefit impact**
Important identified risk	
Infectious endophthalmitis	Infectious endophthalmitis remains one of the most devastating complications of intravitreal injections. In multicenter clinical trials with anti-VEGF therapy the incidence of endophthalmitis per patient has been reported to range from 0.019 to 1.6%. Endophthalmitis caused by Streptococcus species was significantly more frequent after intravitreal injection than after intraocular surgery. Considering the fact that Streptococcus species comprise at least 41% culturable adult salivary flora, the difference in causative organisms in these two settings has been attributed to the contamination of injection field by aerosolization or droplet spread.[4] The most important factor in reducing the risk of endophthalmitis following intravitreal injection is attention to issues before, during, and after the injection.[4]
Intraocular inflammation	Intraocular inflammation is one of the main ocular adverse events associated with intraocular anti-VEGF pharmacologic agents. In the large clinical trials of intravitreal injection of ranibizumab for AMD, the rates of significant ocular inflammation were 1.4–2.9%.[4]
Retinal detachment and retinal tear	The overall incidence of after intravitreal injection of anti-VEGF agents is low (0 to 0.67%). The etiology after intravitreal injection have been proposed to be an induction of posterior vitreous detachment or an incorrect technique of injection. Paying attention to the surgical technique has been advocated to decrease the rate. This includes the precise site of injection (3.5–4 mm posterior to the limbus), using smaller gauge

	needles, and tunnelled insertion of the needle for avoiding vitreous wick and reflux.[4]
Intraocular pressure increase	In adults transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of ranibizumab. Sustained IOP increases have also been identified. Acute rise of IOP after intravitreal injection is injection procedure-related and lasts a few hours at most. Patients with pre-existing glaucoma have higher rates of IOP elevation compared with those without pre-existing glaucoma.[4]
Important potential risk	
None	
Missing information	
None	

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

Not applicable.

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

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

Important Identified Risk: Infectious endophthalmitis	
<u>Potential mechanisms:</u>	Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-

Important Identified Risk: Infectious endophthalmitis	
	A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO in adults.
Evidence source(s) and strength of evidence:	As per the summary of product characteristics (SmPC) section 4.8 "Undesirable effects", frequency of infectious endophthalmitis in patients with ranibizumab treatment is uncommon (≥1/1,000 to <1/100).
Characterisation of the risk:	Intravitreous 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.
Risk factors and risk groups:	To minimize the occurrence of endophthalmitis by administering an IVT injection in a correct manner and to inform and educate physicians and patients on prevention and management of this event.
Preventability:	As per the SmPC Section 4.4 'Special warnings and precautions for use', intravitreous injections, with ranibizumab, have been associated with endophthalmitis. Proper aseptic injection techniques must always be used. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.
Impact on the risk-benefit balance of the product:	The potential impact of Infectious endophthalmitis in patients being given ranibizumab is considered important due to the severity of such events and potential life-threatening conditions. However,

Important Identified Risk: Infectious endophthalmitis	
	routine pharmacovigilance measures as contained in the product information are considered sufficient to manage this risk.
Public health impact:	The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the proposed product label.

Important Identified Risk: Intraocular inflammation	
Potential mechanisms:	Ranibizumab is a humanised recombinant monoclonal antibody fragment 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 neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO in adults.
Evidence source(s) and strength of evidence:	When compared to baseline, 1 subject in the experimental arm had increased intraocular pressure reported in study QL1205-001. As per the summary of product characteristics (SmPC) section 4.8 “Undesirable effects”, frequency of uveitis in patients with ranibizumab treatment is common (≥1/100 to <1/10).
Characterisation of the risk:	Intravitreous injections, including those with ranibizumab, have been associated with intraocular inflammation, which can possibly lead to a loss of

Important Identified Risk: Intraocular inflammation	
	vision and in sometimes even to the loss of the eye itself.
Risk factors and risk groups:	To minimize the occurrence by administering an IVT injection in a correct manner and to inform and educate physicians and patients on prevention and management of this event. Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation.
Preventability:	As per the SmPC Section 4.4 'Special warnings and precautions for use', intravitreous injections, with ranibizumab, have been associated with intraocular inflammation. Proper aseptic injection techniques must always be used. Patients should be instructed to report any symptoms suggestive of intraocular inflammation without delay.
Impact on the risk-benefit balance of the product:	The potential impact of intraocular inflammation in patients being given ranibizumab is considered important due to the severity of such events and potential life-threatening conditions. However, routine pharmacovigilance measures as contained in the product information are considered sufficient to manage this risk.
Public health impact:	The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the proposed product label.

Important Identified Risk: Retinal detachment and retinal tear	
Potential mechanisms:	Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against

Important Identified Risk: Retinal detachment and retinal tear	
	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 neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO in adults.
Evidence source(s) and strength of evidence:	As per the summary of product characteristics (SmPC) section 4.8 "Undesirable effects", frequency of retinal detachment and retinal tear in patients with ranibizumab treatment is common (≥1/100 to <1/10).
Characterisation of the risk:	Rhegmatogenous retinal detachment occurs when the liquefied vitreous enters between the choroid and the pigmented epithelium detaching the retinal layer from the underlying choroid. 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. Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision.
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.

Important Identified Risk: Retinal detachment and retinal tear	
Preventability:	As per the SmPC Section 4.4 'Special warnings and precautions for use', intravitreous injections, with ranibizumab, have been associated with retinal tear and detachment. Proper aseptic injection techniques must always be used. Patients should be instructed to report any symptoms suggestive of retinal detachment or retinal tear without delay.
Impact on the risk-benefit balance of the product:	The potential impact of retinal tear and detachment in patients being given ranibizumab is considered important due to the severity of such events and potential life-threatening conditions. However, routine pharmacovigilance measures as contained in the product information are considered sufficient to manage this risk.
Public health impact:	The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the proposed product label.

Important Identified Risk: Intraocular pressure increase	
Potential mechanisms:	Ranibizumab is a humanised recombinant monoclonal antibody fragment 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 neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or to visual impairment caused by either

Important Identified Risk: Intraocular pressure increase	
	diabetic macular oedema or macular oedema secondary to RVO in adults.
Evidence source(s) and strength of evidence:	As per the summary of product characteristics (SmPC) section 4.8 "Undesirable effects", frequency of Intraocular pressure increased in patients with ranibizumab treatment is very common (≥1/10).
Characterisation of the risk:	Following an intravitreal injection of ranibizumab, a transient increase in IOP may be anticipated.
Risk factors and risk groups:	Pre-existing high IOP
Preventability:	As per the SmPC Section 4.4 'Special warnings and precautions for use', both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. Patients should be informed of the symptoms of these potential adverse reactions and instructed to inform their physician 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.
Impact on the risk-benefit balance of the product:	The potential impact of intraocular pressure increase in patients being given ranibizumab is considered important due to the severity of such events and potential life-threatening conditions. However, routine pharmacovigilance measures as contained in the product information are considered sufficient to manage this risk.

Important Identified Risk: Intraocular pressure increase	
Public health impact:	The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the proposed product label.

Important Potential Risk: None

SVII.3.2. Presentation of the missing information

None

Module SVIII - Summary of the safety concerns

Summary of safety concerns	
Important identified risk	Infectious endophthalmitis Intraocular inflammation Retinal detachment and retinal tear Intraocular pressure increase
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION 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 checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concern specified below:

- Infectious endophthalmitis
- Use of Rimmyrah in paediatric patients including off-label use

The targeted follow-up checklists are 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 module VI.

III.2 Additional pharmacovigilance activities

None.

III.3 Summary table of additional pharmacovigilance activities

Not applicable. No additional pharmacovigilance activities are proposed.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan
V.1 Routine risk minimisation measures

Safety concern **Important identified risk**	**Routine risk minimisation activities**
Infectious endophthalmitis	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, 4.8 and 6.6. Package Information Leaflet (PIL) section 2, 3 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations are included in SmPC section 6.6 and PIL sections 2, 3 and 4. Other routine risk minimisation measures beyond the Product Information: None. Legal Status: Restricted medical prescription.
Intraocular inflammation	Routine risk communication: SmPC sections 4.3 and 4.4. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: It is recommended that patients should be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation and is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: None Legal Status: Restricted medical prescription.

Safety concern **Important identified risk**	**Routine risk minimisation activities**
Retinal detachment and retinal tear	Routine risk communication: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation of careful monitoring and use of proper aseptic injection techniques are included in SmPC section 4.4 and PIL section 2. Other routine risk minimisation measures beyond the Product Information: None Legal Status: Restricted medical prescription.
Intraocular pressure increase	Routine risk communication: SmPC sections 4.4, 4.8 and 4.9. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Ranibizumab should not be administered in the event of an intraocular pressure of ≥30 mmHg. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately, and to take appropriate precautions is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: None Legal Status: Restricted medical prescription.

Important potential risk: None

Missing information: None

V.2 Additional Risk Minimisation Measures

Adult patients

Educational plan for adult patients in the indications of nAMD, CNV, DME, RVO and PDR (Annex 6)

Objectives:
To ensure that patients are adequately informed about the potential to develop intraocular pressure increase, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis after an intravitreal injection of ranibizumab, a patient information booklet (also available in spoken form in audio-CD format) will be developed. The booklets are provided to the physician for distribution to the patient after ranibizumab is prescribed to them. Similarly, Patient information booklets covering the PDR indication will be provided.

Rationale for the additional risk minimization activity:
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 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.

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 intraocular pressure (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 booklet contains 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:
Patient information packs are prepared nationally, in line with the key important risks defined

in the RMP and with each member state's national regulations and legislations. The submission of the material to the respective member state national authorities should take place before the launch of ranibizumab in a new indication (according to the national legislation in the respective countries), and the distribution of the material to all ophthalmology clinics where ranibizumab is expected to be used in adult patients.

Plans to evaluate the effectiveness of the interventions and criteria for success:
Success of the proposed risk minimization measures will be evaluated by the criterion of a consistent spontaneous reporting rate of infectious endophthalmitis, intraocular inflammation, retinal detachment and retinal tear and intraocular pressure increase in adult patients at the time of the PSUR. Educational materials for adult patients will be in place prior to the launch of ranibizumab, and further studies to assess continued effectiveness are not considered to be required.

V.3 Summary table of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infectious endophthalmitis	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8 and 6.6. PIL sections 2, 3 and 4. Restricted medical prescription Additional risk minimisation measures: • Educational plan for adult patients.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow up questionnaire . Additional pharmacovigilance activities: None.
Intraocular inflammation	Routine risk minimisation measures: SmPC sections 4.3 and 4.4. PIL sections 2 and 4. Restricted medical prescription. Additional risk minimisation 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 minimisation measures: SmPC sections 4.4 and 4.8.	Routine pharmacovigilance activities beyond adverse

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
	PIL sections 2 and 4. Restricted medical prescription. <u>Additional risk minimisation measures:</u> Educational plan for adult patients	reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Intraocular pressure increase	<u>Routine risk minimisation measures:</u> SmPC sections 4.4, 4.8 and 4.9. PIL sections 2 and 4. Restricted medical prescription. <u>Additional risk minimisation measures:</u> 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 Rimmyrah 10 mg/ml solution for injection

This is a summary of the risk management plan (RMP) for Rimmyrah 10 mg/ml solution for injection. The RMP details important risks of Rimmyrah 10 mg/ml solution for injection, how these risks can be minimised, and how more information will be obtained about Rimmyrah 10 mg/ml solution for injection's risks and uncertainties (missing information).

The summary of product characteristics (SmPC) of Rimmyrah 10 mg/ml solution for injection and its package leaflet give essential information to healthcare professionals and patients on how Rimmyrah 10 mg/ml solution for injection should be used.

Important new concerns or changes to the current ones will be included in updates of Rimmyrah 10 mg/ml solution for injection s RMP.

I. The medicine and what it is used for

Rimmyrah 10 mg/ml solution for injection is authorised for use in adults for the treatment of 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 neovascularisation (CNV). (see SmPC for the full indication). It contains Ranibizumab as the active substance and it is for intravitreal use.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Rimmyrah 10 mg/ml solution for injection, together with measures to minimise such risks, and the proposed studies for learning more about Rimmyrah 10 mg/ml solution for injection 's risks are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised 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 minimise its risks.

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

In the case of Rimmyrah 10 mg/ml solution for injection, these measures are supplemented with additional risk minimisation 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.

II.A List of important risks and missing information

Important risks of Rimmyrah 10 mg/ml solution for injection are risks that need special risk management activities to further investigate or minimise 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 Rimmyrah 10 mg/ml solution for injection. 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 risk	• Infectious endophthalmitis • Intraocular inflammation • Retinal detachment and retinal tear • Intraocular pressure increase
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important identified risk: Infectious endophthalmitis	
Evidence for linking the risk to the medicine	As per the summary of product characteristics (SmPC) section 4.8 “Undesirable effects”, frequency of infectious endophthalmitis in patients with ranibizumab treatment is uncommon (≥1/1,000 to <1/100).
Risk factors and risk groups	To minimize the occurrence of endophthalmitis by administering an IVT injection in a correct manner and to inform and educate physicians and patients on prevention and management of this event.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3, 4.4, 4.8 and 6.6. Package Information Leaflet (PIL) section 2, 3 and 4. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk</u>: Recommendations are included in SmPC section 6.6 and PIL sections 2, 3 and 4. Other routine risk minimisation measures

Important identified risk: Infectious endophthalmitis	
	Legal Status: Restricted medical prescription. **Additional risk minimisation measures:** Educational plan for adult patients.

Important identified risk: Intraocular inflammation	
Evidence for linking the risk to the medicine	As per the summary of product characteristics (SmPC) section 4.8 "Undesirable effects", frequency of uveitis in patients with ranibizumab treatment is common (≥1/100 to <1/10).
Risk factors and risk groups	To minimize the occurrence by administering an IVT injection in a correct manner and to inform and educate physicians and patients on prevention and management of this event. Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3 and 4.4. PIL sections 2 and 4. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk</u>: It is recommended that patients should be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation and is included in SmPC section 4.4. Other routine risk minimisation measures Legal Status: Restricted medical prescription. **Additional risk minimisation measures:** Educational plan for adult patients.

Important identified risk: Retinal detachment and retinal tear	
Evidence for linking the risk to the medicine	As per the summary of product characteristics (SmPC) section 4.8 "Undesirable effects", frequency of retinal

	detachment and retinal tear in patients with ranibizumab treatment is common (≥1/100 to <1/10).
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 minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation of careful monitoring and use of proper aseptic injection techniques are included in SmPC section 4.4 and PIL section 2. Other routine risk minimisation measures Legal Status: Restricted medical prescription. **Additional risk minimisation measures:** Educational plan for adult patients.

Important identified risk: Intraocular pressure increase	
Evidence for linking the risk to the medicine	As per the summary of product characteristics (SmPC) section 4.8 "Undesirable effects", frequency of Intraocular pressure increased in patients with ranibizumab treatment is very common (≥1/10).
Risk factors and risk groups	Pre-existing high IOP.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, 4.8 and 4.9. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Ranibizumab should not be administered in the event of an intraocular pressure of ≥30 mmHg

	Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately, and to take appropriate precautions is included in SmPC section 4.4. Other routine risk minimisation measures Legal Status: Restricted medical prescription. **Additional risk minimisation measures:** Educational plan for adult patients.

Important potential risk: None

Missing information: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation
There are no studies which are conditions of the marketing authorisation or specific obligation of Rimmyrah 10 mg/ml solution for injection.

II.C.2 Other studies in post-authorisation development plan
There are no studies required for Rimmyrah 10 mg/ml solution for injection.

PART VII: ANNEXES

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Annex 4 - Specific adverse drug reaction follow-up forms
Targeted Follow-up Checklist: Infectious Endophthalmitis
In addition to collecting routine information for this AE, please ensure the following additional information is provided and/or confirmed.
Event Description:
• Date of last ranibizumab injection before event onset:
• Number of ranibizumab injections received before event onset:
• Eye(s) affected: □ Right eye □ Left eye □ Both eyes
• 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 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?
Relevant medical history (concurrent and pre-existing conditions):
• Did the patient receive prior laser therapy?
□ Yes □ No □ Unknown
• If yes, please provide date and which eye(s) was treated
• Any medications administered via intravitreal injection previous to AE?
□ Yes □ No □ Unknown
• 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

Targeted Follow-up Checklist: Follow-up Questionnaire for use of Rimmyrah in paediatric patients including paediatric off-label use

Patient demography and indication

A. What was the age of the child when Rimmyrah was started? ____ _

B. What is the age group of the child at the time of reported event?

□ Neonate (0 - ≤ 27 days) □ Infant (28 days to 23 months) □ Child (2 to 11 years)

□ Adolescent (12 to 17 years)

C. What was the age of the child at the time of reported event? ____ _

D. What is the ocular condition being treated?

□ Retinopathy of Prematurity (ROP)

• If ROP, please specify gestational age at birth ____ and birth weight of the child ----

□ Choroidal neovascularization (CNV), please specify reason for CNV ____ _

□ Macular edema

□ Other, specify ____ _

E. Which eye(s) is affected? □ Right □ Left □ Both

Patient history

F. Did the patient receive intravitreal injections prior to event? □ Yes □ No □ Unknown

• If YES, please describe, including

A. Which eye(s) was treated? □ Right □ Left □ Both

B. Which anti-VEGF did the patient receive previously?

□ Ranibizumab □ Aflibercept □ Bevacizumab □ Unknown

□ Other, specify ____ _

• If ranibizumab injection was given:

- What is the number of injections received before event onset? ____ _
- What is the date of last injection before event onset? ____ _
- What dose was used?
- What regimen was used (e.g. PRN, monthly, duration)?

G. Did the patient receive laser therapy prior to the event? □ Yes □ No □ Unknown

• If YES, please provide:

• Which eye(s) was treated □ Right □ Left □ Both

Date of last treatment -----

Change in visual acuity in treated eye(s)

H. Did the patient have any improvement of visual acuity? □ Yes □ No □ Unknown

• lf YES, please provide available information on visual acuity gain: _____ _

• lf NO, was there vision loss: □ Yes □ No

• Please provide any other relevant information on visual acuity data: _____

Funduscopic examination findings in treated eye

l. Did the patient have any funduscopic exam? □ Yes □ No □ Unknown

• lf YES, please describe results and/or any other relevant information: _____

Imaging data (e.g. OCT or fluorescein angiography) in treated eye

J. Did the patient have an OCT or fluorescein angiography exam? □ Yes □ No □ Unknown

• lf YES, please describe result or any other relevant information on imaging data (i.e. change in central subfield thickness, intraretinal cyst, CNV lesion, etc): _____

Annex 6 - Details of proposed additional risk minimisation activities
Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreements with the National Competent Authorities in each Member State where Rimmyrah 10 mg/ml solution for injection is marketed, at launch and after launch all ophthalmological clinics where Rimmyrah 10 mg/ml solution for injection is expected to be used are provided with an up-to-date patient information pack.

Key messages of the additional risk minimization measures for adult patients in the indications of nAMD, CNV, DME, RVO and PDR

The patient information pack

The patient educational material will be developed and distributed to the local representatives of the Marketing Authorization Holder, and from the local organization to the physician who can distribute it further to their patients, in order to support the safe use of ranibizumab. The patient information booklet provides 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 ranibizumab 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-CD that contain following key elements:

- Patient information leaflet
- How to prepare for Rimmyrah treatment
- What are the steps following treatment with Rimmyrah
- Key signs and symptoms of serious adverse events including increased intraocular pressure, intraocular inflammation, retinal detachment & 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 potential adverse events of ranibizumab, a patient information booklet (also available in spoken form in is available. The booklets are provided to the physician for distribution to the patient after ranibizumab is prescribed to them.

The booklets aim to provide adequate patient education on:
• What is nAMD, CNV (including secondary to PM), DR with or without DME, and RVO
• How does ranibizumab work, what to expect from ranibizumab treatment, and how is ranibizumab administered
• What are the key signs and symptoms of serious adverse events including increased intraocular pressure, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis
• When to seek urgent attention from the health care provider

Key safety messages are focused on facilitating the patient recognizing the key signs and symptoms of potential adverse reactions to ensure the patient informs their ophthalmologist of

these potentially severe outcomes. The following are the key safety messages to be communicated to allow early diagnosis and appropriate treatment of these events:
• It is important that patients monitor any changes in the condition of their eye and their overall wellbeing in the week following injection with ranibizumab
• 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 booklet contains follow-up recommendations for adequate care after the injection, including recommendations to contact the physician in case of additional questions.

Patient information packs are prepared nationally, in line with the key important risks defined in the RMP and with each member state's national regulations and legislations. Local MAHs are responsible to convey the key safety messages into the local versions of the educational materials. The submission of the material to the respective member state national authorities should take place before the launch of ranibizumab in a new indication (according to the national legislation in the respective countries), and the distribution of the material to all ophthalmology clinics where ranibizumab is expected to be used for treatment of adult patients.