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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lucentis

International non-proprietary name: ranibizumab

Procedure No. EMEA/H/C/000715/II/0076

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNV	Choroidal neovascularisation
DCCT	Diabetes Control and Complications Trial
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRCR.net	Diabetic Research Clinical Research Network
DRSS	Diabetic Retinopathy Severity Score
ETDRS	Early Treatment Diabetic Retinopathy Study
ETDRS-DRSS	Early Treatment Diabetic Retinopathy Study – Diabetic Retinopathy Severity Scale
EU	European Union
FDA	US Food and Drug Administration
HbA1c	Hemoglobin A1c
JCHR	Jaeb Center for Health Research
LOCF	Last observation carried forward
ME	Macular edema
MPA	Medical Products Agency
nAMD	Neovascular AMD
NPDR	Non-proliferative diabetic retinopathy
OCT	Optical coherence tomography
PDR	Proliferative diabetic retinopathy
PRN	Pro re nata (as needed)
PRP	Panretinal photocoagulation
PSUR	Periodic Safety Update Report
REFINE	RFB002D2305 (referred to as Study D2305)
RESTORE	RFB002D2301 (referred to as Study D2301)
REVEAL	RFB002D2303 (referred to as Study D2303)
RMP	Risk Management Plan
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics UK United Kingdom
US	United States
VEGF	Vascular endothelial grow factor
VEGF-A	Vascular endothelial growth factor A

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 13 November 2018 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) in adults for Lucentis;
as a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated with the safety information.

The Package Leaflet is updated in accordance.

RMP version 19.0 is also being submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0142/2018 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products, because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek scientific advice at the CHMP.

2. Scientific discussion

2.1. Introduction

Lucentis® (ranibizumab) is a recombinant humanised immunoglobulin (Ig) G1 kappa monoclonal antibody fragment that binds to vascular endothelial growth factor A (VEGF-A) and has been developed for intraocular use. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors, thus blocking the effects of VEGF on vascular permeability, angiogenesis, and neovascularisation. Vascular endothelial growth factor is over-expressed in ocular conditions that result

in ocular neovascularisation and retinal edema and lead to vision loss. VEGF-A has been shown to cause neovascularisation and vascular leakage in models of ocular angiogenesis. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

Ranibizumab is currently approved in more than 100 countries worldwide for the treatment of neovascular (wet) age-related macular degeneration (nAMD), visual impairment due to choroidal neovascularisation (CNV), diabetic macular edema (DME), and macular edema secondary to branch or central retinal vein occlusion (RVO). In the US, ranibizumab 0.3 mg (Genentech Inc.) is also approved for diabetic retinopathy (DR).

In the EU, ranibizumab intravitreal injection at a dose of 0.5 mg is currently approved for the treatment in adults of:

- neovascular (wet) age-related macular degeneration (AMD) (referred to as nAMD throughout the text)
- visual impairment due to choroidal neovascularisation (CNV)
- visual impairment due to diabetic macular edema (DME)
- visual impairment due to macular edema secondary to retinal vein occlusion (RVO) (branch RVO or central RVO)

With the present submission, Novartis seeks approval for the use of ranibizumab in adults for the treatment of moderately severe to severe non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR).

Disease background

Diabetic retinopathy (DR) is a microangiopathy that leads to hypoxia-triggered up-regulation of pro-angiogenic, proinflammatory, and vascular permeability factors, including vascular endothelial grow factor (VEGF), and to the development of subsequent vessel leakage, subclinical inflammation, and neovascularisation in the retina. It occurs as a complication of both Type 1 and Type 2 diabetes mellitus and is strongly associated with other microvascular complications of diabetes – and poor control of hyperglycemia.

Globally, DR is a leading cause of visual impairment and blindness. The Meta-analysis for Eye Disease Study Group estimated that, in 2010, 35 % of adults with diabetes had some form of DR, which amounts to approximately 93 million individuals worldwide (Yau et al 2012). In 2017, it was estimated that approximately 58 million individuals in Europe had diabetes (Types 1 and 2) (International Diabetes Federation 2017).

Despite best efforts to optimally control blood glucose, if DR already has developed and left untreated, it continues to worsen, with increasing risk of vision-threatening complications, including diabetic macular edema (DME), macular ischemia, and proliferative diabetic retinopathy (PDR).

Classification of DR

Diabetic retinopathy is classified as either non-proliferative diabetic retinopathy (NPDR) or PDR, based on the absence or presence of abnormal new vessels, respectively. NPDR is the earliest stage of DR, which is characterised by abnormalities visible by ophthalmoscopy that include microaneurysms, intraretinal hemorrhages, exudates, retinal nerve fiber layer infarcts (cotton wool spots), and, in more severe cases, venous beading and intraretinal microvascular abnormalities. Worsening of NPDR to PDR is characterised by neovascularisation and is regarded as a serious, clinically important progression of the pathology, as well as marking the transition of the disease to an advanced stage (Wykoff et al. 2018). PDR is associated with a high risk of visual morbidity arising from vitreous hemorrhage, traction

retinal detachment, and neovascular glaucoma (Aiello et al. 1998, Wykoff et al. 2018). Patients can also develop DME at any stage during the progression of DR (Ciulla et al. 2003).

DR pathophysiology and the role of vascular endothelial growth factor (VEGF)

Vascular endothelial growth factor has been implicated in all aspects of vascular pathology in DR (Campochiaro 2015). Increased levels of VEGF in vitreous were shown in animal models of diabetes, as well as in NPDR and PDR patients compared with control healthy subjects (Aiello et al 1994, Ambati et al 1997, Sone et al 1997). Vitreous VEGF levels in DR patients have been shown to correlate with the severity of DR (Funatsu and Yamashita 2003, Funatsu et al 2005, Funatsu et al 2006, Praidou et al 2011).

Current treatment options for DR

Treatment of mild NPDR involves management of the patient's diabetes; at this stage, intervention for the treatment of NPDR is in general not recommended, and NPDR is monitored annually, with the patient encouraged to maintain control of diabetes as well as possible (Royal College of Ophthalmologists 2012). Ocular therapy is warranted once progression to PDR occurs, or if a patient develops DME. The standard-of-care for PDR is panretinal photocoagulation (PRP), and based on AAO guidelines, anti-VEGF therapy and PRP are recommended for PDR with or without DME; focal and/or grid laser may also be used when clinically significant DME is present (Royal College of Ophthalmologists 2012, American Academy of Ophthalmology Retinal (AAO) 2017).

Panretinal photocoagulation is a laser treatment, which involves applying laser burns scattered throughout the retina away from the macula. With the goal of reducing the risk of vision loss, PRP leads to tissue coagulation and subsequent regression or stabilization of the neovascularisation. According to the Diabetic Retinopathy Study, PRP reduced the risk of severe visual loss (visual acuity $\leqslant$5/200 patients) by approximately 50 % over 5 years (Diabetic Retinopathy Study Research Group 1981, Diabetic Retinopathy Study Research Group 1987).

Typically, the PRP procedure involves the application of 1200–1600 laser burns, approximately 500 µm in size, applied throughout the retinal tissue but away from the macula, destroying viable areas of the retina. The destructive nature of this treatment is associated with ocular adverse effects (ETDRS Research Group 1991a, Fong et al 2007, Heng et al 2013, Reddy and Husain 2018). Consequences of PRP include irreversible destruction of peripheral retinal tissue, including potentially severe and permanent peripheral visual field loss, night blindness, loss of colour vision, reduced contrast sensitivity, recurrent vitreous hemorrhages, and PRP-induced DME exacerbation with central vision loss (Fong et al 2007, Ip et al 2012). Patients who undergo PRP may experience spatial orientation deficits related to peripheral vision loss, contributing to difficulties with executing activities of daily living (ETDRS Research group 1991a, Fong et al 2007, Royal College of Ophthalmologists 2012, Heng et al 2013, AAO 2017).

Vitreous surgery may be considered in patients with high-risk PDR. The risks of invasive surgical intervention include infection, iatrogenic cataract, and intraocular hemorrhage (Stefansson 2001, AAO 2017).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

An Environmental Risk Assessment concluding that based on the nature of ranibizumab as a recombinant monoclonal antibody fragment there is no likely risk to the environment. This is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP, as declared by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1. Summary of clinical studies (total study population).

Study	Study design	Treatments	N[a]
Protocol S ML27976	Randomised, active-controlled, parallel-assignment, non-inferiority Phase 3 study comparing ranibizumab 0.5 mg intravitreal injections with deferred PRP to standard PRP therapy in adult patients with PDR in 1 or both eyes with or without DME at baseline; primary analysis at 2 years and follow-up to 5 years	*Treatment group 1:* Ranibizumab 0.5 mg intravitreal injection at baseline and every 4 weeks through 12 weeks; thereafter, re-treatment based on investigator assessment of neovascularisation	191
		Treatment group 2: PRP at baseline, completed in 1-3 visits	203
RESTORE D2301	1-year, randomised, double-masked, active-controlled efficacy/safety study comparing ranibizumab 0.5 mg intravitreal injections with adjunctive administration of ranibizumab 0.5 mg intravitreal injections and active laser, and with laser treatment in adult patients with DME at baseline (only 1 eye)	Treatment group 1: Ranibizumab 0.5 mg PRN intravitreal injections (plus sham laser)	116
		Treatment group 2: Adjunctive administration of ranibizumab 0.5 mg PRN intravitreal injections with active laser	118
		Treatment group 3: Laser treatment (plus sham injections)	111
REVEAL D2303	1-year, randomised, double-masked, active-controlled efficacy/safety study comparing ranibizumab 0.5 mg PRN with photocoagulation treatment in adult Asian patients with DME at baseline (only 1 eye)	Treatment group 1: Ranibizumab 0.5 mg PRN intravitreal injections (plus sham laser)	133
		Treatment group 2: Adjunctive administration of ranibizumab 0.5 mg PRN intravitreal injections (plus active laser)	132
		Treatment group 3: Laser treatment (plus sham injections)	131
REFINE D2305	1-year, randomised, double-masked, laser-controlled efficacy/safety study comparing ranibizumab 0.5 mg PRN with photocoagulation treatment in adult Chinese patients with DME at baseline (only 1 eye)	Treatment group 1: Ranibizumab 0.5 mg PRN intravitreal injections (plus sham laser)	307
		Treatment group 2: Laser treatment (plus sham injections)	77

[a] N for Protocol S is the number of eyes. For Novartis studies, it is the number of patients. Note that the 'N' is the total number of eyes or patients for the entire study population.

2.4. Clinical efficacy

2.4.1. Main study

Protocol S

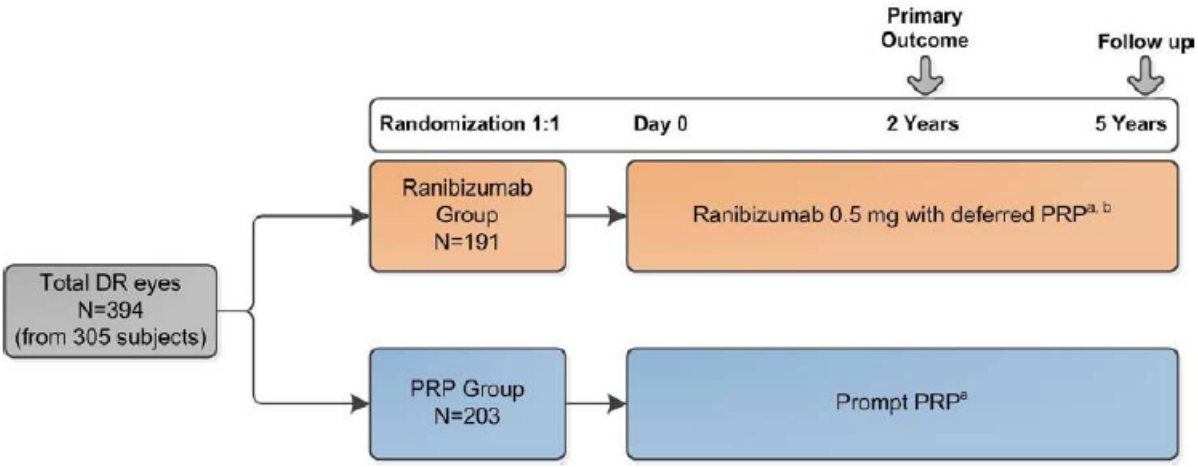
Protocol S compared the efficacy of ranibizumab 0.5 mg with PRP in diabetic patients with PDR. It was a JCHR (DRCR.net) -sponsored Phase 3, multi-center, randomised, active-controlled, parallel-assignment, non-inferiority study for which the primary efficacy analysis was at 2 years, with follow-up up to 5 years. Protocol S enrolled 305 patients (394 study eyes) with PDR, with or without concomitant DME at baseline. Patients had Type 1 or Type 2 diabetes with PDR and had not yet received PRP in at least one eye. One or two eligible study eyes could be enrolled.

The sponsor designed and conducted the study and was responsible for the overall study management (monitoring), data management, and drug safety process for this clinical study. Genentech had an opportunity to review and comment the JCHR (DRCR.net) protocol. However, JCHR (DRCR.net) was under no obligation to incorporate those suggestions. Genentech was not involved in the conduct of the study but did provide ranibizumab to defray the study costs. Genentech also conducted the statistical analysis of the data for this report.

Patients with one study eye were randomly assigned to either PRP or intravitreal ranibizumab 0.5 mg. If DME was present at baseline in eyes assigned to the PRP group, a baseline ranibizumab injection was administered, and PRP treatment was initiated within 14 days (Figure 1). Eyes in both treatment groups could receive study ranibizumab for DME at any time during the study. PRP was permitted in the ranibizumab group only if failure or futility criteria were met. For patients with 2 study eyes enrolled, 1 eye was randomly assigned to the PRP group, and the other eye was assigned to the ranibizumab group.

Ranibizumab treatment initiation consisted of injections at baseline and every 4 weeks up to Week 12 (total of 4 injections), and thereafter, treatment was given as needed based on disease activity.

Figure 1. Overview of study design.



DR = diabetic retinopathy; PRP = panretinal photocoagulation.

Note: Subjects could have 2 study eyes enrolled. For the visit schedule see Section 3.1 of the Protocol

[a] Intravitreal ranibizumab could be given as needed for DME

[b] Ranibizumab group: PRP was allowed for cases of treatment failure

Methods

Study participants

The study included male and female patients ≥18 years of age with either Type 1 or Type 2 diabetes mellitus (according to American Diabetes Association or WHO guidelines) with and without DME, who had at least one eye who fulfilled the study eye criteria including presence of PDR and a BCVA score of 24 (approximate Snellen equivalent 20/320) or greater on the day of randomisation. – Patients were excluded if they had received any anti-VEGF or pro-VEGF treatment within 4 months prior to randomisation, and who had macular edema due to a cause other than diabetes.

Treatments

Arm I (ranibizumab): 0.5 mg intravitreal injection at randomisation and at follow-up visits at 4, 8, and 12 weeks. Beginning at the 16-Week visit, eyes were evaluated for retreatment based on appearance of neovascularisation. Although PRP was deferred, PRP was allowed in cases of treatment failure.

Arm II (PRP/laser): full session of 1200 to 1600 burns using 500 µm burns on the retina or the equivalent area treated when using indirect laser delivery systems or laser was completed within 56 days of randomisation. Study eyes in the PRP group could receive supplemental PRP if neovascularisation worsened during the study following completion of the initial PRP session.

Both: Eyes in both groups could receive ranibizumab as needed for diabetic macular edema (DME), at baseline or if DME developed during the course of the study.

Objectives

The **primary objective** of the Protocol S study was to determine if visual acuity outcomes at 2 years in eyes with proliferative diabetic retinopathy (PDR) that received ranibizumab with deferred panretinal photocoagulation (PRP) were non-inferior to those in eyes that received standard prompt PRP therapy.

Secondary objectives included:

- Comparing other visual function outcomes in eyes that received ranibizumab with deferred PRP with those in eyes that received prompt PRP.
- Determining percent of eyes that did not require PRP when ranibizumab was given in the absence of prompt PRP.
- Comparing safety outcomes between treatment groups.
- Comparing associated treatment and follow up exam costs between treatment groups.

JCHR (DRCR.net) was responsible for the design and conduct of the study. Subsequent to finalization of the protocol, Genentech, Inc. (Genentech) identified additional diabetic retinopathy (DR) severity outcomes of interest:

- Proportion of eyes with ≥ 3-step improvement from baseline in ETDRS-DRSS at 1 year and 2 years
- Proportion of eyes with ≥ 2-step improvement from baseline in ETDRS-DRSS at 1 year and 2 years
- Proportion of eyes with ≥ 3-step worsening from baseline in ETDRS-DRSS at 1 year and 2 years
- Proportion of eyes with ≥ 2-step improvement from baseline in ETDRS-DRSS from PDR at baseline to NPDR at 1year or 2 years

Deviating from the clinical trial protocol, the **key outcomes** to support this extension were:

- Proportion of eyes/patients with at least *2-step improvement* from baseline in DRSS
- Proportion of eyes/patients with at least *2-step worsening* from baseline in DRSS
- Proportion of eyes/patients with at least *3-step improvement* from baseline in DRSS
- Proportion of eyes/patients with at least *3-step worsening* from baseline in DRSS

Outcomes/endpoints

The **primary efficacy variable** was the mean change from baseline in Best Corrected Visual Acuity (BCVA) score at 2 years.

Secondary multiple efficacy variables including continuous (e.g. binocular visual acuity at 2 years), binary (e.g. proportion of eyes that gained at least 15 letters in BCVA score from baseline at 2 years, proportion of eyes with >= 2-step improvement from baseline in the ETDRS-DRSS score at 2 years), and time-to-event scores (e.g. development of DM through 2 years).

Additional secondary efficacy variables included:
1) Proportion of eyes with ≥ 3-step improvement from baseline in ETDRS-DRSS at 1 year and 2 years,
2) Proportion of eyes with ≥ 2-step improvement from baseline in ETDRS-DRSS at 1 year and 2 years,
3) Proportion of eyes with ≥ 3-step worsening from baseline in ETDRS-DRSS at 1 year and 2 years,
4) Proportion of eyes with ≥ 2-step improvement from baseline in ETDRS-DRSS from PDR at baseline to NPDR at 1year or 2 years.

Safety endpoints consisted of collecting all AEs, serious adverse events (SAEs), with their severity and relationship to study treatment, pregnancies, physical examinations, laboratory tests and ophthalmic examinations.

Subgroups were analysed according to the CSP for the BCVA endpoint (mean change from baseline in BCVA at 2 years) and ETDRS-DRSS response endpoint by baseline variables, including race, sex, baseline endpoint, baseline DME status, prior DME treatment, baseline DR severity, individual sites with at least 20 subjects enrolled, baseline OCT and additionally age (<65 vs. >= 65 years) and number of eyes enrolled (1 eye vs. 2 eyes).

The primary endpoint was defined as 'Mean change from baseline in BCVA score at 2 years' and tested using a global type I error of 5 % (confidence level of 95 %). Multiple secondary efficacy endpoints

were defined. Additional efficacy endpoints were added to the CSP and SAP, respectively, after the 2-year data cut-off, but before Genentech-Roche and JHCR received any study results.

The MAH states that the ETDRS-DRSS endpoint is not applicable in the PRP treatment group, as eyes that received PRP had large portions of their peripheral retinas destroyed because of iatrogenic PRP-induced scars. These eyes could no longer achieve NPDR status (i.e. ETDRS-DRSS score less than 60) at any time point after PRP treatment was received. Therefore, the MAH was requested to address the issue of differential sensitivity to change of the ETDRS-DRSS endpoint in the PRP group, and the degree of bias the comparison between the ranibizumab and PRP treatment groups might show.

In response, the company presented an analysis adjusting for this ETDRS-DRSS bias in the PRP (laser) group, whose response may have been affected by the truncation of the endpoint. The results were similar to the original result showing the non-inferior to PRP treatment vs PRP treatment.

Adding secondary endpoints and finalising the SAP after data cut-off may be seen as a deviation from ICH E9, which states that in blinded studies finalising the SAP before unblinding is acceptable. However, subjects, investigators, and study coordinators were not masked in this double-masked study, and, therefore, finalising the SAP before database lock is recommended. However, since the MAH stated that the SAP was finalized before availability of data, this can be considered acceptable.

The type 1 error of comparative tests of secondary endpoint is not globally controlled, which may lead to an inflation of type I error and over-interpretation of results. This issue may be mitigated by the fact that many of the secondary endpoints are expected to be correlated and show consistent results across independent samples (c.f. Protocol S, Novartis studies), and the observed effect size, respective significance levels, of the key outcomes.

The MAH was asked to discuss the overall type I error, i.e. the risk of a false positive conclusion, considering multiple testing of all primary and (additional) secondary endpoints, primary and secondary visits, and additional contributing issues, such as lack of adjustment for correlatedness of eyes per subject (overdispersion), underestimation of variability by last observation carried forward (LOCF) imputation, differential sensitivity to change of endpoints (ETDRS-DRSS), and analysis in the intention-to-treat population. In response, the company presented results from the suggested analyses and relevant discussion of each of the raised issues, which are potentially affecting the risk of false positive results. The arguments and results convincingly show that this risk is controlled at an acceptable level at or below the pre-specified type I error level for each of the raised issues. The risk that all issues jointly might have caused false positive results is not expected to exceed the pre-specified type I error either.

Furthermore, the MAH was requested to justify the full session of 1200 to 1600 burns using 500 µm burns. This appears to translate into an incomplete PRP in a subset of patients, i.e. suboptimal treatment with markedly fewer burns compared with conventional PRP. In response, the company states that treatment guidelines for PRP defined the application of 1200–1600 burns with a spot size on the retina of approximately 500 µm using conventional laser (or equivalent when using a laser producing an automated pattern) given over 1 to 3 sessions. Overall, the company's response was considered acceptable.

Sample size

The sample size estimate was computed for the primary study objective, to determine whether visual acuity in the ranibizumab group is non-inferior to visual acuity in the PRP group at 2 years. Based on the objectives of this study and the potential deleterious effects on visual function by PRP, a non-

inferiority margin of 5 letters was judged to be clinically acceptable. The sample size was calculated to be 177 eyes in each group. This was increased to 190 eyes per group (380 total eyes) to account for loss to follow-up. Assuming 20 % of study subjects have two study eyes (based on enrolment in previous JCHR (DRCR.net) studies), this equates with approximately 316 study subjects. The observed sample size was 305 patients and 394 eyes.

Randomisation

Subjects with one study eye were randomly assigned (stratified by site and presence or absence of central involved DME) with equal probability (1:1) to one of the treatment groups: 1) PRP group, 2) Ranibizumab group. Subjects with two study eyes (both eyes eligible at the time of randomisation), were randomised with equal probability to either of the:

- PRP group in the eye with greater optical coherence tomography (OCT) central subfield and the ranibizumab group in the eye with lower OCT central subfield thickness,
- Ranibizumab group in the eye with greater OCT central subfield and the PRP group in the eye with lower OCT central subfield thickness.

If both eyes had the same OCT central subfield thickness, the right eye was considered the eye with the greater OCT central subfield thickness. For the purpose of stratification, the presence of DME was defined on OCT central subfield thickness as $\geqslant$ 250 microns on Zeiss Stratus OCT (or equivalent thickness on spectral domain OCT machine).

Subjects were randomised on the same day that treatment was to be initiated. For subjects with two study eyes that were treated with ranibizumab at baseline, both eyes could be injected on the same day or on separate days as long as the second eye was injected within one week of randomisation.

Blinding (masking)

Study monitors who reviewed all AEs were masked to the assigned treatments. The reading center graders who evaluated the fundus photographs and the visual acuity and OCT technicians were also all masked to treatment group assignments at annual visits. – Subjects, investigators, and study coordinators were not masked to treatment assignments because of the nature of the treatments.

Based on Genentech's own judgment, potential treatment group unmasking due to the ability to observe PRP scars on fundus photographs should not cause substantial bias or impact the interpretation of the overall ETDRS-DRSS results.

The applied masking procedure is considered appropriate under the circumstances of the therapeutic procedures. Subjects, investigators, and study coordinators were not masked. However, based on the objective type of key endpoints (esp. BCVA and ETDRS-DRSS) and masking of assessors, the conclusion of the MAH that potential bias or impact on the interpretation on BCVA or ETDRS-DRSS results should not be substantial can be supported.

Statistical methods

The primary analysis was performed in the ITT ("randomised eyes") population with missing values imputed by the "last observation carried forward" (LOCF) method.

The null hypothesis that ranibizumab is inferior to laser treatment was tested using the **primary endpoint** "Mean change from baseline in BCVA score at 2 years" (see continuous variables below for statistical model), using a non-inferiority margin of 5 letters, and secondary endpoints (continuous, binary, time-to-event). However, selected secondary and additional secondary endpoints based on

ETDRS-DRSS 2-step or 3-step change responder endpoints (improvement or worsening) were presented as **key outcomes** (see binary variables below for statistical model) in the marketing authorization application.

For stratified analyses of **continuous variables**, the estimates and CIs of the mean for each treatment group and the difference in means between treatment groups were based on the analysis of variance (ANOVA) or the analysis of covariance (ANCOVA) model used to analyse the endpoint. For unstratified analyses of means, the estimates and CIs were based on the observed means, difference in observed means, and the Student t distribution.

For stratified analyses of **binary variables**, the proportion for each treatment group and the overall difference in proportions between treatment groups were estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata using the Cochran–Mantel–Haenszel (CMH) weights. The stratification variables were the same as those used in the stratified test for treatment difference. CIs of the proportion for each treatment group and the overall difference in proportions between treatment groups (unstratified or stratified) were calculated using the normal approximation to the binomial distribution method. For unstratified analyses of proportions, the proportion for each treatment group and the overall difference in proportions between treatment groups were estimated using the observed proportions and the difference in the observed proportions.

All efficacy analyses (unless otherwise noted) were stratified by baseline DME status, and number of study eyes enrolled. In addition to p-values for statistical tests, the point estimates and confidence intervals (CIs) were provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment group and the difference in means or proportions between the two treatment groups. All CIs were two sided and at the 95 % level.

Missing data was imputed by using the 'last value carried forward' (LOCF) method, however, additional sensitivity analysis for mean change from baseline in BCVA at 2 years and ETDRS-DRSS step change endpoints at 2 years were performed based on 1) observed data, and 2) MCMC multiple imputation.

Safety analyses were performed in the 'safety-evaluable eyes' and 'safety-evaluable subjects' datasets. Safety endpoints consisted of AEs with their severity and relationship to study treatment, pregnancies, physical examinations, laboratory tests and ophthalmic examinations during the 2-year period up to and including the 2-year visit.

The non-inferiority margin of 5 letters for the primary endpoint can be considered wide and based on previous CHMP advice a 3–4 letter margin would have been better justified. However, this has no implications as the adjusted least squares mean treatment group difference was 3.5 letters (95 % CI: 0.2, 6.7 letters) and non-inferiority of Lucentis vs. PRP was consequently demonstrated.

In Protocol S non-inferiority hypotheses were tested in a (modified) ITT population, which may not always be conservative. Therefore, the MAH was asked to also provide results of the key outcome parameters and key visits in a per protocol population. In response, the MAH provided results for BCVA and DRSS on the per protocol set of eyes which showed to be similar to the results from the analyses on all randomized eyes (ITT population).

From statistical perspective, the LOCF method for imputation of missing data is in general not recommended. Depending on the proportion and type of missing data per treatment group, the method may under- or overestimate the results and underestimate variability. Here, additional sensitivity analysis based on observed data (valid under missing-completely-at-random assumption) and MCMC-based multiple imputation (valid under missing-at-random assumption) are performed, which showed results consistent with the primary analysis.

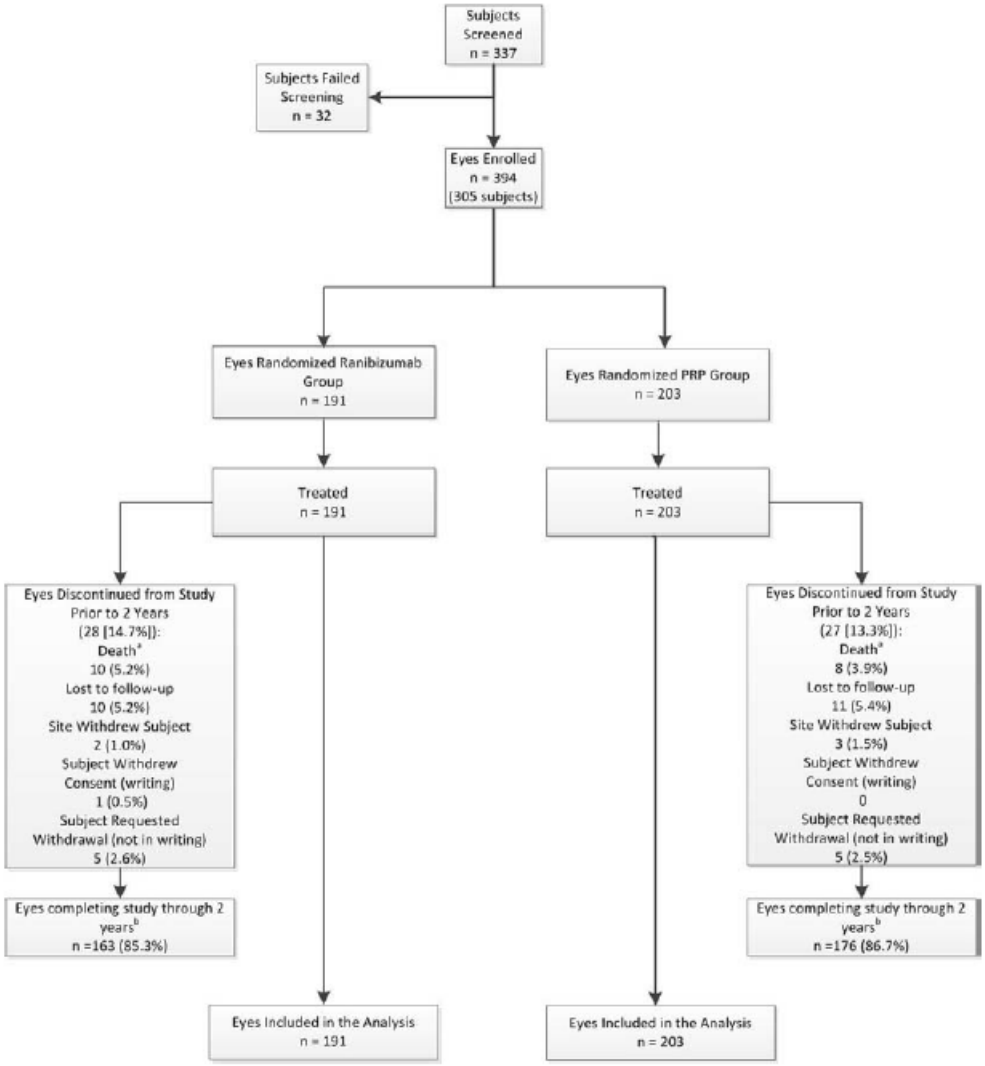
It has not been explained why in the summary and overview the primary endpoint of visual acuity is presented in section on additional efficacy outcomes.

The analysis units of the Protocol S study are eyes, which may be of the same patient and therefore correlated. Systematic differences between eyes from patients, which contributed one eye, and eyes from patients, which contributed two eyes, are modelled by the covariate or strata "one vs. two eyes". However, this model does not adjust for underestimation of the variability of the outcomes because of the correlatedness of observations (c.f. overdispersion). Therefore, the provided confidence intervals may to be too narrow and lead to false positive conclusions. This issue may be aggravated by the combination with LOCF method, which may also underestimate variability. The MAH was asked to discuss this issue and provide appropriate sensitivity analyses, for example, by using a generalized (mixed) effects model for the primary endpoint and presented key outcomes using the patient identifier as random (or fixed) effects variable. In response, the company provided the results using a generalised linear mixed effects model, including the correlation between both eyes using imputed data based on LOCF or multiple imputation. The results of the estimates and 95 % confidence intervals were similar to the results from the original analyses, although the 95 % confidence intervals of the sensitivity analyses were somewhat wider (as expected).

Results

Participant flow

Figure 2. Patient disposition, Protocol S.



[a] Includes 4 deaths in subjects with 2 study eyes (there were a total of 14 deaths through 2 years of the study).

[b] Eyes are considered to have completed the study through 2 years if the Week 104 visit was completed, or if discontinuation from the study occurred >756 days from randomization (104 weeks+4 weeks, per protocol specified visit schedule).

Recruitment

Subjects were recruited at 57 clinical sites in the United States of America with the first subject/first visit on 27 February 2012, and the last subject/2-year visit on 15 January 2015.

Conduct of the study

Amendments

The protocol was finalised on 6 October 2011 (version 1). It was amended after enrolment of the first subject and finalised on 28 October 2014 (version 2). The purpose of this amendment was to extend the treatment schedule up to 5 years to collect long-term safety and efficacy data.

Additional analyses

Genentech developed a SAP that describes the analysis of the Protocol S study efficacy and safety data used to support the approval of ranibizumab in the treatment of DR independent of DME status. Genentech's SAP describes the analysis methods used to analyse the pre-specified endpoints from the JCHR (DRCR.net) protocol and additional efficacy and safety outcome measures evaluated by Genentech, which were not identified in the JCHR (DRCR.net) protocol. In addition, there was no strict Type I error management plan for the proposed analyses of the Protocol S study data.

The addition of secondary endpoints after the 2-year data cut-off is acceptable, provided that the MAH was not influenced by the collected data (as stated).

While the type I error is considered controlled for the primary endpoint 'Mean change from baseline in BCVA score at 2 years', the presentation of results is primarily based on multiple ETDRS-DRSS step change responder endpoints and multiple visits, for which no strict type I error control is applied, which may lead to an inflation of type I error and over-interpretation of results (see above).

Protocol deviations

Major deviations with a severity classification of 1 or 2 were defined as critical deviations and typically involve potential significant impact to subject safety or a major effect on the evaluation of study outcome. A total of 23 subjects (approximately 8 %) had at least one major protocol deviation through 2 years; 10 subjects (9.8 %) in the ranibizumab-1 study eye group, 4 subjects (3.5 %) in the PRP "1 study eye group", and 9 subjects (10.1 %) in the 2 study eyes group (Table 2). The most common deviation was 'Injection not performed', occurring in 5 subjects in the ranibizumab-1 study eye group, 0 subjects in the PRP-1 study eye group and 8 subjects (9.0 %) in the 2 study eyes group. This deviation pertains to ranibizumab injections. One randomised subject (a subject with one study eye enrolled and randomised to the PRP group) had an exclusion criterion missed.

Table 2. Major protocol deviations through 2 years, safety evaluable subjects.

Deviation	Subjects with 1 Study Eye: Ranibizumab (N=102)	Subjects with 1 Study Eye: PRP (N=114)	Subjects with 2 Study Eyes (N=89)
Total number of subjects with at least one major protocol deviation	10 (9.8%)	4 (3.5%)	9 (10.1%)
Total number of major protocol deviations	12	4	11
Injection not performed	5 (4.9%)	0	8 (9.0%)
Rescue PRP given without prior approval	2 (2.0%)	0	0
Visit completed by uncertified Investigator	1 (1.0%)	0	1 (1.1%)
Incorrect consent completed	1 (1.0%)	0	0
Incorrect eye injected with study drug.	1 (1.0%)	0	0
Ineligible patient- minor *	0	1 (0.9%)	0
Intraocular injection not given on day of randomization	1 (1.0%)	0	0
PRP treatment not given on day of randomization	0	1 (0.9%)	0
Protocol visit missed - primary outcome	0	1 (0.9%)	0
Injection performed with commercial drug instead of study provided drug (same formulation)	0	1 (0.9%)	0

Multiple incidents per subject are counted only once.
*On manual review of fundus photographs in preparation for the primary manuscript, it was noted that the eye had advanced AMD and met exclusion for other ocular condition present.

Baseline data

In Protocol S, demographic and baseline characteristics and the baseline ocular characteristics were balanced across the two treatment groups (Table 3).

Table 3. Demographics and baseline characteristics, randomised eyes.

	Ranibizumab (N=191)	PRP (N=203)
Age (yr)		
n	191	203
Mean (SD)	50.4 (11.5)	50.5 (11.7)
Median	51.0	51.0
Min - Max	20 - 79	22 - 83
Age group (yr)		
n	191	203
<65	173 (90.6%)	187 (92.1%)
>=65	18 (9.4%)	16 (7.9%)
Sex		
n	191	203
Male	108 (56.5%)	111 (54.7%)
Female	83 (43.5%)	92 (45.3%)
Number of Eyes Enrolled		
n	191	203
One Study Eye	102 (53.4%)	114 (56.2%)
Two Study Eyes	89 (46.6%)	89 (43.8%)
Ethnicity		
n	191	203
Hispanic or Latino	48 (25.1%)	51 (25.1%)
Not Hispanic or Latino	136 (71.2%)	144 (70.9%)
Unknown/not reported	7 (3.7%)	8 (3.9%)
Race		
n	191	203
American Indian or Alaska Native	1 (0.5%)	0
Asian	2 (1.0%)	3 (1.5%)
Black or African American	40 (20.9%)	43 (21.2%)
White	135 (70.7%)	143 (70.4%)
More than one race	1 (0.5%)	2 (1.0%)
Unknown/not reported	12 (6.3%)	12 (5.9%)
Duration of Diabetes at Randomization (yr)		
n	191	203
Mean (SD)	18.0 (10.8)	16.6 (9.8)
Median	18.0	16.0
Min - Max	0 - 60	0 - 49
Diabetes Type		
n	191	203
Type 1	43 (22.5%)	41 (20.2%)
Type 2	140 (73.3%)	155 (76.4%)
Uncertain	8 (4.2%)	7 (3.4%)
Insulin Use		
n	191	203
Yes	135 (70.7%)	149 (73.4%)
No	56 (29.3%)	54 (26.6%)
Glycosylated Hemoglobin (HbA1c)		
n	184	198
Mean (SD)	9.02 (2.27)	9.10 (2.16)
Median	8.60	8.85
Min - Max	4.8 - 17.3	4.8 - 17.3
Baseline Systolic BP (mmHg)		
n	191	203
Mean (SD)	134.5 (19.9)	134.7 (18.9)
Median	135.0	135.0
Min - Max	85 - 180	83 - 177
Baseline Diastolic BP(mmHg)		
n	191	203
Mean (SD)	80.3 (11.0)	80.0 (11.7)
Median	81.0	80.0
Min - Max	52 - 108	46 - 108

Age is at Randomization.

The mean age of enrolled patients was approximately 51 years; 44 % were women, 71 % were White, and 75 % had Type 2 diabetes. The mean HbA1c at baseline was similar between the ranibizumab and PRP groups (9.02 % vs. 9.10 %, respectively, i.e. approximately 75 mmol/ml) as was the mean duration of diabetes at baseline (18.0 vs. 16.6 years, respectively).

The mean baseline visual acuity level was similar between the ranibizumab and PRP groups (75.0 vs. 75.2 letters, respectively). A total of 88 (22.3 %) eyes had baseline DME and 306 (77.7 %) eyes did not have DME at baseline.

Table 4. Baseline ocular characteristics in the study eye, randomised eyes.

	Ranibizumab (N=191)	PRP (N=203)
Study eye		
n	191	203
Right Eye	94 (49.2%)	98 (48.3%)
Left Eye	97 (50.8%)	105 (51.7%)
Visual acuity, number of letters (0-100)		
n	191	203
Mean (SD)	75.0 (12.8)	75.2 (12.5)
Median	77.0	78.0
Min - Max	25 - 97	26 - 96
Visual acuity, number of lines (0-20)		
n	191	203
Mean (SD)	14.99 (2.56)	15.04 (2.49)
Median	15.40	15.60
Min - Max	5.0 - 19.4	5.2 - 19.2
Visual acuity, method		
n	191	203
EVA-ETDRS	191 (100.0%)	203 (100.0%)
Visual acuity, approximate Snellen equivalent		
n	191	203
20/200 or worse	5 (2.6%)	2 (1.0%)
Better than 20/200 to worse than 20/40	35 (18.3%)	41 (20.2%)
20/40 or better	151 (79.1%)	160 (78.8%)

The baseline DRSS levels were balanced across the 2 treatment groups. In the ranibizumab and PRP groups, respectively, the most common baseline DR severity levels were moderate PDR (levels 65A-65C) (35.6 % and 33.0 %), high-risk PDR (levels 71A-71D) (24.6 % and 26.1 %), and mild PDR (levels 61A-61B) (15.7 % and 15.3 %). Of note, evaluation of DR for inclusion into the study was determined by the investigator; DR severity was assessed by the central reading center.

The study groups were sufficiently balanced at baseline. More than 70 % of subjects had Type 2 diabetes. Assessed by current European treatment guidelines, the glycaemic control was poor with mean HbA1c levels at baseline as high as 75 mmol/mol. The company was requested to discuss the external validity of the results. In response, the MAH presented data that the observed mean HbA1c in the US population enrolled in Protocol S is similar to the European population with PDR and thus sufficiently representative and reflective of a generally poor glycaemic control in this population.

Numbers analysed

The analysis populations are summarised in Table 5. The ITT population (all randomised eyes) was the analysis population used for the efficacy analyses. The safety-evaluable populations, defined on the basis of treatment actually received, were the analysis populations used for the safety analyses; safety

evaluable eyes were used for ocular safety analyses and safety evaluable subjects were used for non-ocular safety analyses. – 54.2 % of subjects in the comparator group received also ranibizumab (Table 6).

As 54.2 % of subjects in the comparator group received also ranibizumab the MAH was requested to present a sensitivity analysis of subgroups receiving only PRP treatment and only ranibizumab treatment. In response, the MAH presented sensitivity subgroup analyses of the primary endpoint demonstrating consistency with the original application, showing descriptively superiority of the 'ranibizumab only' vs. 'PRP only' treatment group at multiple timepoints.

Table 5. Analysis Population.

			Subjects with 1 Study Eye		Subjects with 2 Study Eyes
	Ranibizumab	PRP	Ranibizumab	PRP	
Randomized Eyes (ITT)	191	203	-	-	-
Safety Evaluable Population					
Safety Evaluable Eyes	191	203	-	-	-
Safety Evaluable Subjects	-	-	102	114	89

ITT = Intent to treat.

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Table 6. Randomised treatment versus actual treatment through 2 years: randomised eyes (Protocol S, Table 51).

Actual treatment received	Ranibizumab N=191	PRP N=203
Ranibizumab only	178 (93.2 %)	0
PSP only	0	93 (45.8%)
Ranibizumab and PRP	13 (6.8 %)	110 (54.2%)
Actual treatment received includes study treatment received from Randomisation to the 2-year visit in the study eye only.		

Outcomes and estimation

Protocol S

The majority of eyes randomised to ranibizumab (94.8 %) and PRP (94.6 %) completed the study through at least 1 year; through 2 years, 85.3 % of eyes in the ranibizumab group and 86.7 % of eyes in the PRP group completed the study. The most common reasons for discontinuation prior to 2 years were death and patient lost to follow-up in the ranibizumab group (5.2 % each) and patient lost to follow-up (5.4 %) and death (3.9 %) in the PRP group.

Effect on visual acuity

The main outcome of the study was the mean visual acuity letter score improvement from baseline at 2 years, which was 2.7 letters in the ranibizumab group and -0.7 letters in the PRP group (Table 7, Figure 3). The adjusted least squares mean treatment group difference was 3.5 letters (95 % CI: 0.2,

6.7 letters). The pre-specified non-inferiority margin for the primary endpoint was 5 letters. Non-inferiority was thus reached.

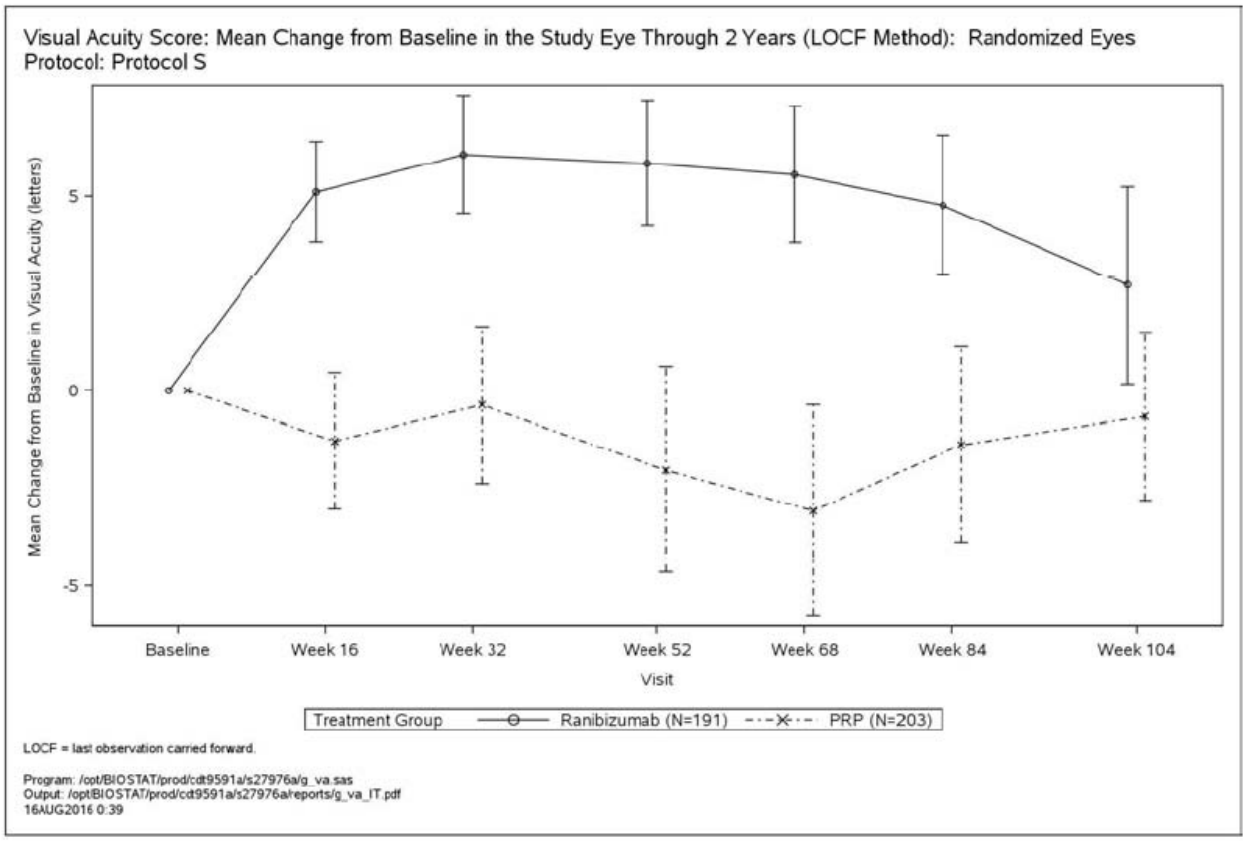
The finding was supported by sensitivity analyses (different methods of handling missing data) and the consistent results across subgroups based on the baseline characteristics (age, race sex, baseline BCVA, baseline DME status, prior DME treatment, baseline DR severity, number of eyes enrolled and baseline OCT.

Table 7. Mean change in BCVA from baseline in the study eye at 2 years (LOCF method), randomised eyes.

	Ranibizumab (N=191)	PRP (N=203)
Week 104 (2 Years)		
Number of letters change from baseline		
N	191	203
Mean (SD)	2.7 (17.8)	-0.7 (15.5)
SE	1.3	1.1
Median	5.0	1.0
Q1 - Q3	0.0 - 12.0	-4.0 - 7.0
Range	-86 - 43	-73 - 33
95% CI for mean	(0.2, 5.2)	(-2.8, 1.5)
Difference in means		3.4
95% CI for difference		(0.1, 6.6)
Estimate (pairwise ANOVA)		
LS mean (SE)	4.1 (1.3)	0.7 (1.3)
95% CI	(1.5, 6.7)	(-1.8, 3.2)
Difference in LS means		3.5
95% CI for difference		(0.2, 6.7)
Test for treatment difference		
Student t-test (unstratified)		0.0460
ANOVA t-test (stratified)		0.0382

LOCF = last observation carried forward; LS = least squares.
Stratification variables in stratified analyses: baseline DME status, and number of eyes enrolled. All CIs are two-sided. CIs for means and differences in means are based on Student t-distribution (unstratified). Estimates and CIs for LS means and differences in LS means are from the ANOVA model (stratified).

Figure 3. Mean change in visual acuity from baseline in the study eye over time (LOCF method), randomised eyes.


Visual Acuity Score: Mean Change from Baseline in the Study Eye Through 2 Years (LOCF Method): Randomized Eyes
Protocol: Protocol S
Mean Change from Baseline in Visual Acuity (letters)
5
0
-5
Baseline
Week 16
Week 32
Week 52
Week 68
Week 84
Week 104
Visit
Treatment Group
Ranibizumab (N=191)
PRP (N=203)
LOCF = last observation carried forward.
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A larger proportion of patients in the ranibizumab 0.5 mg group had a ≥2-step improvement in DRSS from baseline at 1 year and at 2 years than in the PRP treatment group. Similar results were observed in patients with and without DME.

At 1 year, 41.8 % of eyes in the ranibizumab group had ≥2-step improvement in DRSS from baseline compared with 14.6 % of eyes the PRP group, a difference of 27.4 %.

At 2 years, 42.3 % of eyes in the ranibizumab group had ≥2-step improvement in DRSS from baseline compared with 23.1 % of eyes the PRP group (19.2 % difference) (Table 8). In the ranibizumab group, results for ≥2-step improvement in DRSS from baseline were observed in 58.5 % of eyes with baseline DME and 37.8 % of eyes without DME, respectively. The consistent improvements in DRSS in the ranibizumab groups (overall and by baseline DME status) were supported by the proportion of eyes with ≥3-step improvement: 29.1 % overall (31.7 % and 28.4 % of eyes with and without baseline DME, respectively).

In the ranibizumab group, at 2 years, 4 eyes (2.1 %) had ≥3-step worsening and 7 eyes (3.7 %) had ≥2-step worsening; in the PRP group 11 eyes (5.5 %) had ≥3-step worsening of and 23 eyes (11.6 %) had ≥2-step worsening.

Table 8. Number (%) of eyes with at least 2-step or 3-step improvement or worsening from baseline in DRSS at the 2-year visit overall and by baseline DME status (eyes with a valid DRSS at baseline) (LOCF Method) (Protocol S).

	Ranibizumab			PRP		
	Overall (N=189)	**Eyes with baseline DME[a] (N=41)**	**Eyes without baseline DME[b] (N=148)**	**Overall (N=199)**	**Eyes with baseline DMEa (N=45)**	**Eyes without baseline DMEb (N=154)**
≥2-step improvement from baseline						
n (%)	80 (42.3)	24 (58.5)	56 (37.8)	46 (23.1)	13 (28.9)	33 (21.4)
95% CI for percentage	(35.3, 49.4)	(43.5, 73.6)	(30.0, 45.7)	(17.3, 29.0)	(15.6, 42.1)	(14.9, 27.9)
≥3-step improvement from baseline						
n (%)	55 (29.1)	13 (31.7)	42 (28.4)	7 (3.5)	2 (4.4)	5 (3.2)
95% CI for percentage	(22.6, 35.6)	(17.5, 46.0)	(21.1, 35.6)	(1.0, 6.1)	(0.0, 10.5)	(0.4, 6.0)
Worsening of ≥ 2-step from baseline						
n (%)	7 (3.7)	0	7 (4.7)	23 (11.6)	4 (8.9)	19 (12.3)
95% CI for percentage	(1.0, 6.4)		(1.3, 8.1)	(7.1, 16.0)	(0.6, 17.2)	(7.1, 17.5)
Worsening of ≥ 3-step from baseline						
n (%)	4 (2.1)	0	4 (2.7)	11 (5.5)	3 (6.7)	8 (5.2)
95% CI for percentage	(0.1, 4.2)		(0.1, 5.3)	(2.4, 8.7)	(0.0, 14.0)	(1.7, 8.7)

[a] Defined as DME on OCT at baseline with visual acuity letter score ≤ 78 (20/32 or worse).
[b] Defined as either no DME on OCT at baseline OR visual acuity letter score ≥ 79 (20/25 or better).

Ranibizumab treatment improved DR, with 2.7 letter gain in the mean BCVA score from baseline to 2 years, compared with 0.7 letter loss in the PRP group. In addition, larger proportions of eyes/patients achieved ≥2-step or ≥3-step DRSS improvement from baseline following ranibizumab treatment compared with PRP.

Comparative tests, estimates of difference and their confidence intervals between groups were initially not provided for subgroups (with DME, without DME, Table 8) and for visit at year 2 (Table 8) and the MAH was asked to provide these additional results. In response, the MAH provided data demonstrating that eyes in the ranibizumab group experienced a (at least nominally) statistically significant and clinically relevant benefit in terms of improvements in DRSS compared with eyes that

received PRP, consistent with results from the original application. This benefit was observed at Year 1 and Year 2, and regardless of the presence or absence of DME at baseline.

Additional efficacy outcomes

Patients with NPDR without DME

While Protocol S aimed to enrol only patients with PDR, the study population also included 23 eyes with moderately severe to severe NPDR without DME (9 in the ranibizumab group and 14 in the PRP group). Of the 9 eyes in the ranibizumab group, 7 had evaluable DRSS at 1 year, and 4 of these 7 eyes had ≥2-step improvement; the remaining 3 eyes had <2-step worsening. Of 14 eyes in the PRP group, 12 had evaluable DRSS at 1 year, and only 1 of these 12 eyes had a ≥2-step improvement, while 11 had ≥2-step worsening. Although the number of patients with moderately severe to severe NPDR without DME included in Protocol S was small, these results indicate difference between ranibizumab and PRP groups for the proportion of patients with ≥2-step improvement.

These data were considered limited and had methodological shortcomings e.g. the subgroup analyses (moderately severe NPDR, severe NPDR and PDR) were not pre-specified. While the link between progression on the DRSS and the risk of developing sight threatening complications is established, the link between an improvement in DRSS and a decreased risk for sight-threatening complications in patients with moderately severe to severe NPDR needs to be shown to support the targeted indication, as the benefit–risk profile may differ between moderately severe and severe DRSS without DME.

Based on the feedback on the limitations of the presented dataset, the applicant decided to revise the indication of the application as follows by excluding NPDR: "Lucentis is indicated in adults for the treatment of proliferative diabetic retinopathy (PDR)"

Development of DME

The time-to-development of DME in eyes without baseline DME was analysed for Protocol S. A lower proportion of patients in the ranibizumab group without baseline DME developed DME compared with the PRP group without baseline DME. At 1 year, of the ranibizumab group without baseline DME (n=149) and the PRP group without baseline DME (n=157), 6 % and 24 %, respectively, had developed DME. At 2 years, 10.5 % of the ranibizumab group without baseline DME and 28.6 % of the PRP group without DME had developed DME.

Improvement from PDR at baseline to NPDR

In the ranibizumab group, at the 1-year or 2-year visits, respectively, 48 eyes (28.2 %, 95 % CI: 21.5 %, 35.0 %) and 46 eyes (27.1 %, 95 % CI: 20.4 %, 33.7 %) with baseline PDR (DRSS ≥60) had improved to NPDR (DRSS <60) as determined on fundus photographs. Improvement from PDR to NPDR was comparable between groups of eyes with or without DME at baseline.

In the PRP group, due to retinal scars caused by PRP treatment, evaluation of improvement to NPDR (DRSS <60) in PRP-treated eyes is not possible. Therefore, in the results, this group of patients were classified as not applicable.

Proportion of eyes with DR complications and eyes receiving vitrectomy

The ranibizumab and PRP groups in Protocol S were compared for the occurrence of the following DR outcomes of interest: retinal detachment, vitreous hemorrhage, vitrectomy, development of neovascular glaucoma, and development of iris neovascularisation. The proportion of eyes with resolution of neovascularisation was also assessed.

Through the 2-year visit, vitrectomy was performed in a lower proportion of eyes in the ranibizumab group (4.5 %) compared with the PRP group (15.9 %). The proportion of eyes with neovascular

glaucoma, neovascularisation of the iris, or vitreous hemorrhage was comparable between the 2 treatment groups, and a numerically lower percentage of patients had retinal detachment in the ranibizumab group compared with the PRP group.

At 1 year, a larger proportion of eyes in the ranibizumab group experienced resolution of neovascularisation compared with the PRP group (treatment difference of 13.3 %, 95 % CI: 3.1 %, 23.4 %). At 2 years, the percentage of eyes with resolution of neovascularisation was similar between the groups.

Humphrey visual field testing

Peripheral visual function was evaluated at 2 years using the Humphrey visual field test and compared with PRP, ranibizumab treatment led to the preservation of peripheral visual function.

Summary of the main study

The following table summarise the efficacy results from the main study supporting the present application. This should be read in conjunction with the discussion on clinical efficacy as well as the benefit–risk assessment (see subsequent sections).

Table 9. Summary of Efficacy for trial Protocol S.

Title: Protocol S			
Study identifier	ML27976, Report Nr. 1066857		
Design	Phase 3, multicenter, randomized, active-controlled, parallel-assignment, double-masked non-inferiority Phase 3 study		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		2 years Not applicable 3 years (after the main phase)
Hypothesis	Non-inferiority (Note: NI margin for BCVA2Y was 5 letters)		
Treatments groups	Arm 1: Ranibizumab		Treatment: 0.5 mg intravitreal injection of ranibizumab at randomisation, 4-, 8-, and 12-week follow-up visits. Beginning at the 16-week visit, eyes were evaluated for retreatment based on appearance of neovascularisation. Duration: 2 years (main) N (randomised eyes): 191
	Arm 2: PRP		Treatment: a full session of 1200 to 1600 burns using 500 µm burns on the retina or the equivalent area treated when using indirect laser delivery systems or laser was completed within 56 days of randomisation. Study eyes in the PRP group could receive supplemental PRP if neovascularisation worsened during the study following completion of the initial PRP session. Duration: 2 years (main) N (randomised eyes): 203
Endpoints and definitions	Primary endpoint	BCVA2Y	Mean change from baseline in BCVA score at 2 years
	Secondary endpoint	DRSS2Y2U+ DRSS2Y2U-	Proportion of eyes in the ranibizumab group with ≥2-step improvement/worsening from baseline in ETDRS-DRSS at 2 years
	Secondary endpoint	DRSS2Y3U+ DRSS2Y3U-	Proportion of eyes in the ranibizumab group with ≥3-step improvement/worsening from baseline in ETDRS-DRSS at 2 years

Database lock	13-Sep-2018 (final) 23-Jul-2015 (2 years analysis cut off)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (modified) BCVA2Y: 2-year visit, DRSS: 1-year visit		
Descriptive statistics and estimate variability	Treatment group	Arm 1 Ranibizumab	Arm 2 PRP
	Number of subject (at BL)	191	203
	BVCA2Y (Mean Change)	2.7	-0.7
	(CI95 %)	[0.2, 5.2]	[-2.8, 1.5]
	DRSS1Y2U+ N (%)	79 (41.8)	29 (14.6)
	CI95 % in %	[34.8, 48.8]	[9.7, 19.5]
	DRSS1Y2U- N (%)	3 (1.6)	23 (11.6)
	CI95 % in %	[0, 3.4]	[7.1, 16.0]
Effect estimate per comparison	BVCA2Y (Mean change)	Comparison groups	Ranibizumab vs. PRP
		Difference in Mean Change	3.5
		95 % CI	[0.2, 6.7]
		P-value	0.0382
	Secondary endpoint: DRSS1Y2U+ (%)	Comparison groups	Ranibizumab vs. PRP
		Difference of Proportions	27.4
		95 % CI	[18.9, 35.9]
		P-value	not reported
	Secondary endpoint: DRSS1Y2U- (%)	Comparison groups	Ranibizumab vs. PRP
		Difference of Proportions	-9.9
		95 % CI	[-14.7, -5.2]
		P-value	not reported
Notes	Results of ETDRS-DRSS ⩾3 step changes responder endpoints were consistent with ETDRS-DRSS ⩾2 step changes responder endpoints. Key outcome endpoints were not adjusted for multiple testing, i.e. type I error is not controlled.		

In the PRP group, due to retinal scarring caused by PRP treatment, evaluation of improvement to NPDR (DRSS <60) is not possible. Therefore, this group has been classified as not applicable.

While the type I error is considered controlled for the primary endpoint 'Mean change from baseline in BCVA score at 2 years', however, the presentation of results is much focused on multiple ETDRS-DRSS step change responder endpoints and multiple visits, for which no strict type I error control is applied, which may lead to an inflation of type I error and over-interpretation of results.

In response to this concern, the MAH provided sensitivity analyses showing a risk at an acceptable level at or below the pre-specified type I error level for each of the raised issues (multiple testing, underestimation of variability etc). The risk that all issues jointly might have caused false positive results is not expected to exceed the pre-specified type I error either.

Analysis performed across trials (pooled analyses and meta-analysis)

Novartis studies (D2301, D2303, D2305)

To evaluate the potential benefit of ranibizumab treatment on the underlying DR in patients with DME, pooled data from three Novartis sponsored studies (D2301, D2303, and D2305) were analysed. This pooled dataset included patients with NPDR, which formed the population of patients with moderately severe NPDR or worse, together with Protocol S.

The three studies were randomised, double-masked, active-controlled, Phase 3 studies in patients with visual impairment due to DME. The studies compared ranibizumab 0.5 mg intravitreal injections (plus sham laser), ranibizumab 0.5 mg intravitreal injections with active laser (D2301 and D2303 only), and laser treatment plus sham injections.

The studies had similar designs. All had a 1-year treatment duration, and in all cases, treatment was to be given monthly and continued until maximum visual acuity was achieved, i.e., until the patient's visual acuity was stable for 3 consecutive monthly assessments performed while on ranibizumab treatment. Treatment was to be resumed when monitoring indicated loss of visual acuity due to DME. – This treatment regimen is consistent with the approved European label in patients with visual impairment due to DME.

Change in DR was investigated as a pre-planned exploratory objective in all 3 clinical studies based on grading of fundus colour photographs taken at Baseline, Month 6 and 1 year. Only one eye was selected and treated as the study eye in all 3 studies.

The similar design of the three studies justifies the pooling of the data. The pooled data have been presented and assessed before in EMEA/H/C/000715/II/0069, when it was concluded that there was no statistical evidence of heterogeneity. However, the limited number of subjects within each study in the subgroup of patients with moderately severe NPDR or worse was recognised.

In the target DR population from the Novartis studies, a larger proportion of patients in the ranibizumab 0.5 mg group had a ≥2-step improvement in DRSS from baseline at 1 year than in the laser group (48.4 % vs 14.6 %, respectively, Table 10). In addition, a smaller proportion of patients in the ranibizumab group than in the laser group had a ≥2-step worsening from baseline (2.1 % vs 8.1 %, respectively). The difference between ranibizumab 0.5 mg and laser in the target DR population was considered clinically relevant for ≥2-step improvement using both last observation carried forward (LOCF) data (29.9 %, 95 % CI: 20.0, 39.7) and observed data (30.3 %, 95 % CI: 19.9, 40.8).

Likewise, a larger proportion of patients in the ranibizumab groups had a ≥3-step improvement in DRSS from baseline at 1 year than in the laser group (21.9 % vs. 6.5 %, respectively). In addition, a smaller proportion of patients in the ranibizumab group than in the laser group had a ≥3-step worsening from baseline (1.0 % vs 4.9 %, respectively).

When ≥2-step improvement in DRSS (10-point scale) from baseline at 1 year was assessed by baseline DRSS group for the target DR population, a larger proportion of patients in the ranibizumab group achieved a ≥2-step improvement from baseline at 1 year compared with the laser group for each DRSS grouping (Table 11). Within the ranibizumab group, the proportions of patients experiencing a ≥2-step improvement were high for all baseline DRSS groups; in moderately severe NPDR and severe NPDR, the proportions were similar, and it was higher in PDR patients.

Table 10. DRSS improvement or worsening from baseline of at least 2- or 3- steps at year 1 in pooled Novartis studies (LOCF Method).

	Pooled Novartis studies[1]

	Ranibizumab 0.5 mg N=192	Laser N=123	Difference in proportion % (CI)
≥2-step improvement from baseline			
n (%)	93 (48.4)	18 (14.6)	29.9 (20.0, 39.7)
≥3-step improvement from baseline			
n (%)	42 (21.9)	8 (6.5)	13.4 (5.8, 21.0)
≥ 2-step worsening from baseline			
n (%)	4 (2.1)	10 (8.1)	-6.0 (-11.3, -0.8)
≥ 3-step worsening from baseline			
n (%)	2 (1.0)	6 (4.9)	-3.7 (-7.7, 0.3)

LOCF = last observation carried forward.

[1] Pooled patient population includes patients with moderately severe NPDR or worse at baseline in the Full analysis set in specific treatment group

Differences in proportion are based on stratified analysis using Cochran-Mantel-Haenszel weights. Stratification factors for Protocol S include number of study eyes and baseline DME status. Stratification factors for Novartis studies include study ID.

Table 11. Proportion (%) of patients with at least 2-step improvement from baseline in DRSS (10-point scale) in study eye at 1 year, Full Analysis Set (LOCF), Pooled Novartis studies, target DR population.

Baseline DRSS	Ranibizumab 0.5 mg N=192 n/M (%)	Laser N=123 n/M (%)
Moderately severe NPDR	33/75 (44.0)	7/52 (13.5)
Severe NPDR	24/57 (42.1)	3/41 (7.3)
PDR	36/60 (60.0)	8/30 (26.7)

M= total number of patients with evaluable DRSS at both baseline and the visit for a specific subgroup, N= The total number of patients with evaluable DRSS at both baseline and at least 1 post-baseline visit, n= number of patients who satisfied the condition at the visit.

Patients with NPDR without DME

While Novartis studies enrolled only patients with DME, DME could resolve during the course of the study following treatment with ranibizumab. At 6 months, DME had resolved (central subfield thickness <250 µm) in 46 patients with moderately severe to severe NPDR. A *post hoc* analysis of DRSS change from 6 months to 1 year was performed. Of the 46 patients, 25 received at least 1 ranibizumab injection between 6 months and 1 year and 21 patients did not receive an injection within this period. In patients who received at least 1 injection, the proportion with ≥2-step improvement in DRSS over 6 months was numerically larger (28.0 %, 7 patients) and twice that of patients who did not receive any injection (14.3 %, 3 patients).

Although the DRSS results in patients with NPDR without DME were consistent with those observed for patients with NPDR with DME, or PDR regardless of the presence of DME, the numbers are few and the interpretation of the results is weakened by the post hoc nature of the analysis. Combined with the even smaller number of subjects in Protocol S, these data cannot be considered sufficient to support the NPDR indication by itself.

In summary, in light of the CHMP's comments regarding the limited data in patients with moderately severe and severe NPDR (as well as issues related to the standard of care in this population), the MAH proposed to revise the indication excluding NPDR patients.

Development of PDR

In the subgroup of target DR patients with moderately severe to severe NPDR at baseline, at 1 year, a smaller proportion of patients treated with ranibizumab experienced progression from NPDR to PDR compared with those who received laser treatment: 10 (7.6 %) patients in the ranibizumab group and 11 (11.8 %) patients in the laser group progressed.

Effect on visual acuity

In all 3 studies, the primary efficacy endpoint was met. Ranibizumab monotherapy was superior compared with laser therapy in the improvement of visual acuity in patients with visual impairment due to DME. The mean average BCVA change from Month 1 to Year 1 compared with baseline in the total patient population ranged from +5.9 to +6.8 letters in the ranibizumab group and +0.8 to +1.4 letters in the laser group.

The results from pooled data are in line with the findings of Protocol S. However, although the DRSS results in patients with NPDR without DME were consistent with those observed for patients with NPDR with DME, or PDR regardless of the presence of DME, the numbers are few and the interpretation of the results is weakened by the post hoc nature of the analysis. Combined with the even smaller number of subjects in Protocol S, this data was not considered sufficient to support the NPDR without DME indication. See above.

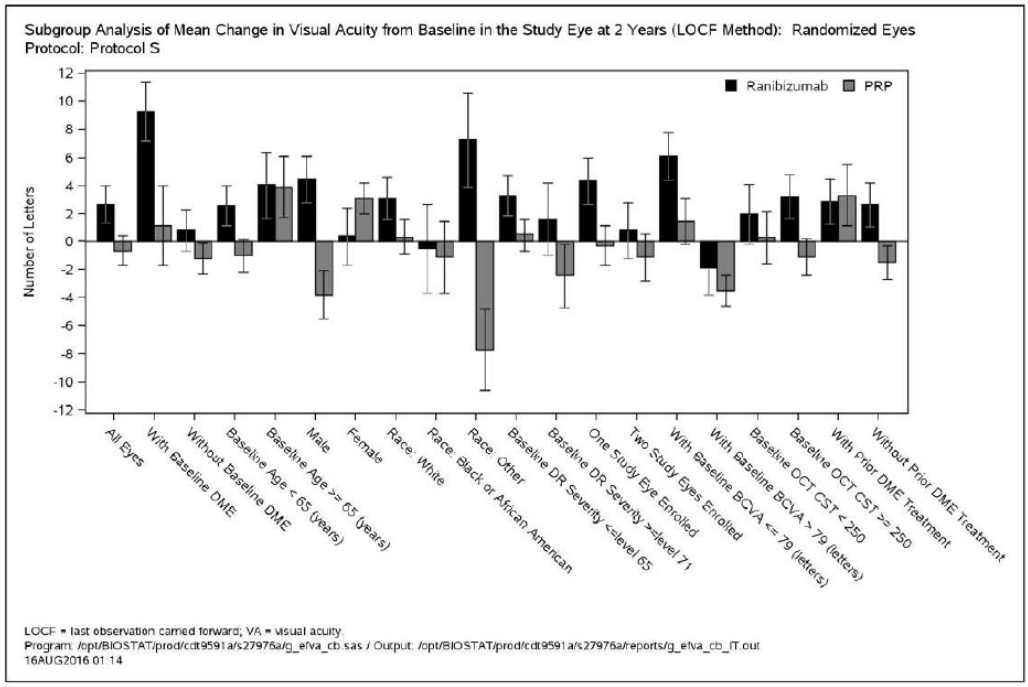
Clinical studies in special populations

Subgroups of the study population

Protocol S

Subgroup analyses for the mean change in visual acuity from baseline at 2 years are presented in Figure 4.

Figure 4. Subgroup analysis of mean change in visual acuity from baseline in the study eye at 2 years (LOCF method), randomised eyes.



For the visual acuity endpoint, the treatment effect of ranibizumab versus PRP was generally consistent with the overall results across the subgroups (mean change from baseline by BCVA, DME status, prior DME treatment, baseline ETDRS-DRSS, baseline OCT, race, sex). The additional subgroups by age and number of study eyes enrolled were added by Genentech.

The results for subgroups with small sample sizes should be interpreted with caution: baseline age 65 (18 eyes in ranibizumab group and 16 eyes in PRP group); and other race (16 eyes in ranibizumab group and 17 eyes in PRP group).

Eyes with lower baseline BCVA scores (baseline BCVA <79 letters) had larger visual acuity improvements compared with eyes with higher baseline BCVA scores (baseline BCVA 79 letters), because no further improvement was possible in the eyes with better baseline vision.

The subgroup defined by baseline DME was considered the main subgroup of interest. Table 12 shows the mean change from baseline in BCVA at 2 years across the subgroups by baseline DME status. Eyes with baseline DME (based on OCT and visual acuity criteria) had larger visual acuity improvements compared with eyes without DME at baseline, partly because of the limited room for improvement in already well-seeing non-DME eyes.

Table 12. Mean change in visual acuity from baseline in the study eye at 2 years by baseline DME status (LOCF method), randomised eyes.

	Eyes with Baseline DME		Eyes without Baseline DME	
	Ranibizumab (N=42)	PRP (N=46)	Ranibizumab (N=149)	PRP (N=157)
Number of letters change from baseline				
N	42	46	149	157
Mean (SD)	9.3 (13.6)	1.2 (19.4)	0.8 (18.4)	-1.2 (14.1)
SE	2.1	2.9	1.5	1.1
Median	10.5	4.0	4.0	0.0
Q1 - Q3	1.0 - 17.0	-3.0 - 14.0	-1.0 - 9.0	-4.0 - 5.0
Range	-28 - 43	-73 - 33	-86 - 30	-67 - 26
95% CI for mean	(5.1, 13.6)	(-4.6, 6.9)	(-2.1, 3.8)	(-3.4, 1.0)

LOCF = last observation carried forward.

For the ETDRS-DRSS endpoints of the proportion of eyes with ≥3-step and ≥2-step improvement from baseline in ETDRS-DRSS at 2 years (Figure 5, Figure 6), the treatment effect of ranibizumab versus PRP was generally consistent with the overall results across the subgroups examined.

The results for subgroups with small sample sizes should again be interpreted with caution: baseline age ≥65 (18 eyes in ranibizumab group, and 16 eyes in PRP group); and other race (15 eyes in ranibizumab group, and 16 eyes in PRP group).

ETDRS-DRSS step improvement was associated with baseline DR severity score. Across both treatment groups, a higher proportion of eyes with higher baseline DR severity scores (baseline ETDRS-DRSS level 71) had 3-step and 2-step improvement from baseline compared with eyes with lower baseline DR severity scores (baseline ETDRS-DRSS level 71).

The subgroup defined by baseline DME was considered the main subgroup of interest (Table 13). Efficacy was demonstrated by the percentage of eyes in the ranibizumab group achieved ≥2-step (48.8 % and 39.9 %) and ≥3-step (31.7 % and 48.8 %) improvement in ETDRS-DRSS from baseline at 2 years, across both subgroups with and without baseline DME. The figures in PRP group were modest.

Figure 5. Subgroup analysis of proportion of eyes with ⩾3-step improvement in ETDRS-DRSS in the study eye at 2 years (LOCF method), randomised eyes with valid ETDRS-DRSS at baseline.

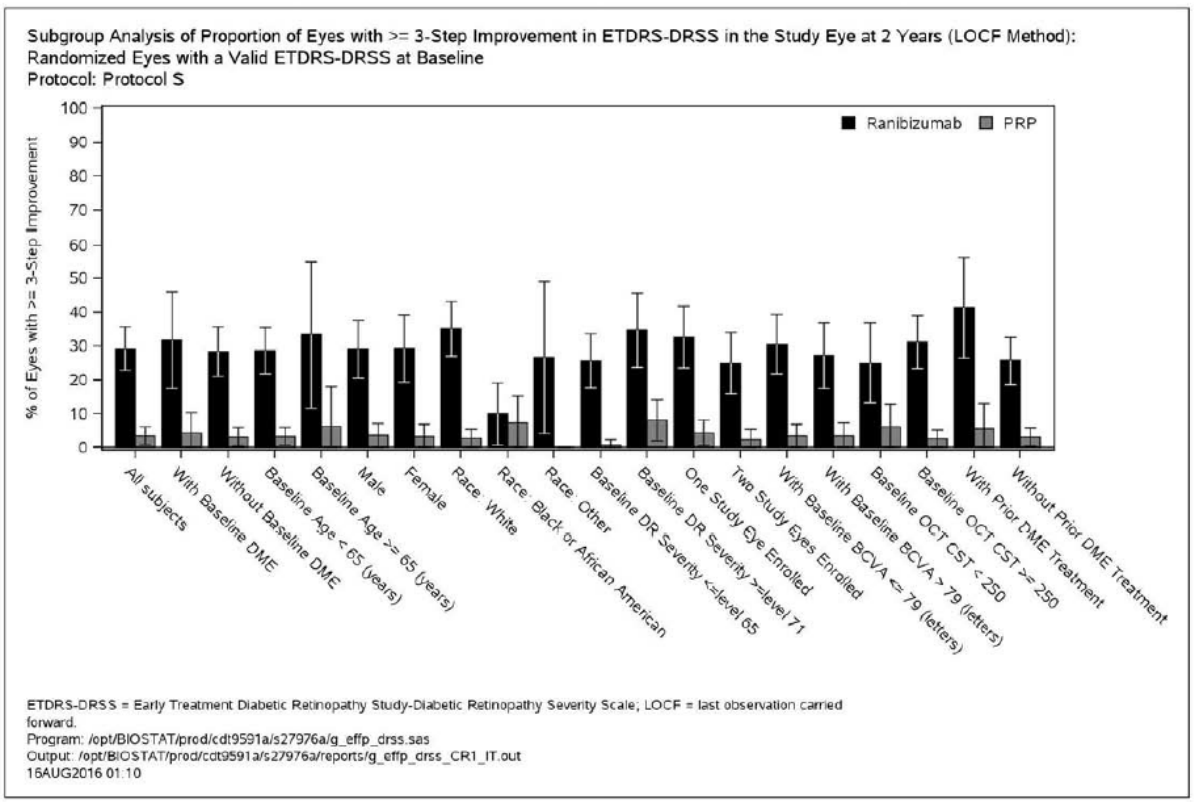


Figure 6. Subgroup analysis of proportion of eyes with ⩾2-step improvement in ETDRS-DRSS in the study eye at 2 years (LOCF method), randomised eyes with valid ETDRS-DRSS at baseline.

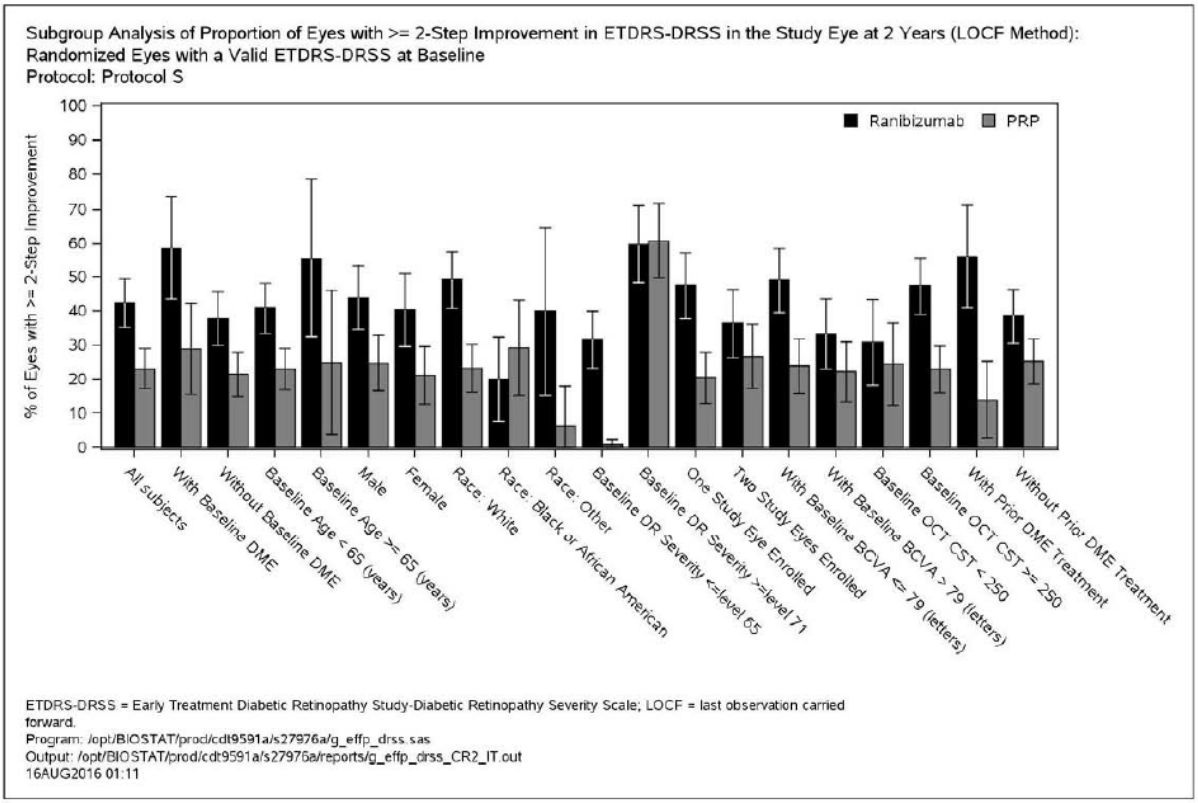


Table 13. Proportion of eyes with ⩾2-step and ⩾3-step improvement or worsening in ETDRS-DRSS from baseline in the study eye at 2 years by baseline DME status (LOCF method), randomised eyes with a valid ETDRS-DRSS at baseline.

	Eyes with Baseline DME		Eyes without Baseline DME	
	Ranibizumab (N=41)	PRP (N=45)	Ranibizumab (N=148)	PRP (N=154)
Improvement of >= 3 steps from baseline at 1 Year				
N	41	45	148	154
n (%)	13 (31.7%)	0	41 (27.7%)	6 (3.9%)
95% CI for percentage	(17.5%, 46.0%)	(0.0%, 0.0%)	(20.5%, 34.9%)	(0.8%, 7.0%)
Improvement of >= 2 steps from baseline at 1 Year				
N	41	45	148	154
n (%)	20 (48.8%)	5 (11.1%)	59 (39.9%)	24 (15.6%)
95% CI for percentage	(33.5%, 64.1%)	(1.9%, 20.3%)	(32.0%, 47.8%)	(9.9%, 21.3%)
Worsening of >= 3 steps from baseline at 1 Year				
N	41	45	148	154
n (%)	0	3 (6.7%)	1 (0.7%)	5 (3.2%)
95% CI for percentage	(0.0%, 0.0%)	(0.0%, 14.0%)	(0.0%, 2.0%)	(0.4%, 6.0%)
Worsening of >= 2 steps from baseline at 1 Year				
N	41	45	148	154
n (%)	1 (2.4%)	3 (6.7%)	2 (1.4%)	20 (13.0%)
95% CI for percentage	(0.0%, 7.2%)	(0.0%, 14.0%)	(0.0%, 3.2%)	(7.7%, 18.3%)

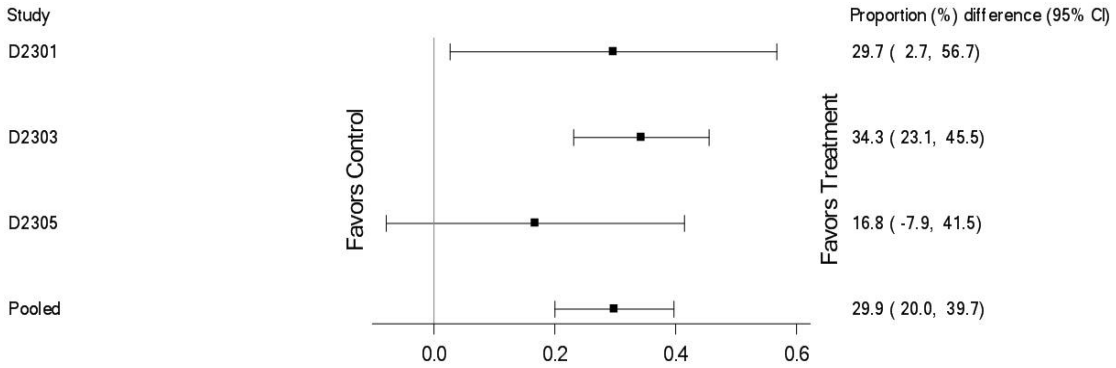
Novartis studies (D2301, D2303, D2305)

To assess consistency of the treatment effects across different diabetic characteristics in the target DR population, subgroup analyses were performed for at least 2- and 3-step changes from baseline in DRSS by baseline HbA1c (<8 %, ≥8 %, i.e. <64 mmol/mol, ≥64 mmol/mol) and duration of diabetes (time since most recent diagnosis <10 years, ≥10 years). A subgroup analysis of ≥2-step improvement from baseline in DRSS by race (Caucasian vs. Asian) was also performed.

Demographic factors

Treatment response (≥2-step improvement in DRSS) was similar regardless of race (Caucasian in D2301 vs. Asian in D2303 and D2305). A homogeneous treatment effect with ranibizumab was demonstrated in the target DR population. The MAH proposes that this demonstrates that the Asian populations in Studies D2303 and D2305 are relevant for a global population.

Figure 7. Forest plot for proportion of DRSS at least 2-step improvement between treatment of study eye at 1 year (Pooled and by individual Novartis study, target DR population).



Treatment: Ranibizumab, Control: Laser

For individual study result, proportion difference is unadjusted and confidence interval (CI) is based on normal approximation
For overall result, proportion difference is based on weighted estimate using Mantel–Haenszel weights and CI is based on normal approximation of the weighted estimates
For individual study results, CIs of proportion difference are based on normal approximation. For pooled results, proportion difference is based on weighted estimates using Mantel–Haenszel weights and CIs are based on a normal approximation of the weighted estimates.

Table 14. Mean HbA1c and change from baseline by visit and treatment for patients with baseline moderately severe NPDR or worse, Full Analysis set; observed, Pooled Novartis Studies.

Visit – Treatment	n	HbA1c mean	Change from baseline
Baseline			
Ranibizumab 0.5 (N=205)	204	7.42	
Laser (N=134)	134	7.50	
Month 3			
Ranibizumab 0.5 (N=205)	194	7.42	-0.02
Laser (N=134)	120	7.35	-0.13
Month 6			
Ranibizumab 0.5 (N=205)	192	7.49	0.06
Laser (N=134)	113	7.33	-0.14
Month 9			
Ranibizumab 0.5 (N=205)	182	7.51	0.05
Laser (N=134)	110	7.49	0.00
Month 12			
Ranibizumab 0.5 (N=205)	180	7.54	0.11
Laser (N=134)	111	7.48	0.00
N: The total number of patients with Moderately Severe NPDR or worse at baseline, in the analysis set in specific treatment group.			

n: The number of patients with a value for both baseline and the specific post-baseline visit

Hb1Ac level

Glycosylated HbA1c was assessed at baseline and at Months 3, 6, 9 and 12 in the Novartis studies and was stable and controlled over time. For the 1-year duration of the studies, glycemic control was stable for the pooled Novartis dataset, as demonstrated by similar and consistent mean HbA1c levels at each study visit across the groups as well as a nominal change from baseline in HbA1c levels (Table 14).

To evaluate the impact of glycemic control at baseline on the change in DR severity, a subgroup analysis by baseline HbA1c levels (<8 %, ≥8 %) was performed in the target DR population. Results indicated a positive response to ranibizumab 0.5 mg treatment regardless of the baseline HbA1c level.

Duration of diabetes

An analysis of 2- and 3-step changes from baseline in DRSS by duration of diabetes (<10 years or ≥10 years) was performed in the target DR population. A similar response to treatment was observed regardless of duration of disease.

Across the subgroups examined, the treatment effect of ranibizumab versus PRP for mean change in visual acuity and the proportion of eyes with ≥2-step improvement in ETPRS-DRSS from baseline was generally consistent with the overall results. Results of the subgroup analysis of the proportion of eyes with ≥3-step improvement from baseline were similar. Regarding the pooled data set, by current European standards, it is debatable whether consistent levels above 7 % (>53 mmol/mol) represent satisfactory diabetes control. In response to this concern, the MAH presented data that the observed mean HbA1c in the US population enrolled in Protocol S is similar to the European population with PDR and thus is sufficiently representative and reflective of a generally poor glycemic control in this population.

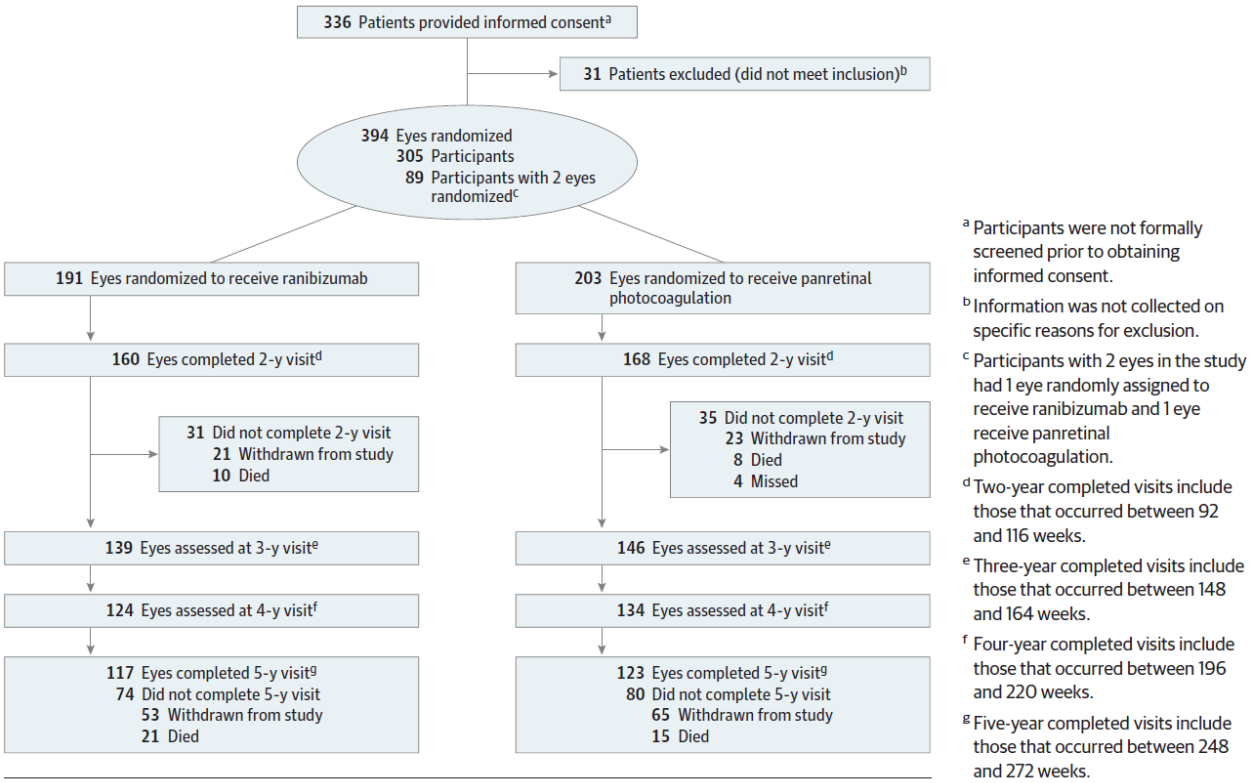
Published supportive studies (long-term data)

Five-year efficacy data from Protocol S have been published by Gross et al. (2018) and the publication was submitted with this application. 2- and 3-year efficacy data are also available from the RISE and RIDE studies (Nguyen et al. 2012, Brown et al. 2013, Ip et al. 2015) and 5 years from Protocol I.

Protocol S was originally planned a 2-year study, with follow-up subsequently amended up to 5 years. At 2 years, a response to treatment with ranibizumab 0.5 mg was observed, with improved mean BCVA and a larger proportion of eyes in the ranibizumab group achieving ≥2-step improvement and ≥3-step improvement in DRSS from baseline than eyes in the PRP group.

Efficacy was maintained across the 5-year treatment duration, as described by Gross et al. (2018). The 5-year visit was completed for 117 (69 %) study eyes in the ranibizumab group and 123 (65 %) study eyes in the PRP group, excluding deaths in both groups (Figure 8).

Figure 8. Completion of 5-year follow-up, Gross et al. (2018).



The mean (SD) changes in visual acuity from baseline in the ranibizumab and PRP groups were comparable 3.1 (14.3) and 3.0 (10.5) letters, respectively (Table 15, Figure 9). Among 90 eyes in the ranibizumab group that had gradable colour fundus photographs at 5 years, 41 (46 %) had ≥2-step improvement in DRSS from baseline, including 30 (33 %) with NPDR, and 9 (10 %) with complete resolution of DR (ETDRS level 20 or better) on fundus photographs. In eyes without DME at baseline (N=192), lower rates of development of DME were observed in the ranibizumab group compared with the PRP group (Hazard Ratio = 0.4; 95 % CI: 0.3, 0.7; P <0.001).

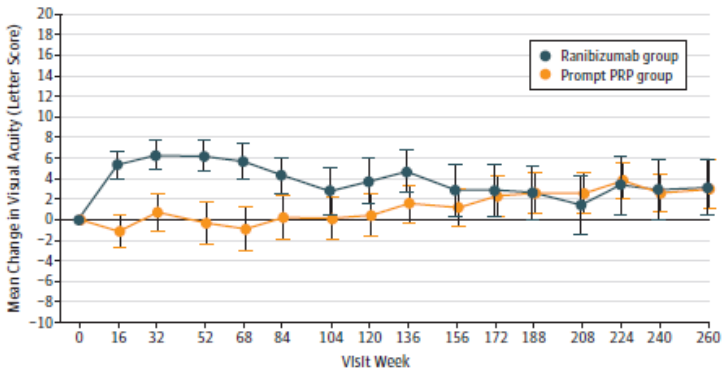
Through 5 years, the proportion of eyes with retinal detachment, neovascular glaucoma, neovascularisation of the iris, or vitreous hemorrhage was similar between the two treatment groups.

There were no signs of development of tolerance or loss of efficacy following long-term administration of ranibizumab in Protocol S.

Table 15. Change in visual acuity at 5 years, Gross et al. (2018).

Variable	Ranibizumab Group[a]	PRP Group[a]	Adjusted Difference (95% CI)[b]	*P* Value[b]
260-wk (5-y) Visit				
No. of eyes	117	123	NA	NA
VA Letter Score at Baseline				
Mean (SD)	77 (12)	78 (11)	NA	NA
Median (IQR)	79 (75 to 85)	80 (72 to 85)	NA	NA
Snellen equivalent, mean	20/32	20/32	NA	NA
VA Letter Score at 5 y				
Mean (SD)	80 (16)	81 (12)	NA	NA
Median (IQR)	84 (78 to 89)	84 (77 to 89)	NA	NA
Snellen equivalent, mean	20/25	20/25	NA	NA
Snellen equivalent, No. (%)				
≥20/20	60 (51)	66 (54)	NA	NA
20/25	25 (21)	18 (15)	NA	NA
20/32	11 (9)	15 (12)	NA	NA
20/40	7 (6)	9 (7)	NA	NA
20/50	4 (3)	5 (4)	NA	NA
20/63	2 (2)	3 (2)	NA	NA
20/80	0	1 (<1)	NA	NA
20/100	0	3 (2)	NA	NA
20/125	0	1 (<1)	NA	NA
20/160	2 (2)	0	NA	NA
≤20/200	6 (5)	2 (2)	NA	NA
Change in VA Letter Score at 5 y				
Mean (SD)[c]	3.1 (14.3)	3.0 (10.5)	0.6 (−2.3 to 3.5)	.68[d]
Median (IQR)	4.0 (−2.0 to 10.0)	3.0 (−3.0 to 8.0)	NA	NA
Letters improvement, No. (%)[e]				
≥15	14 (26)	13 (23)	1 (−12 to 15)	.86
≥10	28 (52)	23 (41)	6 (−10 to 21)	.47
Letters worsening, No. (%)				
≥10	7 (6)	11 (9)	−3 (−11 to 5)	.42
≥15	7 (6)	7 (6)	−1 (−7 to 5)	.84
Area Under the Curve for Change in VA Letter Score Over 5 y				
Mean (SD)	3.3 (9.5)	1.5 (7.5)	1.6 (0 to 3.2)	.05
Median (IQR)	2.8 (−1.3 to 6.3)	1.0 (−3.0 to 5.3)	NA	NA

Figure 9. Mean change in visual acuity from baseline over time for the overall cohort Gross et al (2018).



No. of eyes					
Ranibizumab group	191	160	139	124	117
Prompt PRP group	203	168	146	134	123
Change in visual acuity, mean (SD)					
Ranibizumab group		2.8 (15.2)	2.9 (14.9)	1.4 (15.7)	3.1 (14.3)
Prompt PRP group		0.2 (13.7)	1.2 (11.4)	2.6 (11.0)	3.0 (10.5)
Adjusted difference (95% CI)		2.2 (-0.5 to 5.0)	1.6 (-1.1 to 4.3)	-0.7 (-4.0 to 2.5)	0.6 (-2.3 to 3.5)
P value		.11	.24	.66	.68

Treatment group means are calculated from observed data for the overall cohort and are truncated to 3 SD from the mean to minimize the effect of outliers. Differences (ranibizumab group minus panretinal photocoagulation [PRP] group), CIs, and 2-sided *P* values were obtained by intention-to-treat analysis using of analysis of covariance, with adjustment for baseline visual acuity, laterality, baseline central subfield thickness, correlation between 2 study eyes of the same participant, and multiple imputation for missing data.

Although efficacy of ranibizumab was maintained during the Protocol S follow-up up to 5 years, the advantage of ranibizumab over PRP in visual acuity waned and the ranibizumab and PRP groups proved comparable with an improvement of 3.1 and 3.0 letters, respectively. The researchers correctly conclude that either ranibizumab or PRP are viable treatment options for patients with PDR.

The comparator group appears to have slightly improved over time. The MAH present data on rescue treatment in the comparator group over time. A sensitivity analysis of PRP only compared with ranibizumab only should be presented.

In response, the MAH presented a sensitivity analysis of 'PRP only' compared with 'ranibizumab only' treatment for mean best corrected visual acuity (BCVA) change at 2 years and Early Treatment Diabetic Retinopathy Study (ETDRS)-DRSS ≥ 2 step at 1, 2, or 5 years after baseline was performed. , The results showed consistency with results from the original application, showing descriptively superiority of the 'ranibizumab only' vs. 'PRP only' treatment group at multiple timepoints.

RIDE and RISE were 3-year studies in patients with Type 1 or Type 2 diabetes with DME comparing the efficacy and safety of ranibizumab with sham (Ip et al 2012, Nguyen et al 2012, Brown et al 2013, Ip et al 2015). The studies were identically designed, randomised, Phase 3, double-masked, multicenter sham injection-controlled studies. After the main analyses of data at 2 years, sham-arm patients were allowed to crossover to the ranibizumab 0.5 mg arm, but the masked treatment period continued to Year 3, after which, additional analyses were performed.

The main efficacy outcomes from RISE and RIDE for Years 2 and 3 are summarised in Ip et al. (2012) and Ip et al. (2015), respectively. Additionally, a *post hoc* analysis from Wykoff et al. (2018) evaluated DR outcomes through 3 years in patients with moderately severe or severe NPDR who were at the highest risk for progressing to PDR. The results in patients with moderately severe to severe NPDR are summarised below as they are proposed to be relevant to the current patient population.

Improvement/worsening in DRSS from baseline

Total population (Ip et al. 2012, Ip et al. 2015). Overall, patients with DR treated with ranibizumab 0.5 mg improved in DRSS compared with patients in the sham control groups. At 1 year, for the pooled RISE and RIDE population, 30.8 % of patients in the ranibizumab 0.5 mg group had ≥2-step improvement in DRSS from baseline compared with 2.5 % in the sham treatment group; at 2 years, 35.9 % of patients in the ranibizumab 0.5 mg group had ≥2-step improvement in DRSS from baseline compared with 5.4 % in the sham treatment group.

Treatment benefits observed in the ranibizumab groups at 2 years were maintained up to 3 years. Sham patients who crossed over to receive ranibizumab 0.5 mg after 2 years (the sham/0.5-mg group) did not experience the same magnitude of benefit as those treated with ranibizumab from the beginning (Ip et al 2012, Ip et al 2015).

Patients with moderately severe or severe NPDR at baseline (Wykoff et al. 2018). In patients with moderately severe or severe NPDR at baseline (DR levels 47/53), at 2 years, rates of ≥2-step improvement were greater in the ranibizumab group compared with sham control (ranibizumab 0.5 mg (N=74) vs. sham (N=86): 81.1 % vs. 11.6 %, respectively) (Wykoff et al 2018, [SCE-Section 3.2.2.1]). Improvements in DRSS in the ranibizumab groups were sustained through 3 years.

Development of PDR

Total population (Nguyen et al. 2012, Ip et al. 2015). At 2 years, a lower proportion of patients in the ranibizumab 0.5 mg group compared with the sham group progressed to PDR in RIDE (3.9 % vs. 11.5 %, p=0.0206) and in RISE (5.6 % vs. 15 %, p = 0.0114) (Nguyen et al 2012). By year 3, in the

pooled RISE/RIDE data, 17.1 % of eyes in the ranibizumab 0.5 mg group developed PDR compared with 39.1 % of eyes in the sham/ranibizumab 0.5 mg group (P < 0.0001) (Ip et al 2015).

Patients with moderately severe or severe NPDR at baseline (Wykoff et al. 2018). Ranibizumab treatment significantly reduced the probability of patients experiencing a new proliferative event (Wykoff et al 2018). By 2 years, the probability of experiencing a new proliferative event was 10.2 % in patients treated with ranibizumab 0.5 mg and 26.6 % in sham-treated patients, and by 3 years, the probability was 11.9 % in ranibizumab 0.5 mg and 35.2 % in sham/ranibizumab 0.5 mg-treated patients. Of note, patients in the sham group who switched to receive ranibizumab 0.5 mg from Year 2 did not experience the same magnitude of benefit as those treated with ranibizumab from the beginning.

Protocol I (DRCR.net et al. 2010, Bressler et al. 2018)

Protocol I was a Phase 3, multicenter, randomised clinical study conducted by the DRCR.net in patients with DME (DRCR.net et al 2010). Patients were randomised to 1 of 4 treatment groups: intravitreal ranibizumab 0.5 mg plus prompt focal/grid laser, intravitreal ranibizumab 0.5 mg plus deferred focal/grid laser, and intravitreal triamcinolone 4 mg plus prompt focal/grid laser compared with prompt focal/grid laser plus sham injection. Intravitreal injections were given every 4 weeks through the 12-week visit; thereafter, retreatments were given following a retreatment algorithm specified in DRCR.net et al 2010.

There was a total of 854 study eyes from 691 patients. Ranibizumab-assigned eyes received prompt laser at baseline or deferred laser beginning at 24 weeks if DME persisted and was no longer improving. The main outcome of the study was BCVA at 1 year, with follow-up planned for 3 years. After completion of the 3-year visit, participants were offered to extend the period of follow-up through 5 years. Assessment of DR was performed by masked graders at a central reading center using colour fundus photographs obtained by certified photographer at baseline and Year 1, and annually between Years 3 and 5 (Bressler et al 2018).

Among eyes with severe NPDR or worse at baseline, at 1 year, 28 % of eyes in the ranibizumab group and 19 % of eyes in the sham + prompt laser group had a ≥2-step improvement in DRSS from baseline (p=0.03) (DRCR.net et al 2010). A lower proportion of eyes in the ranibizumab group had worsening of ≥2-steps from baseline in DRSS than in the sham group (1 % vs. 8 %). At the 2-year follow-up, there were fewer eyes that had received PRP in the ranibizumab group than in the sham group (5 % vs. 22 %). Similarly, fewer eyes in the ranibizumab group had vitreous hemorrhage than in the sham group (5 % vs. 8 %).

Post hoc analyses of the 5-year data were recently published (Bressler et al 2018). These analyses evaluated the change in DR severity by baseline DR severity subgroup in patients treated with ranibizumab. In patients with moderately severe to severe NPDR (level 47/53), improvement in DRSS was sustained over the 5-year follow-up period. At 1, 3, and 5 years, respectively, 40 % (n=121), 38 % (n=103), and 42 % (n=85) of eyes had DR severity improvement.

In RIDE and RISE studies, measured by ≥2-step improvement in DRSS patients with DR and DME treated with ranibizumab improved compared with patients in the sham control groups. This would be expected with sham control. In a post hoc analysis, similar results were obtained at 2 years in patients with moderately severe or severe NPDR at baseline. A lower proportion of patients in the ranibizumab group compared with the sham group progressed to PDR. In the post hoc analysis ranibizumab treatment reduced the probability of patients experiencing a new proliferative event. – Protocol I had a more complex design, but in patients with severe NPDR or worse at baseline, at 1 year, 28 % of eyes in the ranibizumab group and 19 % of eyes in the sham + prompt laser group had a ≥2-step

improvement in DRSS from baseline. – Post hoc, the effects of these studies were sustained over 3 to 5 years.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Overall, the design of the main study (Protocol S) was appropriate. However, it aimed to enrol only patients with PDR, and not patients with NPDR. The assessment of efficacy is complicated by the fact that more than half of the subjects in the comparator group also received ranibizumab (Table 6). There were few protocol deviations, which did not have significant effect on the overall results. The original protocol with 2-year follow-up was extended to 5 years to gain long-term data. The 5-year follow-up has been published recently, with 34 % of subjects lost to follow-up.

The majority of eyes randomised to ranibizumab completed the study through 2 years; 85.3 % of eyes in the ranibizumab group and 86.7 % of eyes in the PRP group. The most common reasons for discontinuation prior to 2 years were death and patient loss to follow-up in the ranibizumab group (5.2 % each) and patient loss to follow-up (5.4 %) and death (3.9 %) in the PRP group.

The pooled DME studies (D2301, D2303, and D2305) had similar design and the pooled analysis is considered justified, but these studies included only patients with DME. The pooled data have been presented and assessed before in EMEA/H/C/000715/II/0069, and some information was included in section 5.1. The limited number of subjects within each study in the subgroup of patients with moderately severe NPDR or severe NPDR without DME was recognised.

Efficacy data and additional analyses

The efficacy findings from Protocol S and its follow-up and the pooled Novartis studies include:

- In Protocol S, at 2 years, the primary endpoint of the study was met in the overall population, demonstrating non-inferiority of ranibizumab compared with PRP for visual acuity. Patient vision improved following ranibizumab treatment, but the mean VA ended up below baseline in the PRP group. After 5 years the difference had waned, and both treatment groups showed an improvement of ca. 3 letters in visual acuity.
- A ≥2-step improvement in DRSS from baseline between ranibizumab 0.5 mg- and PRP- or laser-treated patients were observed:
    - In the overall population in Protocol S, in the ranibizumab group, 41.8 % and 42.3 % of eyes experienced a ≥2-step improvement from baseline at the 1-year and 2-year visits, respectively; the corresponding proportions of eyes in the PRP group were 14.6 % and 23.1 %, respectively. Comparable results were observed by baseline DME status.
    - In the pooled target DR population of the Novartis studies in patients with DME, 48.4 % of patients in the ranibizumab group had a 2-step improvement in DRSS from baseline at 1 year, compared with 14.6 % of patients in the laser group.
- Greater proportions of patients in the ranibizumab treatment groups had ≥3-step improvement in DRSS compared with PRP or laser treatment: 28.6 % vs. 3.0 % in Protocol S at 1 year, 29.1 % vs. 3.5 % in Protocol S at 2 years, and 21.9 % vs. 6.5 % in the pooled Novartis studies at 1 year.

- Results for additional efficacy outcomes related to DR and progression of DR add limited support for the efficacy of ranibizumab 0.5 mg in patients with moderately severe NPDR or worse.
    - In Protocol S, at 2 years:
        - A greater proportion of patients in the PRP group without DME developed DME compared with patients in the ranibizumab group without DME (28.6 % vs. 10.5 %).
        - 27.1 % of eyes (46 eyes) with baseline PDR improved to NPDR in the ranibizumab group.
        - Vitrectomy was performed in a lower proportion of eyes in the ranibizumab group (4.5 %) compared with the PRP group (15.9 %) and a numerically lower percentage of patients had retinal detachment in the ranibizumab group (5.9 %) compared with the PRP group (10.9 %). Other DR-related outcomes (retinal detachment, neovascular glaucoma, neovascularisation of the iris, and vitreous hemorrhage) occurred in similar proportions in both groups.
    - In the Novartis studies, at 1 year:
        - Among patients with moderately severe or severe NPDR and DME at baseline, a smaller proportion of patients treated with ranibizumab monotherapy experienced progression from NPDR to PDR compared with those who received laser treatment alone (7.6 % vs. 11.8 %).

2.4.3. Conclusions on the clinical efficacy

In Protocol S and the DR population from the Novartis studies, positive effects were observed with ranibizumab 0.5 mg, assessed by BCVA (Protocol S) and a ≥2-step improvement in DRSS, and supported by ≥3-step improvement in DRSS, progression to PDR, regression from PDR to NPDR, development of DME, and additional clinically relevant endpoints related to DR.

What changes are clinically meaningful can be debated, and it has been suggested that a cut point for clinically meaningful change in patients with advanced eye disease should be higher than in healthy individuals (Kiser et al. 2005). In the 5-year follow-up 26 % or 52 % improved ≥15 or ≥10 letters in ranibizumab group, and, respectively 23 % or 41 % in the PRP group (Table 15). In this population, even slowing down of deterioration could be considered clinically meaningful. – All data, as presented, however, indicate that ranibizumab is non-inferior to PRP. The data are supported by published data from the RISE, RIDE, and Protocol I studies. The follow-up of Protocol S has been extended to 5 years at which point the ranibizumab and PRP groups proved comparable regarding visual acuity and serious PDR complications. The value of the follow-up results was somewhat compromised by the relatively high loss to follow-up.

The pivotal study Protocol S only included patients with PDR. Data to support an effect in patients with NPDR is only derived from the pooling of previously performed studies in patients with DME. It is acknowledged that results are consistent with results of the Protocol S study, However, considering that PRP is not standard of care in this part of the target population, a sham controlled study would have been appropriate to fully evaluate the benefit of Lucentis.

In conclusion, efficacy of ranibizumab 0.5 mg has been demonstrated in Protocol S in patients with PDR, while data are not sufficient to conclude on NPDR.

2.5. Clinical safety

Introduction

Ranibizumab as a 10 mg/ml solution for intravitreal injection is an established product with an extensive safety record. The safety of ranibizumab is monitored through Periodic Safety Update Reports (PSURs), the Risk Management Plan (RMP), and standard pharmacovigilance practices. Since the International Birth Date (30-June-2006), a cumulative patient exposure, based on the number of ranibizumab vials and ranibizumab pre-filled syringes (PFS) sold worldwide, of approximately 5.4 million patient treatment-years has been recorded for the approved indications up to 31 May 2018 [RMP v. 19.0].

Safety population, evaluations, and patient exposure

Key safety population

The demonstration of safety and tolerability for intravitreal ranibizumab 0.5 mg in patients with moderately severe NPDR or worse is based on 4 studies (Protocol S and Studies D2301, D2303, and D2305) in patients with diabetic eye disease that evaluated treatment with ranibizumab intravitreal injections compared with standard treatment (PRP or active laser treatment). Protocol S and the Novartis studies included patients with a wide spectrum of DR, including NPDR and PDR and patients with and without DME.

Protocol S enrolled adult PDR patients (age ≥18 years) with Type 1 or Type 2 diabetes with or without baseline DME. There was a total of 394 Safety Evaluable Eyes (ranibizumab: 191; PRP: 203) and 305 Safety Evaluable Subjects: ranibizumab-1 study eye: 102; PRP-1 study eye: 114; 2 study eyes: 89 (Table 6).

Safety data from Protocol S are supported by data from the 3 Novartis studies (D2301, D2303, D2305), which comprised adults (age ≥18 years) with DME and Type 1 or Type 2 diabetes (with HbA1c ≤10 % and on stable diabetes medications). Patients in Study D2301 were primarily Caucasian, whereas Studies D2303 and D2305 enrolled only Asian patients (mainly Chinese and Japanese in Study D2303 and Chinese patients only in Study D2305). Safety data were pooled for the Novartis studies for patients with moderately severe NPDR or worse (i.e., the target DR population), as the designs of the studies were similar (same study duration, schedules of study visits, and safety assessments methods).

There was a total of 336 patients in the Safety set of the Novartis studies (ranibizumab: 204; laser: 132). For the safety pooling, the primary focus was on ranibizumab 0.5 mg monotherapy versus laser monotherapy. All patients in the monotherapy treatment arms, who received at least 1 application of study treatment and had at least 1 post-baseline safety assessment, were included in the safety pool.

Safety data for Protocol S and the pooled Novartis studies are presented separately.

Part of the patients in both groups also received the other treatment (Table 6), but safety data has been presented only by the two original treatment groups. The MAH was requested to provide subgroup analyses. In response, the MAH provided analysis of ranibizumab only subgroup and PRP only subgroup, consistent with expected in the diabetic population and the known safety profile of ranibizumab.

Evaluations

Protocol S

In Protocol S, safety was assessed based on ocular and non-ocular AEs and serious adverse events (SAEs) and deaths. MedDRA version 18.1 was used for coding of study AEs, as this version was used in the Protocol S Clinical Study Report. Complete results for all safety variables are summarized in the [SCS].

Novartis performed several analyses in addition to the pre-planned 2-year safety analyses in Protocol S:

- Ocular and non-ocular AEs (any AE) and SAEs were summarized up to 1 year.
- Ocular and non-ocular AEs and SAEs suspected to be related to study drug and/or intravitreal injection were summarized up to 1 year and up to 2 years.

Novartis studies (D2301, D2303, D2305)

Safety was evaluated in the target DR population based on ocular and non-ocular AEs. Data presented include ocular and non-ocular AEs, SAEs, and AEs/SAEs suspected to be related to study drug and/or intravitreal injection, and AEs leading to permanent treatment discontinuation. MedDRA version 21.0 was used for coding of study AEs.

The Safety set for the Novartis studies comprised patients with moderately severe NPDR or worse at baseline who had received at least 1 application of study treatment and had at least 1 post-baseline safety assessment. Patients were analysed according to the treatment received.

Patient exposure

Protocol S

Treatment initiation in Protocol S consisted of injections at baseline and every 4 weeks up to Week 12 (4 injections), after which assessment of stability of disease activity was performed which determined if further treatment was needed.

Up to 1 year (Week 52 visit), the mean number of ranibizumab injections overall was 7.1. In patients randomised to the PRP group, the mean number of ranibizumab injections up to 1 year was 2.3.

Up to 2 years, the mean number of ranibizumab injections in the ranibizumab group was 10.4 overall. In patients randomised to the PRP group, the mean number of injections was 3.4 (Table 16).

Table 16. Protocol S: Number of ranibizumab injections.

	Ranibizumab			PRP		
Ranibizumab injections	**Overall (N=191)**	**Eyes with baseline DME (N=42)**	**Eyes without baseline DME (N=149)**	**Overall (N=203)**	**Eyes with baseline DME (N=46)**	**Eyes without baseline DME (N=157)**
Prior to the 1-year visit						
Mean ± standard deviation	7.1±2.5	8.5±2.5	6.7±2.3	2.3 ±3.3	5.5 ±3.5	1.4 ±2.5
Median injections (min, max)	7.0 (2, 13)	9.0 (5, 13)	6.0 (2, 13)	1.0 (0, 12)	5.0 (1, 12)	0.0 (0, 12)
Prior to the 2-year visit						
Mean ± standard deviation	10.4±4.9	12.4±5.1	9.8±4.7	3.4±4.9	8.2±5.9	2.0±3.5
Median injections (min, max)	10.0 (2, 22)	12.5 (5, 22)	9.0 (2, 21)	1.0 (0, 20)	7.0 (1, 20)	0.0 (0, 18)
Between 1- and 2-year visit						
Mean ± standard deviation	3.3 ± 3.1	3.9 ± 3.3	3.1 ± 3.0	1.1 ± 2.1	2.7 ± 3.2	0.6 ± 1.4
Median injections (min, max)	3.0 (0, 11)	4.0 (0, 10)	2.0 (0, 11)	0.0 (0, 10)	1.0 (0, 10)	0.0 (0, 7)

N=study eyes; DME = Diabetic macular edema; PRP = Panretinal photocoagulation

Novartis studies (D2301, D2303, and D2305)

In the Novartis studies, treatment was given monthly up to Week 8 (3 injections). Thereafter, treatment was given as needed based on DME disease progression/activity leading to reduction of visual acuity.

Although there was a difference of 1 injection during treatment initiation between the Novartis studies and Protocol S (3 vs. 4 injections, respectively), the mean (SD) number of ranibizumab injections administered up to 1 year was similar between the ranibizumab groups of the Novartis studies and Protocol S: 7.7 (2.79) in the Novartis studies and 7.1 (2.5) in Protocol S.

Adverse events

Adverse events

Ocular and non-ocular AEs are presented separately for Protocol S and the pooled Novartis studies. AEs are summarised up to 1 year for Protocol S and the Novartis studies, and also up to 2 years for Protocol S.

Most frequent adverse events

Ocular adverse events

Overall, the types of common ocular AEs observed across the treatment groups in Protocol S and the target DR population from the Novartis studies were consistent with those observed in previous studies in patients with DR and with the known safety profile of ranibizumab for approved indications.

Protocol S

At 1 year, 133 (69.6 %) eyes in the ranibizumab group and 139 (68.5 %) eyes in the PRP group had at least 1 ocular AE (Table 17). The most common ocular AEs in the study eyes were reported in similar proportions of both treatment groups: vitreous floaters (ranibizumab: 20.4 %, PRP: 18.2 %), followed by eye pain (ranibizumab: 11.5 %, PRP: 11.8 %). The AEs of vision blurred, vitreous hemorrhage, and visual acuity reduced were reported in a lower proportion of patients in the ranibizumab group compared with the PRP group. As expected for intravitreal injections, conjunctival hemorrhage was more frequently reported in the ranibizumab group (9.9 %) than in the PRP group (2.0 %).

At 2 years, the most common ocular AEs occurring in either group were vitreous floaters (ranibizumab: 28.3 %, PRP: 27.6 %) followed by vitreous hemorrhage (ranibizumab: 20.4 %, PRP: 26.6 %), and vision blurred (ranibizumab: 16.8 %, PRP: 26.6 %) [SCS-Table 2-2].

Table 17. Ocular AEs in the study eye occurring in at least 5 % of eyes in any treatment group through 1 year (Safety Evaluable Eyes) (Protocol S).

Preferred term	Ranibizumab N=191 n (%)	PRP N=203 n (%)
Total	**133 (69.6)**	**139 (68.5)**
Vitreous floaters	39 (20.4)	37 (18.2)
Eye pain	22 (11.5)	24 (11.8)
Conjunctival haemorrhage	19 (9.9)	4 (2.0)
Vitreous haemorrhage	19 (9.9)	36 (17.7)
Vision blurred	18 (9.4)	42 (20.7)
Unevaluable event*	14 (7.3)	16 (7.9)

Visual acuity reduced	13 (6.8)	23 (11.3)
Dry eye	11 (5.8)	11 (5.4)
Eye irritation	10 (5.2)	5 (2.5)
Eye pruritus	10 (5.2)	7 (3.4)
Visual impairment	10 (5.2)	12 (5.9)
Photopsia	7 (3.7)	11 (5.4)

* Abbreviated terms could not be queried or confirmed and were classified as unevaluable events. Preferred terms are sorted in descending frequency of AEs in "Ranibizumab" column.
– An eye with multiple AEs is counted only once in the “Total” row. "Total" is number of eyes with at least one AE.
– An eye with multiple AEs with the same preferred term is counted only once for that preferred term.

Novartis studies (D2301, D2303, D2305)

In the target DR population, 68 eyes (33.3 %) in the ranibizumab 0.5 mg group and 35 eyes (26.5 %) in the laser group had ocular AEs up to 1 year (Table 18). The most common ocular AEs (≥5 % in either group) were conjunctival hemorrhage (ranibizumab: 7.8 %, laser: 5.3 %) and vitreous hemorrhage (ranibizumab: 3.4 %, laser 4.5 %). Cataract was reported in 5 patients (2.5 %) in the ranibizumab group and in 1 patient (0.8 %) in the laser group. Vitreous floaters (2.9 %) and intraocular pressure increased (2.5 %) were reported only in the ranibizumab treatment group. Eye pain was reported in 8 patients (6.1 %) in the laser group and 6 patients (2.9 %) in the ranibizumab group. Retinal hemorrhage (3.8 %), lacrimation increased (3.0 %), eye irritation (2.3 %), and vision blurred (2.3 %) were reported only in the laser group. All other ocular AEs reported were in comparable proportions in both treatment groups.

Table 18. Ocular adverse events of the study eye, regardless of study drug relationship (at least 2 % in any group) by preferred term (Safety set, target DR population) (Pooled Novartis Studies).

Preferred term	**Ranibizumab 0.5 mg N=204 n (%)**	**Laser N=132 n (%)**
Total	**68 (33.3)**	**35 (26.5)**
Conjunctival haemorrhage	16 (7.8)	7 (5.3)
Vitreous haemorrhage	7 (3.4)	6 (4.5)
Eye pain	6 (2.9)	8 (6.1)
Vitreous floaters	6 (2.9)	0
Cataract	5 (2.5)	1 (0.8)
Conjunctival hyperaemia	5 (2.5)	3 (2.3)
Intraocular pressure increased	5 (2.5)	0
Eye irritation	0	3 (2.3)
Lacrimation increased	0	4 (3.0)
Retinal haemorrhage	0	5 (3.8)
Vision blurred	0	3 (2.3)

Preferred terms are sorted in descending frequency of AEs in "Ranibizumab 0.5mg" column.
- A patient with multiple AEs is counted only once in the “Total” row. “Total” is number of patients with at least one AE.
- A patient with multiple AEs with the same preferred term is counted only once for that preferred term.]

Overall, comparable AE frequencies were seen in both study arms, but conjunctival hemorrhage was more frequent in the ranibizumab group, and vitreous hemorrhage was observed more often in laser group. Both observations could be expected and do not raise safety concerns.

Non-ocular adverse events

Overall, the types of common non-ocular AEs observed across the treatment groups in Protocol S and the Novartis studies were representative of those observed in a severe, chronic diabetic population.

Protocol S

At 1 year, 83 (81.4 %) patients in the ranibizumab-1 study eye group, 72 (63.2 %) patients in the PRP-1 study eye group, and 75 (84.3 %) patients in the 2-study eyes group had at least 1 non-ocular AE (Table 19). The most common non-ocular AEs in the ranibizumab-1 study eye group were hypertension and nasopharyngitis (both 10.8 %). In the PRP-1 study eye group, the most common non-ocular AE were hypertension (12.3 %) and headache (10.5 %), and in the 2-study eyes group, the most common non-ocular AEs were headache (16.9 %) and nasopharyngitis (12.4 %). All other AEs occurred in less than 10.0 % of patients.

At 2 years, the most common non-ocular AEs in the ranibizumab-1 study eye group were hypertension (23.5 %), nasopharyngitis (13.7 %), and cough (13.7 %). In the PRP-1 study eye group, they were hypertension (17.5 %), headache (12.3 %), nasopharyngitis (8.8 %), and nausea (8.8 %); and in the 2-study eye group, they were headache (16.9 %), nasopharyngitis (15.7 %), and hypertension (14.6 %).

Table 19. Non-ocular AEs occurring in at least 5% of patients in any treatment group through 1 year (Safety Evaluable Subjects) (Protocol S).

Preferred term	Patients with 1 Study Eye		Patients with 2 Study Eyes
	Ranibizumab N=102 n (%)	PRP N=114 n (%)	N=89 n (%)
Total	**83 (81.4)**	**72 (63.2)**	**75 (84.3)**
Hypertension	11 (10.8)	14 (12.3)	7 (7.9)
Nasopharyngitis	11 (10.8)	6 (5.3)	11 (12.4)
Nausea	10 (9.8)	7 (6.1)	6 (6.7)
Cough	9 (8.8)	6 (5.3)	8 (9.0)
Headache	9 (8.8)	12 (10.5)	15 (16.9)
Pain in extremity	8 (7.8)	0	1 (1.1)
Vomiting	8 (7.8)	5 (4.4)	5 (5.6)
Chest pain	7 (6.9)	4 (3.5)	2 (2.2)
Influenza	7 (6.9)	7 (6.1)	6 (6.7)
Sinusitis	7 (6.9)	3 (2.6)	1 (1.1)
Dizziness	6 (5.9)	5 (4.4)	5 (5.6)
Dyspnoea	6 (5.9)	4 (3.5)	3 (3.4)
Nephropathy	6 (5.9)	3 (2.6)	4 (4.5)
Anaemia	4 (3.9)	3 (2.6)	5 (5.6)
Blood glucose increased	4 (3.9)	1 (0.9)	5 (5.6)
Fall	4 (3.9)	6 (5.3)	3 (3.4)

– Preferred terms are sorted in descending frequency of AEs in "Patients with 1 Study Eye: Ranibizumab" column.
– A patient with multiple AEs is counted only once in the “Total” row. "Total" is number of patients with at least one AE.
– A patient with multiple AEs with the same preferred term is counted only once for that preferred term.

Novartis studies (D2301, D2303, D2305)

In the target DR population, 111 patients (54.4 %) in the ranibizumab 0.5 mg group and 80 patients (60.6 %) in the laser group had non-ocular AEs up to 1 year (Table 20). The most common non-ocular AEs were nasopharyngitis (8.8 %) and diabetic nephropathy (5.4 %) in the ranibizumab 0.5 mg group and nasopharyngitis (8.3 %) and hypertension (6.1 %) in the laser group.

A greater proportion of patients in the ranibizumab 0.5 mg group than in the laser group had events of diabetic nephropathy (5.4 % vs. 0.8 %). Out of the 11 cases of nephropathy, only 1 case constituted an SAE, and the patient required dialysis. The other 10 cases were of mild or moderate severity. Overall, 4 out of 11 patients with an AE of nephropathy entered the study with a documented history of renal insufficiency or diabetic nephropathy. At screening, all but 1 patient had an abnormal urine protein dip stick result of +2 or +3, 5 of whom also had elevated serum creatinine levels, indicating pre-existing renal conditions. Two of the diabetic nephropathy cases were suspected to be related to study drug by the investigator. Further discussion of the events of diabetic nephropathy is in Section 5.7. Considering the baseline characteristics of the cases reported, this is not considered to raise a safety concern.

Table 20. Non-ocular adverse events, regardless of study drug relationship, (at least 3% in any group) by preferred term (Safety set, target DR population) (Pooled Novartis Studies).

Preferred term	Ranibizumab 0.5 mg N=204 n (%)	Laser N=132 n (%)
Total	**111 (54.4)**	**80 (60.6)**
Nasopharyngitis	18 (8.8)	11 (8.3)
Diabetic nephropathy	11 (5.4)	1 (0.8)
Cough	10 (4.9)	1 0.8)
Hypertension	10 (4.9)	8 (6.1)
Upper respiratory tract infection	10 (4.9)	4 (3.0)
Anaemia	7 (3.4)	0
Insomnia	5 (2.5)	4 (3.0)
Back pain	3 (1.5)	4 (3.0)
Constipation	3 (1.5)	4 (3.0)
Hyperlipidaemia	3 (1.5)	4 (3.0)

– Preferred terms are sorted in descending frequency of AEs in "Ranibizumab 0.5mg" column.
– A patient with multiple AEs is counted only once in the “Total” row. "Total" is number of patients with at least one AE.
– A patient with multiple AEs with the same preferred term is counted only once for that preferred term.

Higher incidences of cough and anemia were also reported in the ranibizumab 0.5 mg group than in the laser group (cough: 4.9 % vs. 0.8 %; anemia: 3.4 % vs. 0 %). Cough and anemia are listed as adverse drug reactions (ADRs) for ranibizumab and are observed in the labelled frequency categories for the DR target population. Thus, these events do not represent new safety signals.

Other common non-ocular AE (occurring in ≥3 % of patients) occurred in similar proportions between the 2 treatment groups and included diabetic nephropathy, hypertension, upper respiratory tract infection, hyperlipidemia, insomnia, back pain, and constipation.

Adverse events suspected of being related to study drug

Protocol S

Ocular AEs suspected of being related to study drug

Up to 1 year, similar proportions of patients in the ranibizumab group (14.1 %) and the PRP group (15.3 %) had at least 1 ocular AE suspected to be related to study drug and/or intravitreal injection. The ocular AEs in the study eye most commonly suspected to be related to study drug in the ranibizumab group were vitreous floaters (ranibizumab: 4.7 %; PRP: 1.5 %), followed by conjunctival hemorrhage (ranibizumab: 4.2 %; PRP: 1.0 %) and eye pain (ranibizumab: 2.6 %; PRP: 3.4 %). Blurred vision (3.0 %), photopsia (1.0 %), visual impairment (1.0 %), and vitreous hemorrhage (1.0 %) were suspected to be related to study drug in the PRP group alone. All other ocular AEs suspected to be related to the study drug occurred in less than 1 % of study eyes in either treatment group.

In the second year of the study, there were few additional ocular AEs in either group that were suspected to be related to study drug and/or intravitreal injection. The most common ocular AEs in the study eye that were suspected to be related to study drug were vitreous floaters (ranibizumab: 6.3 %; PRP: 1.5 %), conjunctival hemorrhage (ranibizumab: 4.7 %; PRP: 1.5 %), and eye pain (ranibizumab: 3.1 %; PRP: 3.9 %).

Conjunctival hemorrhage is an identified AE related to the route of delivery of ranibizumab.

Non-ocular AEs suspected of being related to study drug

Up to 1 year, no patients in the ranibizumab-1 study eye group had a non-ocular AE suspected to be related to study drug. Two patients in the PRP-1 study eye group had procedural headache that was suspected to be related to the study drug. In the 2-study eyes group, 1 patient had an unevaluable event that was suspected to be related to study drug by the investigator. In the second year of the study, no additional non-ocular AEs suspected to be related to study drug were reported.

Novartis studies (D2301, D2303, D2305)

Ocular AEs suspected of being related to study drug

In the target DR population, up to 1 year, similar proportions of eyes in the ranibizumab 0.5 mg group (35 eyes, 17.2 %) and in the laser group (19 eyes, 14.4 %) had ocular AEs suspected of being related to study drug and/or intravitreal injection. In the ranibizumab 0.5 mg group, the most common AEs (≥2 %) suspected to be related to study drug and/or intravitreal injection were conjunctival hemorrhage (6.9 %), vitreous floaters (2.9 %), conjunctival hyperemia (2.5 %), eye pain (2.5 %), and intraocular pressure increased (2.0 %). In the laser group, the most common AEs (≥2 %) suspected to be related to study drug and/or intravitreal injection were conjunctival hemorrhage (5.3 %), eye pain (3.8 %), and conjunctival hyperemia (2.3 %). The suspected ocular AEs of vitreous floaters (2.9 %) and intraocular pressure increased (2.0 %) were reported only for the ranibizumab treatment group, and eye irritation (2 patients, 1.5 %) was reported only in the laser group.

Non-ocular AEs suspected of being related to study drug

In the target DR population, up to 1 year, 6 patients (2.9 %) in the ranibizumab 0.5 mg group and 4 patients (3.0 %) in the laser group had non-ocular AEs suspected of being related to study drug and/or intravitreal injection. All events occurred in only 1 patient each, with the exception of diabetic nephropathy, which occurred in 2 patients (1.0 %) in the ranibizumab 0.5 mg group, among which 1 of the cases had a documented medical history of diabetic nephropathy and chronic renal failure.

In conclusion, there were only few non-ocular related AEs, which occurred in similar frequency and without concentration on a specific event type.

Serious adverse events, deaths and other significant events

Protocol S

Table 21 and Table 22 summarise deaths and serious or clinically relevant AEs up to 1 year in Protocol S for ocular and non-ocular events, respectively. Up to 1 year, there were 5 deaths: 2 patients (2.0 %) in the ranibizumab-1 study eye group, 2 patients (1.8 %) in the PRP-1 study eye group, and 1 patient (1.1 %) in the 2 study eyes group. In the second year of the study, an additional 9 deaths were reported (4 patients (3.9 %) in the ranibizumab-1 study eye group, 2 patients (1.8 %) in the PRP-1 study eye group, and 3 patients (3.4 %) in the 2 study eyes group).

Table 21. Number (%) of eyes that experienced ocular serious adverse events or other significant adverse events through 1 year (Safety Evaluable Eyes) (Protocol S).

Serious or other significant events	Ranibizumab N=191 n (%)	PRP N=203 n (%)
SAE(s)	2 (1.0)	1 (0.5)
AE leading to permanent discontinuation of study treatment	0	0
SAE leading to permanent discontinuation of study treatment	0	0

Table 22. Number (%) of patients who died or experienced non-ocular serious adverse events or other significant adverse events through 1 year (Safety Evaluable Subjects) (Protocol S).

Serious or other significant events	Patients with 1 study eye		2 study eyes
	Ranibizumab N=102 n (%)	PRP N=114 n (%)	N=89 n (%)
Death	2 (2.0)	2 (1.8)	1 (1.1)
SAE(s)	34 (33.3)	28 (24.6)	20 (22.5)
AE leading to permanent discontinuation of study treatment	3 (2.9)	1 (0.9)	1 (1.1)
SAE leading to permanent discontinuation of study treatment	3 (2.9)	1 (0.9)	1 (1.1)

There were few ocular SAEs in any treatment group in the first and second years of Protocol S. Up to 1 year, 34 (33.3 %), 28 (24.6 %) and 20 (22.5 %) patients in the ranibizumab-1 study eye group, PRP-1 study eye group, and 2 study eyes group, respectively, had non-ocular SAEs Up to 2 years, 42 (41.2 %), 33 (28.9 %) and 38 (42.7 %) patients in the ranibizumab-1 study eye group, PRP-1 study eye group, and 2 study eyes group, respectively, had non-ocular SAEs. Up to 2 years, there were no ocular AEs that led to permanent discontinuation and few non-ocular AEs that led to permanent discontinuation.

Novartis studies (D2301, D2303, D2305)

There were no deaths in the target DR population, and no patient in the ranibizumab 0.5 mg group had an ocular SAE in the study eye (Table 23). A total of 9.8 % of patients in the ranibizumab 0.5 mg group had non-ocular SAEs. There were few AEs leading to permanent treatment discontinuation in the ranibizumab 0.5 mg group (4 patients, 2.0 %; 1 patient with an ocular AE in the study eye, and 3 patients with non-ocular AEs).

Deaths

Protocol S

Up to 1 year, a total of 5 deaths occurred: 2 patients (2.0 %) in the ranibizumab-1 study eye group, 2 patients (1.8 %) in the PRP-1 study eye group, and 1 patient (1.1 %) in the 2 study eyes group (Table 22). In the second year of the study, an additional 9 deaths were reported (4 patients (3.9 %) in the ranibizumab-1 study eye group, 2 patients (1.8 %) in the PRP-1 study eye group, and 3 patients (3.4 %) in the 2 study eyes group). None of the SAEs resulting in death were considered related to the study drug and/or intravitreal injection by the investigator. The predominant types of SAEs leading to death in all treatment groups were cardiovascular events or renal complications, which are common comorbid conditions in a chronic diabetic population. Six deaths were due to unknown causes and were listed only as "death".

The MAH has provided appropriate narratives of the 14 fatalities. 9/14 subjects were aged over 50 years with diabetes diagnosed 5 to 35 years earlier. 4/5 of the patients younger than 50 years had had diabetes diagnosed 18 to 20 years ago. The deaths were mainly due to comorbidities related to diabetes.

Novartis studies (D2301, D2303, D2305)

There were no deaths in the target DR population (Table 23).

Table 23. Number (%) of patients who died or experienced serious adverse events or other significant adverse events (Safety set) (Pooled Novartis Studies, target DR population).

Serious or other significant events	Ranibizumab 0.5 mg N=204 n (%)	Laser N=132 n (%)
Death	0	0
SAEs	33 (16.2)	26 (19.7)
Study eye	0	2 (1.5)
Non-Ocular	20 (9.8)	22 (16.7)
AE leading to permanent discontinuation of study treatment	4 (2.0)	10 (7.6)
Study eye	1 (0.5)	4 (3.0)
Non-Ocular	3 (1.5)	5 (3.8)
SAE leading to permanent discontinuation of study treatment	2 (1.0)	6 (4.5)
Study eye	0	1 (0.8)
Non-ocular	2 (1.0)	5 (3.8)

– Fellow eye (S)AEs are also included in the total rows for each category. Thus, for some categories the totals are notably greater than the sum of study eye and non-ocular (S)AEs.

It is noted that for ranibizumab the frequency of SAEs is almost twice as high in Protocol S than in the pooled data. The difference is not self-explanatory. The MAH was requested to elaborate on eventual differences in disease severity or comorbidities in the Protocol S population, including an additional analysis on SAEs in patients on receiving ranibizumab or laser.

In the provided discussion in the response, no critical imbalances were found in the base line medical history for the treatment groups, and consistent with the diabetic population.

The study procedure may well have contributed to the imbalance, with more study visits in the ranibizumab group compared to the Novartis group in Protocol S. As the majority of patients appear to have pre-existing medical conditions that can explain the cardiovascular and renal adverse events, it is agreed that no new safety concern is detected from these data.

Serious adverse events

Ocular serious adverse events

Protocol S

There were few ocular SAEs in any treatment group. – Up to 1 year, 2 eyes (1.0 %) in the ranibizumab group and 1 eye (0.5 %) in the PRP group had at least 1 ocular SAE (events of endophthalmitis, sudden visual loss visual impairment, and vitreous floaters in 1 eye each in the ranibizumab group and vitreous hemorrhage in 1 eye in the PRP group). In the second year, there were 2 additional SAEs of vitreous hemorrhage (1 each in the ranibizumab and PRP groups). None of the SAEs were suspected to be related to the study drug and/or intravitreal injection by the investigator except for the SAE of endophthalmitis.

Novartis studies (D2301, D2303, D2305)

In the target DR population, no eyes had ocular SAEs in the ranibizumab 0.5 mg group, and 2 (1.5 %) eyes had ocular SAEs in the laser group (both events of vitreous hemorrhage). Neither of these SAEs was suspected by the investigator to be related to the study drug and/or intravitreal injection.

Non-ocular serious adverse events

Protocol S

Up to 1 year, 34 (33.3 %), 28 (24.6 %), and 20 (22.5 %) patients in the ranibizumab-1 study eye group, PRP-1 study eye group, and 2 study eyes group, respectively, had non-ocular SAEs (Table 5-6). Due to the more frequent visits in the ranibizumab group compared with the PRP group, there may have been a bias toward a higher frequency of reporting in the ranibizumab versus the PRP group. In the ranibizumab-1 study eye group, the most common non-ocular SAE was chest pain (6 patients, 5.9 %), followed by asthenia, cardiac failure congestive, and dyspnea (4 patients each, 3.9 %). In the PRP-1 study eye group, the most common SAE was dyspnea (4 patients, 3.5 %) (all other SAEs occurred in 2 or fewer patients), and in the 2 study eye group, all SAEs occurred in 2 or fewer patients. None of the non-ocular SAEs through 1 year were suspected to be related to the study drug and/or intravitreal injection by the investigator.

Up to 2 years, 42 (41.2 %), 33 (28.9 %) and 38 (42.7 %) patients in the ranibizumab-1 study eye group, PRP-1 study eye, and 2 study eyes group, respectively, had non-ocular SAEs. The most common non-ocular SAEs (>5 %) in the ranibizumab-1 study eye group were chest pain (8 patients, 7.8 %) and cardiac failure congestive (6 patients, 5.9 %) followed by acute kidney injury, dyspnea, and renal failure (5 patients each, 4.9 %). In the PRP-1 study eye group, the most common non-ocular SAE was dyspnea (5 patients, 4.4 %) (all other SAEs occurred in fewer than 5 patients), and in the 2 study eye group, the most common non-ocular SAE was pneumonia (4 patients, 4.5 %) (all other SAEs

occurred in fewer than 4 patients). None of the non-ocular SAEs through 2 years were suspected to be related to the study drug and/or intravitreal injection by the investigator.

Novartis studies (D2301, D2303, D2305)

In the target DR population, 20 patients (9.8 %) in the ranibizumab 0.5 mg group and 22 patients (16.7 %) in the laser group had non-ocular SAEs. All SAEs in the ranibizumab 0.5 mg group occurred in 1 patient only; in the laser group, cerebral infarction occurred in 2 patients (1.5 %). In the ranibizumab 0.5 mg group, the SAE of myocardial infarction (1 patient) was suspected by the investigator to be related to study drug and/or intravitreal injection. In the laser group, the SAEs of angina pectoris (1 patient), epulis (1 patient), and urinary tract infection (1 patient) were suspected by the investigator to be related to study drug and/or intravitreal injection.

The SAE frequency in the treatment arm appears to be higher in Protocol S, especially in year 2 compared with the comparator arm, and the opposite was observed in the Novartis studies. None of the SAEs observed in the treatment arm of Protocol S were evaluated as treatment related by the study investigators. The MAH was requested to discuss the observed imbalances seen in the Protocol S cohort in relation to baseline co-morbidities presented in treatment and control arm, taking into consideration the requested sub-analyses based on monotherapies.

The response concerning the imbalance is discussed above.

Discontinuation due to adverse events

Ocular adverse events leading to treatment discontinuation

Protocol S

Up to 2 years, there were no ocular AEs leading to permanent treatment discontinuation.

Novartis studies (D2301, D2303, D2305)

In the target DR population, there was 1 ocular AE that led to permanent treatment discontinuation in the ranibizumab 0.5 mg group: vitreous hemorrhage (1 patient, 0.5 %). In the laser group, events of retinal hemorrhage (2 patients, 1.5 %), macular fibrosis (1 patient, 0.8 %), and vitreous hemorrhage (1 patient, 0.8 %) led to permanent treatment discontinuation.

Non-ocular adverse events leading to treatment discontinuation

Protocol S

The incidence of non-ocular AEs that led to permanent discontinuation of study treatment was low in all treatment groups. Up to 1 year, 3 patients (2.9 %) in the ranibizumab-1 study eye group and 1 patient each in the PRP-1 study eye group and the 2 study eyes group had non-ocular AEs that led to permanent discontinuation. All these events were serious.

In the second year of the study, non-ocular AEs that led to permanent treatment discontinuation were reported in 3 patients (2.9 %) in the ranibizumab-1 study eye group, 1 patient (0.9 %) in the PRP-1 study eye group, and 3 patients (3.4 %) in the 2 study eyes group.

In total, within 2 years, the most common non-ocular AEs that led to permanent treatment discontinuation was death in all 3 groups (2 patients in each group).

Novartis studies (D2301, D2303, D2305)

There were few non-ocular AEs in the target DR population that led to treatment discontinuation. In the ranibizumab 0.5 mg group, 3 patients (1.5 %) had the following non-ocular AEs leading to

permanent treatment discontinuation: myocardial infarction (1 patient), metabolic disorder (1 patient), and bile duct cancer (1 patient). In the laser group, 5 patients (3.8 %) had the following non-ocular AEs leading to permanent treatment discontinuation: angina pectoris (1 patient), intestinal obstruction (1 patient), hepatitis B (1 patient), colon cancer (1 patient), and cerebral infarction (1 patient).

Laboratory findings

There were no planned laboratory outcome measures in Protocol S. HbA1c was collected at baseline, but no further analysis was performed.

In the Novartis studies, hematology, HbA1c, serum biochemistry, and urinalysis assessments for the total populations were performed; no clinically relevant differences between treatment arms were observed.

Glycosylated hemoglobin (HbA1c) (Novartis studies)

In the Novartis studies, glycosylated HbA1c was assessed at baseline and at Months 3, 6, 9 and 12. In the target DR population, for the duration of the studies, glycemic control was stable, as demonstrated by a similar and consistent mean HbA1c at each study visit across the groups as well as a nominal change from baseline in HbA1c level.

Long-term safety data

Protocol S (Gross et al. 2018)

Five-year safety data for Protocol S were recently reported by Gross et al (2018). The 5-year visit was completed by 184 of 277 participants (66.4 %). In the ranibizumab and PRP groups, the mean (SD) numbers of ranibizumab injections were 19.2 (10.9) and 5.4 (7.9), respectively. Overall, safety results were consistent with those reported for 1 and 2 years. No notable differences between ranibizumab and PRP treatment groups were observed for major systemic AEs. No new safety concerns were identified.

Safety in special populations

Study subgroups

Intrinsic factors

Protocol S

In Protocol S, ocular and non-ocular AEs were analysed by baseline DME status and by subgroups on the basis of age (<65, ≥65 years), race (White, Black or African-American, or Other), and sex (Male, Female).

The proportion and the types of common ocular AEs observed in DR patients without baseline DME were generally similar to those observed in DR patients with DME at baseline [SCS-Section 5.1.1]. The ability to make a direct comparison of ocular AEs between the 2 groups was limited due to smaller number of eyes/patients in the DR groups with baseline DME.

As a result of the small sample size and low event numbers in the ≥65 year subgroup, the interpretation of age subgroup data is limited for ocular and non-ocular AEs. Similarly, because the majority of the patients were White, the interpretation of data by racial subgroup is limited for ocular and non-ocular AE. No notable differences in the incidence of ocular and non-ocular AEs were observed between sex subgroups up to 2 years, but interpretation of data is limited due to the small sample size and low event numbers in each subgroup.

Novartis studies (D2301, D2303, D2305)

In the target DR population, subgroup analysis of ocular and non-ocular AEs was performed for age (<65, ≥65 years), sex, and race (Caucasian, Asian, other). As a result of the small sample size and low event numbers in some of the subgroups, the interpretation of this data is limited. Overall, no clinically relevant differences were observed in these subgroups.

Extrinsic factors

Due to the low systemic concentration following the intravitreal injection of ranibizumab, no interactions are anticipated with use of concomitant drugs, tobacco, alcohol, or food intake.

The observed results in patients with previous retinal laser photocoagulation or with laser photocoagulation administered adjunctively during the study did not reveal relevant interaction with the intravitreal ranibizumab administration.

Adverse drug reactions

The safety profile of ranibizumab in diabetic patients is well-established for the treatment of visual impairment due to DME and is consistent with the general safety profile of ranibizumab in other approved indications.

Ocular and non-ocular events in ranibizumab-treated patients with moderately severe to severe NPDR or PDR, observed for up to 2 years in Protocol S and up to 1 year the pooled Novartis studies, were consistent with what would be expected in a diabetic patient population with DR, or have been described with similar frequency and severity in previous clinical trials with ranibizumab.

Ocular AEs

Ocular AEs that occurred in >2 % of patients in the ranibizumab group over control (PRP or laser) in Protocol S (through 2 years) or the target DR population of the pooled Novartis studies (through 1 year) included conjunctival hemorrhage, eye irritation, cataract subcapsular, photophobia, vitreous floaters, and intraocular pressure increased. These events are listed as ADRs for ranibizumab and were observed in the labelled frequency categories or below for patients with moderately severe NPDR or worse. Retinal exudates were reported at higher frequency in ranibizumab-treated eyes as compared with PRP (4.2 % vs. 0.5 %) only for Protocol S, while a single event of retinal exudates was reported for a laser-treated patient in the pooled Novartis studies. Exudates are a well-described retinal abnormality in patients with DR and not considered an adverse reaction due to treatment with ranibizumab.

Non-ocular AEs

The types of non-ocular AEs observed in Protocol S and the pooled Novartis studies were representative of those seen in a diabetic patient population with DR or have been described in previous studies using ranibizumab in patients with other indications. About half of the PRP treatment group in Protocol S also received ranibizumab in the study eye for the treatment of DME, with an average of 3.4 ranibizumab injections for up to 2 years [Protocol S - Section 7.1]. Therefore, there was no control group without ranibizumab exposure in Protocol S. In consequence and considering the large safety database for diabetic patients from previous clinical trials with ranibizumab (Zarbin et al 2017), numerical imbalances across treatment groups observed only in Protocol S have not been accounted for in the definition of non-ocular ADRs.

In the pooled Novartis studies, non-ocular AEs that occurred in >2 % patients of the ranibizumab group over laser control included diabetic nephropathy (5.4 % vs. 0.8 %), cough (4.9 % vs. 0.8 %), and anemia (3.4 % vs. 0 %). Cough and anemia are listed as ADRs for ranibizumab and are in the

labelled frequency categories for the DR target population. Overall, 10 out of the 11 patients with an event of diabetic nephropathy in the ranibizumab group had abnormal urinalysis results at screening, indicating pre-existing renal conditions.

In Protocol S, events associated with renal dysfunction were balanced across treatment groups (including events of nephropathy, renal failure, renal disorder, renal impairment, and proteinuria), though acute kidney injury was reported at higher frequency in the ranibizumab 1-study eye group and 2 study eye group as compared with the PRP 1-study eye group (4.9 % and 5.6 % vs. 1.8 %).

The underlying diabetes in patients with DME is a risk factor for nephropathy, and the systemic exposure of ranibizumab is very low (Avery et al. 2017). Previous evaluations of renal failure, proteinuria, and thrombotic microangiopathy have not shown evidence of a relationship between ranibizumab and renal toxicity, and the safety profile of ranibizumab in diabetic patients is well established for a large patient population [PSUR 01-Jul-2013 to 30-Jun-2014]. A pooled analysis of 6 randomised, controlled clinical trials from Genentech and Novartis comparing ranibizumab 0.5 mg versus sham injection and laser in diabetic patients with DME showed similar rates for renal failure and proteinuria events. Compared with this database of diabetic patients treated with ranibizumab, imbalances in nephropathy cases between treatment groups observed in this study does not constitute a new safety signal (Zarbin et al. 2017).

2.5.1. Discussion on clinical safety

Overall, safety data from Protocol S and the pooled studies indicate that the safety profile of ranibizumab in patients with proliferative diabetic retinopathy (PDR) is consistent with the well-established safety profile of ranibizumab in approved indications, including DME. No new or unexpected safety signals were identified. The types of AEs observed were representative of those seen in a diabetic patient population with DR or have been described in previous ranibizumab studies in patients with other indications.

Overall, comparable AE frequencies were seen in both study arms, but conjunctival hemorrhage was more frequent in the ranibizumab group, and vitreous hemorrhage was observed more often in laser group. Both observations could be expected and do not raise safety concerns.

There were few ocular SAEs in the study eye across the four studies and only one ocular AE in the ranibizumab group led to permanent study discontinuation (vitreous hemorrhage).

Common non-ocular AEs observed in the ranibizumab groups were few and typical of a diabetic patient population with DR, occurred in similar frequency and without concentration on a specific event type.

A greater proportion of patients in the ranibizumab group developed diabetic nephropathy. The majority of these subjects had abnormal urine protein result or elevated serum creatinine levels already at screening, thus the finding is not considered a safety concern.

Previous evaluations of renal failure, proteinuria, and thrombotic microangiopathy have not shown evidence of a relationship between ranibizumab and renal toxicity, and the safety profile of ranibizumab in diabetic patients is well established for a large patient population.

Long-term safety data (2, and up to 5 years) from Protocol S were consistent with the 1-year safety data.

Part of the patients in both groups also received the other treatment (Table 15), and additional safety analyses were performed of the ranibizumab only subgroup and PRP only subgroup. Ocular AEs were generally similar in reporting frequencies in both the ranibizumab only and the PRP only groups (78.1% vs 72.0% eyes with at least one ocular AE) whereas non-ocular AEs was slightly higher in

patients that received ranibizumab only compared to those treated exclusively with PRP (90.7% versus 77.6%). However, it is agreed with MAH that the more frequent injections, and more frequent visits following ranibizumab treatment may have contributed to the higher proportion of non-ocular adverse events in the ranibizumab group compared to the PRP only group.

It is noted that the MAH had chosen different cut-off levels from 2 to 3 to 5 % for reported adverse events.

The SAE frequency in the treatment arm appears to be higher in Protocol S, especially in year 2 compared with the comparator arm, and the opposite was observed in the Novartis studies and this has been sufficiently discussed by the MAH in the 1st round.

None of the SAEs discussed were suspected by the Investigator to be causally related to treatment with ranibizumab and the baseline medical history at diagnoses did not reveal any critical imbalances across SOCs for both treatment groups. Consistent with the diabetic study population, the most frequently reported medical history SOCs were cardiac, vascular, and renal disorders. As diabetes is a known risk factor for cardiovascular and renal complications, events reflecting such complications are expected for this patient population and overall do not reveal a new safety concern for IVT treatment with ranibizumab in diabetic patients with DR.

2.5.2. Conclusions on clinical safety

The safety profile of ranibizumab in diabetic patients is well-established for the treatment of visual impairment due to DME. The safety profile is consistent with the general safety profile of ranibizumab in other approved indications. Endophthalmitis is an identified risk, which rises with repeated injections.

No new or unexpected safety signals were identified in ranibizumab-treated patients with moderately severe to severe NPDR or PDR, observed for or up to 24 months in Protocol S and for up to 12 months the pooled studies. The types of ocular and non-ocular adverse events (AEs) observed in the study populations were typical for this patient population. The safety data indicate that ranibizumab administered up to 2–5 years in this population is safe and well-tolerated.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Risk management plan

The MAH submitted an updated RMP version with this application. The proposed RMP change for the RMP version 19.0 compared with RMP version 17.2 is the addition of safety data from the Protocol S study and the diabetic retinopathy population of Novartis-sponsored clinical studies RESTORE, REVEAL and REFINE to support the new indication.

The safety profile of ranibizumab in diabetic patients is well-established for the treatment of visual impairment due to DME and consistent with the general safety profile of ranibizumab in other approved indications.

No new or unexpected safety signals were identified in ranibizumab-treated patients with moderately severe to severe NPDR or PDR, observed for or up to 24 months in Protocol S and for up to 12 months the pooled Novartis studies.

There is no change in the safety concerns compared with version 17.2 of the RMP. Identified risks associated with intravitreal injection including infectious endophthalmitis, intraocular inflammation, retinal detachment and retinal tear, and intraocular pressure increase are also relevant for patients with moderately severe to severe NPDR and PDR.

The list below shows the major modifications/changes for Safety RMP version 19.0 (v19.0) from RMP version 17.2.

Part	Major changes compared with RMP v 17.2
I	Updated to include new proposed indication of moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).
II	Sections 'Epidemiology of the indications and target populations', and 'Clinical trial exposure' are updated to include information regarding the proposed additional indication. Section 'Important exclusion criteria in pivotal studies' is updated to reflect the proposed additional indication. 'Post-authorization experience' has been updated considering the new data cut-off date. No changes have been made in Section 'Additional EU requirements for the Safety specification'. Human relevance part of the 'Non-clinical part of the safety specification' has been updated to align with information provided in the ranibizumab SmPC. Section 'Presentation of important identified risks and important potential risks' updated to include incidence of proposed additional indication.
III	No change.
IV	No change.
V	Section 'Additional risk minimization measure' has been updated to include Educational plan for patients with NPDR and PDR
VI	Section 'The medicine and what it is used for' has been updated to include information regarding the proposed additional indication.
VII	Updated.

Annex 6 was updated to reflect the proposed additional indication. Annex 7 was updated with new statistical outputs and new reference materials. Annex 8 was updated accordingly.

Following the 1st RSI, the safety specification was updated and the missing information 'Potential effect on diabetic retinopathy of stopping periodic anti-VEGF injections' was removed from the safety concerns as Protocol S with a 5-year follow-up, has provided relevant information.

Other RMP versions under evaluation

At the time of the initial submission, there were two versions for ongoing Lucentis procedures II-74-G (version 18.2) and II-76 (version 19.1). During the 2nd RSI, the RMP version 18.2 was approved (July 25, 2019) within the procedure EMEA/H/C/000715/II/0074/G (indication prematurity retinopathy).

Subsequently, RMP version 18.2 is used as basis for the updated RMP to be submitted in response to 2nd RSI of procedure II-76 (including the changed indication). The version of the response is thus numbered 20.0.

The track changed version of the document will highlight the changes from version 18.2 to 20.0. Changes in the indication between version 19.1 and 20.0 for diabetic retinopathy indication will be highlighted in colour.

Details of the currently approved RMP:

Version number: Version 18.2
Approved with procedure: EMEA/H/C/000715/II/0074/G
Date of approval (opinion date): 25 July 2019

4. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are proposed to be updated to reflect the new indication and submitted data. The Package Leaflet (PL) is then updated accordingly.

A positive Opinion (PO) for the ongoing parallel procedure EMEA/H/C/000715/II/0074/G (related to the addition of pediatric indication in Retinopathy of Prematurity) was received on 25th July 2019. Thus, the MAH used the final English PI for procedure II-74-G as basis for the updated PI in response to the 2nd RSI for procedure II-76.

Additionally, the MAH took the opportunity of the response to the 2nd RSI for procedure II-76 to perform some editorial changes in the Package Leaflet. Those are administrative changes related to the update in the list of representatives of the MAH and do not require any linguistic review.

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the Package Leaflet has been submitted by the MAH and has been found acceptable, because the change introduced in the leaflet is minimal and has no impact on the legibility of the leaflet.

5. Benefit–Risk Balance

5.1. Therapeutic context

5.1.1. Disease or condition

Diabetic retinopathy (DR) is a microangiopathy that leads to hypoxia-triggered up-regulation of pro-angiogenic, proinflammatory, and vascular permeability factors, including vascular endothelial grow factor (VEGF), and to the development of subsequent vessel leakage, subclinical inflammation, and neovascularisation in the retina. It occurs as a complication of both Type 1 and Type 2 diabetes mellitus and is strongly associated with other microvascular complications of diabetes.

Despite best efforts to optimally control blood glucose, if DR is left untreated, it continues to worsen, with increasing risk of vision-threatening complications, including diabetic macular edema (DME), macular ischemia, and proliferative diabetic retinopathy (PDR).

Diabetic retinopathy is classified as either non-proliferative diabetic retinopathy (NPDR) or PDR, based on the absence or presence of abnormal new vessels, respectively. NPDR is the earliest stage of DR and often occurs unnoticed by patients, without significant vision loss. Optimal diabetes control, together with monitoring, is known to prevent progression of diabetic retinopathy, and this is the

current mainstay of treatment. On the other hand, sufficient metabolic control is not always possible to achieve and some subjects progress even if well controlled.

Worsening of NPDR to PDR is characterised by neovascularisation and regarded as a serious, clinically important progression of the pathology, as well as marking the transition of the disease to an advanced stage. PDR is also associated with a high risk of visual morbidity arising from vitreous hemorrhage, traction retinal detachment, and neovascular glaucoma (Aiello et al 1998, Wykoff et al 2018). Patients can also develop DME at any stage during the progression of DR.

Vascular endothelial growth factor is implicated in all aspects of vascular pathology in DR shown in both animal models and in NPDR and PDR patients compared with control healthy subjects. Vitreous VEGF levels in DR patients have been shown to correlate with the severity of DR.

5.1.2. Available therapies and unmet medical need

The standard-of-care for PDR is panretinal photocoagulation (PRP). Focal or grid laser may also be used when clinically significant DME is present. Vitreous surgery may be considered in patients with high-risk PDR.

There remains an unmet medical need for additional treatment options for DR.

5.1.3. Main clinical studies

The pivotal study was Protocol S which compared the efficacy of ranibizumab 0.5 mg with PRP in diabetic patients with PDR. It was a JCHR (DRCR.net) -sponsored Phase 3, multi-center, randomised, active-controlled, parallel-assignment, non-inferiority study for which the primary efficacy analysis was at 2 years, with follow-up up to 5 years. Protocol S enrolled 305 patients (394 study eyes) with PDR, with or without concomitant DME at baseline. Patients had Type 1 or Type 2 diabetes with PDR and had not yet received PRP in at least one eye. One or two eligible study eyes could be enrolled.

In addition, the MAH has submitted results from pooled data from three Novartis sponsored studies (D2301, D2303, and D2305). The three studies were randomised, double-masked, active-controlled, Phase 3 studies in patients with visual impairment due to DME. The studies compared ranibizumab 0.5 mg intravitreal injections (plus sham laser), ranibizumab 0.5 mg intravitreal injections with active laser (D2301 and D2303 only), and laser treatment plus sham injections.

As supportive data, the **RIDE and RISE** studies are also referred to. They were 3-year studies in patients with Type 1 or Type 2 diabetes with DME comparing the efficacy and safety of ranibizumab with sham. The studies were identically designed, randomised, Phase 3, double-masked, multicenter sham injection-controlled studies. After the main analyses of data at 2 years, sham-arm patients were allowed to crossover to the ranibizumab 0.5 mg arm, but the masked treatment period continued to Year 3, after which, additional analyses were performed.

5.2. Favourable effects

In Protocol S, the main outcome was the mean visual acuity letter score improvement from baseline at 2 years, which was 2.7 letters in the ranibizumab group and -0.7 letters in the PRP group. The adjusted least squares mean treatment group difference was 3.5 letters (95 % CI: 0.2, 6.7 letters). The pre-specified non-inferiority margin for the primary endpoint was 5 letters. Non-inferiority was thus reached. After 5 years the difference had waned, and both treatment groups showed an improvement of ca. 3 letters in visual acuity.

In the overall population in Protocol S, in the ranibizumab group, 41.8 % and 42.3 % of eyes experienced a ≥2-step improvement in DRSS from baseline at the 1-year and 2-year visits, respectively; the corresponding proportions of eyes in the PRP group were 14.6 % and 23.1 %, respectively. Comparable results were observed by baseline DME status.

In the pooled target DR population of the Novartis studies in patients with DME, 48.4 % of patients in the ranibizumab group had a 2-step improvement in DRSS from baseline at 1 year, compared with 14.6 % of patients in the laser group.

Greater proportions of patients in the ranibizumab treatment groups had ≥3-step improvement in DRSS compared with PRP or laser treatment: 28.6 % vs. 3.0 % in Protocol S at 1 year, 29.1 % vs. 3.5 % in Protocol S at 2 years.

In the pooled DME studies, a larger proportion of patients in the ranibizumab 0.5 mg group had a ⩾2-step improvement in DRSS from baseline at 1 year than in the laser group (48.4 % vs 14.6 %, respectively).

5.3. Uncertainties and limitations about favourable effects

At 5 years follow-up, the advantage of ranibizumab had waned, the treatments proved to be comparable regarding visual acuity, absence of PDR and neovascularisation. However, the relevance of this finding is difficult to assess, given the fact that both the treatment and comparator arms included a substantial number of patients who received both treatments (as many as 54.2 % of subjects in the comparator group received also ranibizumab) as well as the relatively high loss to follow-up.

5.4. Unfavourable effects

Overall, safety data from Protocol S and the pooled studies indicate that the safety profile of ranibizumab in patients with PDR is consistent with the well-established safety profile of ranibizumab in approved indications, including DME. No new or unexpected safety signals were identified. The types of AEs observed were representative of those seen in a diabetic patient population with DR or have been described in previous ranibizumab studies in patients with other indications.

Comparable AE frequencies were seen in both study arms, but conjunctival hemorrhage was more frequent in the ranibizumab group, and vitreous hemorrhage more often in the laser group. Both observations could be expected and do not raise new safety concerns.

Long-term safety data (2, and up to 5 years) from Protocol S were consistent with the 1-year safety data.

5.5. Uncertainties and limitations about unfavourable effects

For ranibizumab, the frequency of SAEs in Protocol S was almost twice as high as in the pooled data, 36 vs 20 SAEs. However, the majority of patients had pre-existing medical conditions that could explain the reported events.

5.6. Effects Table

Table 24. Effects Table for Lucentis in moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) in adults.

Effect	Short description	Unit	Ranibizumab	PRP or laser	Uncertainties / Strength of evidence	References
Favourable Effects						
BCVA	Visual acuity at 2 years	letters	Average increase 2.7	Average decrease 0.7	Only 2 years of follow-up	Protocol S
BCVA	Visual acuity at 5 years	letters	Average increase 3.1	Average increase 3.0	5 years of follow-up, but 34 % of subjects lost to follow-up	Gross et al. 2018
DRSS	Diabetic Retinopathy Severity Scale	step	⩾2-step improvement in 41.8 %	⩾2-step improvement in 14.6 %	1.6 vs. 11.6 % had ⩾2-step worsening	Protocol S
			⩾3-step improvement in 28.6 %	⩾3-step improvement in 3.0 %	0.5 vs. 4.0 % had ⩾3-step worsening	Protocol S
Unfavourable Effects						
Ocular risks	Vitreous floaters	N (%)	39 (20.4) 54 (28.3)	37 (18.2) 56 (27.6)	> 50 % of subjects in the PRP group received also ranibizumab	Protocol S Y-1 Protocol S Y-2
		N (%)	6 (2.9)	0		Pooled studies
	Eye pain	N (%)	22 (11.5) 27 (14.1)	24 (11.8) 30 (14.8)		Protocol S Y-1 Protocol S Y-2
		N (%)	6 (2.9)	8 (6.1)		Pooled studies
	Vitreous hemorrhage	N (%)	39 (20.4)	54 (26.6)		Protocol S Y-2
		N (%)	7 (3.4)	6 (4.5)		Pooled studies
	Conjunctival hemorrhage	N (%)	19 (9.9) 21 (11.0)	4 (2.0) 7 (3.4)		Protocol S Y-1 Protocol S Y-2
		N (%)	16 (7.8)	7 (5.3)		Pooled studies
	Endophthalmitis	N (%)	1 (<1 %)	0		Gross 2018
	Inflammation	N (%)	3 (2)	10 (5)		Gross 2018
	Retinal tear	N (%)	1 (<1 %)	0		Gross 2018
	Elevation of IOP	mmHg	30 (16)	36 (18)		Gross 2018

Abbreviations: BCVA = Best Corrected Visual Acuity; DRSS = Diabetic Retinopathy Severity Scale

5.7. Benefit–risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

The current variation aims for an indication to use ranibizumab for the treatment of moderately severe/severe PDR. From a pharmacological point of view, the hypothesis of a beneficial effect may be considered plausible. The submitted clinical study and analysis of pooled data from studies in patients with DME, point to non-inferior efficacy compared with PRP/laser with respect to VA and a higher efficacy as evaluated by change in DRSS. The majority of analysed endpoints showed better clinical results for ranibizumab at 1 or 2 years, although the proportion of eyes with neovascular glaucoma,

neovascularisation of the iris, or vitreous hemorrhage was comparable between the ranibizumab and PRP groups. At 5 years the treatments proved to be comparable regarding visual acuity, absence of PDR and neovascularisation.

The safety profile of ranibizumab in patients with diabetes is well-established and no new safety concerns were identified.

5.7.2. Balance of benefits and risks

The data support a positive benefit-risk balance of Lucentis in patients with PDR.

5.8. Conclusions

The overall benefit–risk balance of Lucentis remains positive and extension of indication to PDR in adults is supported.

6. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of proliferative diabetic retinopathy (PDR) in adults for Lucentis; as a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated with the safety information. The Package Leaflet is updated in accordance. RMP version 19.0 is also being submitted.