HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

21 November 2012

LUCENTIS 10 mg/ml, injectable solution

Vial of 0.23 ml (CIP code: 34009 378 101 5 9)

APPLICANT: NOVARTIS PHARMA S.A.S.

INN	ranibizumab
Code ATC (2011)	S01LA04 (ocular anti-neovascularisation agent)
Reason for the review	**Renewal of inclusion** **Re-assessment of IAB at the company's request in accordance with article R.163-12 of the Social Security Code (CSS) in the indication: "Treatment of visual impairment due to diabetic macular oedema (DME)"**
List(s) concerned	**National Health Insurance** (CSS L.162-17) **Hospital Use** (CSP L.5123-2)
Indication(s) concerned	– **"Treatment of the neovascular (wet) form of age-related macular degeneration (AMD)"** – **"Treatment of visual impairment due to diabetic macular oedema (DME)"** – **"Treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)"**

AB	**AMD:** **The actual benefit of LUCENTIS 10 mg/ml is still substantial in the treatment of exsudative age-related macular degeneration (AMD) with subfoveal choroidal neovascularisation.** **DME:** ▪ **The actual benefit of LUCENTIS 10 mg/ml is still substantial in patients with visual impairment of 5/10 or less as a result of diabetic macular oedema in diffuse forms of the disease or with leaks close to the centre of the macula in whom diabetic care has been optimised.** ▪ **It remains insufficient in the other situations.** **Branch RVO and central RVO:** **The actual benefit of LUCENTIS 10 mg/ml remains substantial in the treatment of visual impairment due to macular oedema secondary to branch RVO or central RVO.**
IAB	**AMD:** **In light of the data submitted, the Committee deems that the substantial improvement in actual benefit (IAB II) for LUCENTIS 10 mg/ml is maintained for the management of patients suffering from exsudative AMD with subfoveal choroidal neovascularisation.** **DME:** **In light of the data submitted, the Committee deems that the minor improvement in actual benefit (IAB IV) for LUCENTIS 10 mg/ml is maintained in the treatment strategy for visual impairment due to diabetic macular oedema in diffuse forms of the disease or with leaks close to the centre of the macula in patients whose visual acuity is 5/10 or less and in whom diabetic care has been optimised.** **Branch RVO and central RVO:** **In view of the absence of new data, the Committee deems that the minor improvement in actual benefit (IAB IV) for LUCENTIS 10 mg/ml compared with OZURDEX is maintained in the treatment of visual impairment due to macular oedema secondary to branch or central retinal vein occlusion.**
Therapeutic use	**LUCENTIS is a first-line treatment in:** - **exsudative AMD with subfoveal choroidal neovascularisation;** - **the reduction in visual acuity due to diabetic macular oedema (DME) in diffuse forms of the disease or with leaks close to the centre of the macula in patients with visual acuity of 5/10 or less in whom diabetic care had been optimised;** - **a reduction in visual acuity due to macular oedema secondary to branch RVO or central RVO.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	European decision of 22 January 2007 Amendment to MA: - 19 December 2007 (change of packaging) - 6 January 2011 (extension of indication to diabetic macular oedema) - 27 May 2011 (extension to macular oedema due to branch retinal vein or central retinal vein occlusion)
Prescription and dispensing conditions/special status	List I Prescription restricted to ophthalmology specialists

ATC Classification	(2011)	
	S	Sensory organs
	S01	Ophthalmologicals
	S01L	Medicines for ocular vascular problems
	S01LA	ocular anti-neovascularisation agents
	S01LA04	ranibizumab

02 BACKGROUND

The company is applying for a renewal of inclusion of LUCENTIS on the list of proprietary medicinal products refundable by the National Health Insurance [proprietary medicinal product included for a period of 5 years from 30/06/2007 by decree of 19/06/2007 (Official Gazette of 30/06/2007)].
The company is also applying for the IAB of LUCENTIS in the indication for visual impairment due to DME to be regraded from minor (IAB IV in patients with visual acuity of 5/10 or less due to diabetic macular oedema in diffuse forms of the disease or leaks close to the centre of the macula whose diabetic care has been optimised: Committee opinion of 20 June 2011) to moderate (IAB III).

When it was first included, the Transparency Committee considered that LUCENTIS offered a major improvement in actual benefit (IAB II) for the management of exsudative AMD, only in subfoveal forms of the disease.

On 18 January 2012 the Transparency Committee examined the application for LUCENTIS to be included on the Social Security and Hospital use list for the extension of indications to "treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion or central retinal vein occlusion (RVO)". The Committee considered that the AB of LUCENTIS was substantial in this indication and that this proprietary medicinal product offered a minor improvement in actual benefit (IAB IV) compared with OZURDEX. No new data have been submitted since this opinion.

03 THERAPEUTIC INDICATIONS

"LUCENTIS is indicated in adults for:
– the treatment of neovascular (wet) age-related macular degeneration (AMD)
– the treatment of visual impairment due to diabetic macular oedema (DME)
– the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)"

04 DOSAGE

“Single-use vial for intravitreal use only.

LUCENTIS must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Treatment of wet AMD

In wet AMD the recommended dose for LUCENTIS is 0.5 mg given monthly as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml.
Treatment is given monthly and continued until maximum visual acuity is achieved, i.e. the patient's visual acuity is stable for three consecutive monthly evaluations performed while on ranibizumab treatment.
Thereafter patients should be monitored monthly for visual acuity.
Treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly evaluations (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month.

Treatment of visual impairment due to either DME or macular oedema secondary to RVO

The recommended dose for LUCENTIS is 0.5 mg given as a single intravitreal injection in visual impairment due to DME or macular oedema secondary to RVO. This corresponds to an injection volume of 0.05 ml.

Treatment is given monthly and continued until maximum visual acuity is achieved, i.e. the patient's visual acuity is stable for three consecutive monthly evaluations performed while on ranibizumab treatment. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended.

Thereafter patients should be monitored monthly for visual acuity.

Treatment is resumed when monitoring indicates loss of visual acuity due to DME or to macular oedema secondary to RVO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly evaluations (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month.

LUCENTIS and laser photocoagulation in DME and in macular oedema secondary to branch RVO

There is some experience of LUCENTIS administered concomitantly with laser photocoagulation (see section 5.1 of the SPC). When given on the same day, LUCENTIS should be administered at least 30 minutes after laser photocoagulation. LUCENTIS can be administered in patients who have received previous laser photocoagulation.

Special populations

Hepatic impairment: LUCENTIS has not been studied in patients with hepatic impairment. However, no special considerations are needed in this population.

Renal impairment: Dose adjustment is not needed in patients with renal impairment (see section 5.2 of the SPC).

Paediatric population: LUCENTIS must not be given to children or adolescents because of a lack of data on the safety and efficacy in these sub-populations.

Elderly: No dose adjustment is required in the elderly. There is limited experience in patients older than 75 years with DME.

Ethnicity: Experience with treatment is limited in groups other than Caucasians.”

05 CLINICALLY RELEVANT COMPARATORS

05.1 Medicines

See table 1.

05.2 Other health technologies

The other non-medical treatments in DME are laser photocoagulation and vitrectomy.

Grid laser photocoagulation can be used to treat branch RVO.

Conclusion

None of the comparators have all of the indications of LUCENTIS. LUCENTIS is the only medicine with Marketing Authorisation for the treatment of visual impairment secondary to DME.

Table 1: Comparator medicines

INN	Identical pharmaco-therapeutic class	Name (Company)	Indication	Date of opinion	AB	IAB	Reim-bursement
pegaptamib	yes	MACUGEN (Pfizer)	Treatment of neovascular (wet) age-related macular degeneration (AMD)	29/11/2006	Sub-stantial	(IAB V) compared with VISUDYNE in the indications common to both proprietary medicinal products. (IAB III) for the management of patients suffering from exsudative subfoveal AMD in whom VISUDYNE is not indicated, particularly in scarcely visible choroidal neovascularisation.	Yes Yes
aflibercept	yes	EYLEA (Bayer Santé)	Treatment of neovascular (wet) age-related macular degeneration (AMD)	Currently being evaluated by the Transparency Committee	-	-	-
verteporfin	No L01XD02	VISUDYNE (Novartis S.A.S.)	- Treatment of adult patients suffering from exsudative (wet) age-related macular degeneration (AMD) with predominantly classic subfoveal choroidal neovascularisation (CNV) - Treatment of adult patients with subfoveal choroidal neovascularisation secondary to pathological myopia:	03/10/2012 (re-registration)	Sub-stantial Sub-stantial	No change in IAB: The improvement in actual benefit is major (level I). (Opinion of 11/10/200) No change in IAB: The improvement in actual benefit is major (level I) (Opinion of 20/11/2002)	yes yes
dexamethasone	No S01BA01	OZURDEX (Allergan)	- Treatment of patients with macular oedema due to retinal vein occlusion (branch RVO or central RVO) - Treatment of adults with inflammation of the posterior segment of the eye due to non-infectious uveitis.	17/11/2010 03/10/2012	Sub-stantial Sub-stantial	IAB IV for treatment of macular oedema following RVO (branch RVO or central RVO). IAB III for treatment of adult patients suffering from inflammation of the posterior segment of the eye due to non-infectious uveitis.	Yes Currently being examined

06 REMINDER OF PREVIOUS EVALUATIONS

Date of opinion	28 March 2007 (registration)
Indication	"Treatment of neovascular (wet) age-related macular degeneration (AMD)"
AB	Age-related macular degeneration (AMD) is the leading cause of blindness in France in patients over 50 years old. The severe forms of AMD which are responsible for the largest number of cases of severe reduction in visual acuity include the exsudative or neovascular forms. This proprietary medicinal product is a curative treatment for the consequences of the disease. <u>Public health benefit:</u> The public health burden of exsudative subfoveal AMD is moderate. Improvement in the management of AMD is a public health need (GTNDO priority[1]). In light of the available data and in view of the existing treatments, the proprietary medicinal product LUCENTIS is expected to have a moderate impact on morbidity from AMD (mostly in terms of maintaining visual acuity). However, it is not clear whether trial results can be extrapolated to clinical practice because of: - doubts about maintaining long-term efficacy, - lack of knowledge about the optimal number of intravitreal injections and questions about retreatment criteria, - doubts about mastering and strictly observing the injection procedure, both of which are essential in order to reduce serious local adverse events, Despite all of this, the proprietary medicinal product LUCENTIS should provide an additional response to the identified public health need. As a result LUCENTIS is expected to have a public health benefit. This benefit is moderate. The efficacy and safety of LUCENTIS have been studied in studies which have only included patients with AMD and subfoveal choroidal neovascularisation (CNV). The efficacy/adverse effects ratio for this proprietary medicinal product in these patients is considered to be high. Ranibizumab is a first-line therapy. There are treatment alternatives (MACUGEN, VISUDYNE). The actual benefit of LUCENTIS is **substantial in subfoveal exsudative AMD.** In the absence of efficacy and safety data on LUCENTIS in extra-foveal exsudative AMD, the Committee cannot make a statement about the actual benefit of LUCENTIS in this type of disease.
IAB	LUCENTIS 10 mg/ml, injectable solution offers a substantial improvement in actual benefit (**level II**) in the management of patients suffering from **AMD with subfoveal choroidal neovascularisation.**

[1] Groupe Technique National de Définition des Objectifs (National Objective Setting Technical Group) (DGS-2003)

Studies requested	The Transparency Committee would like data on the follow-up of patients suffering from AMD treated with LUCENTIS in France. The purpose of this is to document in the actual treatment situation: - the conditions for starting treatment (characteristics of patients treated, previous treatments, concomitant treatments, etc.). - the conditions of use for the proprietary medicinal product, particularly the dosage regimen (dosage and frequency of injections) and the methods used to monitor visual acuity, - the impact of the treatment on the medium and long-term change in visual acuity and on quality of life and avoidance of disability in these patients. - the impact of safety on continuing the treatment, - the predictive factors for response to treatment. If planned or ongoing studies, particularly as part of the European Risk Management Plan, cannot answer all of the questions raised by the Transparency Committee, a specific study should be carried out. The length of the study, determined by the independent scientific committee, will need to be justified and sufficient to meet the Committee's request.

Date of opinion	22 June 2011 (extension of indication)
Indication	"Treatment of visual impairment due to diabetic macular oedema in adults".
AB	Diabetic macular oedema is a complication of diabetic retinopathy. It is asymptomatic but progresses gradually towards poor vision and blindness which is a disability and causes a marked deterioration in quality of life. This proprietary medicinal product is a curative treatment for the reduction in visual acuity due to diabetic macular oedema. <u>Public health benefit:</u> Diabetic retinopathy is a major cause of poor vision and the leading cause of blindness in people under 60 years old in the general population in all industrialised countries.[2,3] Diabetic macular oedema (DME) is the leading cause of visual impairment in diabetic patients. Approximately 5% of diabetic patients are estimated to develop macular oedema.[4] There are limited epidemiological data available on the prevalence of DME in France. The burden of macular oedema is due to the visual impairment and to the incapacities and deterioration in quality of life which it causes. It can also have significant psychosocial or even occupational consequences, which are particularly important in young patients. The public health burden of DME is considered to be moderate. Reducing the frequency and severity of the complications of diabetes, improving the screening and treatment of systemic diseases causing ophthalmological complications and improving quality of life in people suffering from chronic diseases are established public health priorities (objectives 55 and 66 of the 9 August 2004 Public Health Policy Law, Improvement Plan for quality of life of people suffering from chronic disease 2007-2011).

[2] Porta M, Bandello F. Diabetic retinopathy. A clinical update. Diabetologia 2002; 45 (12): 1617-34.
[3] Frank RN. Diabetic retinopathy. N Engl J Med 2004; 350 (1): 48-58.
[4] Delcourt C, Massin P, Rosilio M. Epidemiology of diabetic retinopathy: expected *vs* reported prevalence of cases in the French Population. Diabetes Metab 2009; 35 (6): 431-8.

	In light of the available data, the proprietary medicinal product LUCENTIS is expected to have a minor impact compared with laser photocoagulation on the morbidity of DME (mostly in terms of improving visual acuity) and on the quality of life of patients who are treated. This impact however is considered to be moderate in the sub-population of patients who cannot be treated with laser. However, it is not clear whether the trial results can be extrapolated to clinical practice because of: - doubts about maintaining the long-term efficacy in a population suffering from a chronic disease such as diabetes; - lack of knowledge about the optimum number of intravitreal injections, the need for frequent reinjections and questions about the retreatment criteria; - inadequate data in poorly controlled diabetic patients. It would also be expected to have an impact on organisation of care because of the very regular follow-up visits required for patients in view of their mobility. Despite all of this, the proprietary medicinal product LUCENTIS should provide an additional response to the identified public health need. As a result, LUCENTIS is expected to have a public health benefit in this indication. This benefit is **low**. The efficacy/adverse effects ratio is high. Additional data are required to confirm the long-term efficacy of ranibizumab monotherapy. Laser photocoagulation is the reference treatment for visual impairment due to diabetic macular oedema. In the absence of long-term data and because of the demanding treatment regimen requiring monthly injections until visual acuity has stabilised in three consecutive monthly evaluations on treatment, LUCENTIS should be restricted to patients who cannot be treated with laser, i.e., those with diffuse macular oedema or leaks close to the centre of the macula. Ranibizumab treatment can be started when visual acuity is 5/10 or less and when diabetic management has been optimised. An alternative treatment exists: laser photocoagulation for focal disease. The actual benefit of LUCENTIS 10 mg/ml solution for injection is **substantial** in patients with visual impairment of 5/10 or less due to diabetic macular oedema in the diffused form of the disease or with leaks close to the centre of the macula in whom diabetic management has been optimised. It is **insufficient** in the other situations.
IAB	As there are no data on the continued long-term efficacy of LUCENTIS 10 mg/ml solution for injection monotherapy on visual acuity, the proprietary medicinal product is considered to offer a minor improvement in actual benefit, **(IAB IV**) in the treatment strategy for visual impairment due to diabetic macular oedema in the diffuse form of the disease or with leaks close to the centre of the macula in patients with visual acuity of 5/10 or less and in whom diabetic management has been optimised.
Studies requested	In view of: - the lack of knowledge about the optimum number of intravitreal injections and the need for frequent reinjections combined with very regular patient follow-up visits. - insufficient long-term efficacy data on sustaining the improvement in visual acuity (in a population suffering from a chronic disease such as diabetes) and on quality of life and avoidance of disability; - insufficient data in poorly controlled diabetic patients (HB1Ac, blood pressure). - the uncertainty about the position of the treatment compared with laser, the Transparency Committee requests that the company provide additional data to allow an evaluation to be carried out of the **the position of LUCENTIS** compared with alternative available treatments (laser, corticosteroids, others) in the treatment of macular oedema in France **and on the impact of LUCENTIS** on the (medium- and long-term) change in visual acuity, and on the quality of life and avoidance of disability in patients who are treated. Predictive indicators for response to treatment will need to be analysed. Data will need to be presented on: - the conditions for starting treatment (characteristics of the patients who are treated, particularly type and length of history of the diabetes) and on follow-up (monitoring HB1Ac and blood pressure, previous treatments, concomitant treatments); - the conditions of use for the proprietary medicinal product, particularly injection

	frequencies and methods used to monitor visual acuity; - treatment compliance and reasons for continuing and stopping treatment (safety, lack of efficacy, others); If the planned or ongoing studies, particularly as part of the European Risk Management Plan, cannot answer all of the questions raised by the Transparency Committee, a specific study should be carried out. The length of the study, determined by the independent scientific committee, will need to be justified and sufficient to answer the Committee's question.

Date of opinion	18 January 2012 (extension of indication)
Indication	"Treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) in adults"
AB	Retinal vein occlusion is an eye disease affecting the retina, and at its centre, the macula, which is responsible for fine vision. It causes a delay in the circulation, together with infiltration and oedema of the macula which is responsible for a fall in visual acuity. The visual prognosis depends on the clinical form of the retinal vein occlusion: two main forms are distinguished, an ischaemic form which has a poor visual prognosis and a well perfused form (so-called oedematous) which has a better prognosis. This proprietary medicinal product is in the category of symptomatic treatments. <u>Public health benefit:</u> The public health burden of retinal vein occlusion is low. A reduction in visual impairment is a public health need (GTNDO priority). In light of the available data, LUCENTIS is expected to have a moderate short-term impact on the morbidity of these diseases mostly in terms of maintaining visual acuity. In the absence of available data, the impact of LUCENTIS on quality of life and organisation of care cannot be quantified. It is debatable whether the study results can be extrapolated to clinical practice particularly because of uncertainty about the management methods (particularly the recommended angiography before treatment), the number of optimal injections and the criteria for retreatment. The proprietary medicinal product LUCENTIS may however provide a partial response to the identified public health need. As a result, LUCENTIS is expected to have a public health benefit in this indication. This benefit is low. The efficacy/adverse effects ratio is high. This medicinal product is a first-line therapy. There is a treatment alternative (OZURDEX). The actual benefit of LUCENTIS 10 mg/ml, injectable solution is **substantial.**
IAB	LUCENTIS offers a minor improvement in actual benefit (**IAB IV**) compared with OZURDEX in the treatment of visual impairment due to macular oedema secondary to branch or central retinal vein occlusion.
Studies requested	The Transparency Committee would like to have additional medium- and long-term data […] in order to re-evaluate LUCENTIS with respect to the following main points: – the characteristics of patients treated for retinal vein occlusion with or without LUCENTIS; – the methods for managing these patients (investigations performed in the evaluation and during follow-up, different treatments used, number of possible retreatments and retreatment time); – the adverse effects of patients treated with LUCENTIS with the incidence of treatment drop-outs and the reasons for these; – the change in the patient's visual acuity and quality of life.

	The length of patient follow-up will need to be justified and sufficient to meet the Transparency Committee's request. These data will need to be available when LUCENTIS is re-evaluated. If planned or ongoing studies, particularly as part of the European Risk Management Plan, cannot answer all of the questions raised by the Transparency Committee, a specific study should be carried out.

07 ANALYSIS OF AVAILABLE DATA

07.1 Efficacy

7.1.1 Age-related macular degeneration

- **Reminder of previously evaluated data (Transparency Committee opinion of 28 March 2007)**

The efficacy and safety of ranibizumab have been studied in three double-blind, randomised, phase III studies against sham intravitreal injections or photodynamic therapy with verteporfin (non-inferiority study).

In these three studies, ranibizumab was administered at a dose of 0.3 mg or 0.5 mg (the dose in the Marketing Authorisation is 0.5 mg). Two studies were conducted using a dosage regimen of one monthly intravitreal injection for 24 months (ANCHOR studies, the 12-month results of which are available, and MARINA study). The third study (PIER) was conducted by a monthly injection regimen for 3 months and then every 3 months for 21 months (total study duration: 24 months; results available at 12 months) in patients suffering from AMD with CNV, with or without visible CNV.
In the MARINA study (n = 716), ranibizumab was compared with sham injections in patients suffering from AMD with pure occult subfoveal CNV or occult CNV with a minimally classic CNV.
In the ANCHOR study (n = 423) ranibizumab was compared with PDT with verteporfin (every 3 months if required for 21 months) in patients suffering from AMD with predominantly classic subfoveal CNV.
In the PIER study (n = 184), ranibizumab was compared with sham injections. All types of CNV were represented amongst the patients included (pure occult, predominantly classic and with a minimally classic CNV).
The two dosage regimens used in these studies were on either side of the dosage regimen in the Marketing Authorisation: three injections initially 1 month apart followed by a maintenance phase with possible retreatment for visual loss equivalent to 5 letters on the ETDRS scale).

The effect size for ranibizumab (0.3 mg or 0.5 mg) from these studies which included patients suffering from AMD with occult subfoveal CNV or minimally classic CNV (MARINA study) or majority visual component (ANCHOR study) or all three types of lesions (PIER study) was high compared with patients receiving sham injections or those treated with verteporfin PDT. 90 to 96% of patients lost less than 15 visual acuity letters (ETDRS) in the ranibizumab groups and the differences compared with sham injections of verteporfin were in the region of 30 to 40%.
Ranibizumab therefore not only greatly delayed the fall in visual acuity but also improved visual acuity in a large proportion of patients (35 to 40% compared with 5.6% with verteporfin in the ANCHOR study and 4.6% with sham injections in the MARINA study). Unfortunately, however, there was no placebo arm in the non-inferiority study against verteporfin and the internal validity of the study cannot therefore be guaranteed. It should be noted that this large proportion of patients gaining at least 15 letters on the ETDRS scale was not found in the PIER study in which ranibizumab was injected every 3 months after the induction phase (11.7% and 13.1% on ranibizumab 0.3 mg and 0.5 mg, with no significant difference against sham injections).

◗ New data

The data included in this evaluation are:

- 2 year results of the initial studies (monthly administration regimen):
  - PIER study:[5,6] ranibizumab 0.3 and 0.5 mg compared with sham injections.
  - ANCHOR study:[7,8] ranibizumab 0.3 and 0.5 mg compared with verteporfin PDT.
- studies which compared the monthly regimen to other administration regimens:
  - EXCITE non-inferiority study,[9] which compared the monthly regimen to the three-monthly regimen (24 months)
  - SAILOR study[10] (12 months) which compared two doses of ranibizumab, 0.3 and 0.5 mg, using a PRN regimen after three consecutive monthly injections
- studies against another anti-VEGF: bevacizumab
  - CATT non-inferiority study,[11] which compared bevacizumab to ranibizumab 0.5 mg by a monthly regimen or PRN following an initial injection (24 months)
  - IVAN non-inferiority study,[12] which compared bevacizumab to ranibizumab 0.5 mg, by a monthly or PRN regimen after three consecutive monthly injections (24 months, results at 12 months)
- a study which evaluated ranibizumab in combination with verteporfin photodynamic therapy (PDT)
  - DENALI study:[13] ranibizumab 0.5 mg + verteporfin compared with ranibizumab 0.5 mg
- long-term follow-up studies: in these extension phases, the efficacy evaluation was a secondary endpoint and all patients were treated with ranibizumab 0.5 mg according to a PRN regimen.
  - HORIZON study:[14] 24 month extension study of the MARINA and ANCHOR pivotal studies and the FOCUS study
  - SECURE study:[15] extension study of the EXCITE and SUSTAIN studies requested by the EMA.

The following studies were not included:

- HARBOR:[16] a non-inferiority study which compared the monthly regimen to the PRN regimen[17] after three consecutive monthly injections (24 months) only published as an abstract.
- SUSTAIN: a 12 month non-comparative study with the primary objective of evaluating safety. This safety study is described in the safety chapter.
- EXTEND-II and EXTEND-III: non-comparative studies which evaluate the efficacy of 0.5 mg of ranibizumab by monthly injections in specific populations over 12 months (Chinese patients in

[5] Regillo CD, Brown DM, Abraham P et al. Randomized, double-masked, sham-controlled trial of Ranibizumab for neovascular age-related macular degeneration: PIER study year 1. Am J Ophthalmol 2008; 145: 239-48.
[6] Abraham P, Yue H and Wilson L. Randomized, double-masked, sham-controlled trial of Ranibizumab for neovascular age-related macular degeneration: PIER study year 2. Am J Ophthalmol 2010; 150: 315-24.
[7] Brown DM, Kaiser PK, Michels M et al. Ranibizumab compared with Verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006; 355: 1432-44.
[8] Brown DM, Michels M, Kaiser PK et al. Ranibizumab compared with Verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. Ophthalmology 2009; 116: 57-65.
[9] Schmidt-Erfurth U, Eldem B, Guyme R et al. Efficacy and safety of monthly compared with quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 2011; 118: 831-39.
[10] Boyer DS, Heier JS, Brown DM et al. A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. Ophthalmology 2009; 116: 1731-39.
[11] The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011; 364: 1897-1908.
[12] Chakravarthy U, Harding SP, Rogers CA et al. Ranibizumab compared with bevacizumab to treat neovascular Age-related macular Degeneration: one year findings from the IVAN randomized trial. Ophthalmology 2012; 119 (7): 1399-411
[13] Unpublished Novartis data (clinical study report)
[14] Singer M, Wong P, Wang P-W and Scott L. HORIZON extension trial of ranibizumab (LUCENTIS®) for neovascular age-related macular degeneration (AMD): two-year safety and efficacy results. Invest Ophthalmol Vis Sci 2009; 50: E-abstract 3093.
[15] Unpublished Novartis data
[16] Busbee BG, Yee W, Li Z et al. Efficacy and safety of 2 mg or 0.5 mg ranibizumab in patients with subfoveal neovascular AMD: HARBOR study. AAO 2011, PA031.
[17] *Pro Re Nata*: "As required" administration regimen

EXTEND-II and South-Korean patients and Taiwan patients in EXTEND-III), the results of which are difficult to extrapolate to the French population.

❑ Two year results of the initial PIER and ANCHOR studies (monthly regimen)

	PIER: 2 year results (Abraham, 2010)
Primary objective of the study	To compare ranibizumab 0.3 and 0.5 mg by monthly intravitreal injections for 3 months then every 3 months for 21 months to sham injections in patients with subfoveal CNV secondary to AMD, with or without visible CNV.
Method	Double-blind, placebo-controlled, randomised, phase III study (sham injection), lasting 24 months
Inclusion criteria	▪ age ≥ 50 years old, ▪ primary active or recurrent subfoveal CNV in the eye studied secondary to age-related macular degeneration (AMD) with or without visible CNV, ▪ total surface area of CNV (including visible and occult components) contained within the lesion ≥ 50% of the total surface area of the lesion. ▪ total surface area of the lesion ≤ 12 papillary diameters, ▪ best corrected visual acuity in the studied eye of between 20/40 and 20/320 (Snellen equivalent) by the ETDRS scale.
Treatment groups	▪ Ranibizumab 0.3 mg (n = 60) ▪ Ranibizumab 0.5 mg (n = 61) ▪ sham injections (n = 63) Note: the 0.3 mg dose does not comply with the MA.
The study process	Length of the study: 24 months. Intravitreal injections of ranibizumab or sham injections, monthly for 3 months then every three months for 21 months. **Amendments to the protocol:** After the 12 month data of the MARINA and ANCHOR pivotal studies were reviewed, the patients in the sham injections group were treated with three-monthly injections of ranibizumab 0.5 mg. An additional amendment then enabled all patients to be given monthly ranibizumab 0.5 mg. The blinding was continued.
Primary endpoint	At 12 months: mean change in BCVA measurements on the ETDRS scale at an initial distance of 4 metres from baseline value.
The secondary endpoints included	At 12 months: percentage of patients who gained ≥ 15 letters compared with baseline value. At 24 months: - mean change in BCVA compared with baseline value - percentage of patients who lost < 15 letters - percentage of patients who gained ≥ 15 letters, compared with baseline value.

Results:

A total of 184 patients were included. 73% of patients completed the study in the placebo group and 88.3% and 88.5% in the ranibizumab 0.3 and 0.5 mg groups respectively.
Before treatment, approximately 40% of study patients had pure occult CNV, 40% had CNV with a minimally classic component and 20% had predominantly classic CNV.

- Review of 12 month results:

The number of visual acuity letters lost at 12 months was significantly lower with 0.5 mg ranibizumab (-0.2 letters) than with the sham injections (-16.3 letters). The curve of change in mean difference in visual acuity from baseline in patients treated with ranibizumab showed that following an initial increase in visual acuity (after 3 months with monthly administration), after 12 months visual acuity returned to its baseline value. 90% of patients, however, had maintained their visual acuity at 12 months.

A significantly higher percentage of patients lost < 15 letters with ranibizumab 0.5 mg (90.2%) than with the sham injections (49.2%).

There was no significant difference in the percentage of patients with a gain of ≥ 15 letters (13.1% with ranibizumab 0.5 mg, compared with 9.5% with the sham injections).

- 24 month results:

After 12 months, the patients in the three groups were switched progressively to a monthly treatment regime with ranibizumab 0.5 mg.

Mean BCVA fell by 21.4 letters in the group with (initial) sham injections at 24 months whereas this remained stable in the group treated (initially) with ranibizumab 0.5 mg (-2.3 letters, p < 0.0001 compared with sham injections).

82% of patients lost < 15 letters with ranibizumab 0.5 mg and 41.3% with sham injections (then ranibizumab 0.5 mg) (p < 0.0002).

There was no difference in the percentage of patients who gained ≥ 15 letters: 8.2% with ranibizumab compared with 4.8% with sham injections.

	ANCHOR study: 2 year results (Brown, 2009)
Primary objective of the study	To demonstrate non-inferiority of ranibizumab 0.3 or 0.5 mg by monthly IVT compared with verteporfin PTD (every 3 months if required for 21 months) in patients with AMD and predominantly classic subfoveal CNV who had not previously been treated with PTD or an anti-angiogenic.
Method	Double-blind, double-placebo, randomised, phase III study lasting 24 months.
Inclusion criteria	▪ age ≥ 50 years old, ▪ eligible for photodynamic therapy (PDT) in the eye studied according to product recommendations, ▪ patients awaiting verteporfin (PDT) ▪ subfoveal CNV secondary to AMD ▪ visible CNV (increased fluorescence limits clearly delineated in the early phase of angiography) ≥ 50% of the total surface area of the lesion. ▪ lesion ≤ 5400 µm along its greatest linear dimension, ▪ better corrected visual acuity (BCVA) between 20/40 and 20/320 (Snellen equivalent).
Treatment groups	▪ ranibizumab 0.3 mg + sham PDT injection (n = 140) ▪ ranibizumab 0.5 mg + sham PDT injection (n = 140): Marketing Authorisation dose. Monthly injections of ranibizumab (maximum: 24 injections over 24 months) Note: the 0.3 mg dose does not comply with the MA. ▪ verteporfin PDT every 3 months, if necessary, for 21 months + monthly sham intravitreal injection (n = 143)
The study process	The patients were treated for 12 months following the methods described above. **Amendment to the protocol**: after the 12 month results were analysed,

	an amendment to the protocol allowed patients in the verteporfin group who had not yet received their 23rd sham intravitreal injection to be given monthly injections of ranibizumab 0.3 mg (the blinding was continued). From the 18th month, 50 patients in the verteporfin group (35%) switched progressively to monthly IVT of ranibizumab 0.3 mg.
Primary endpoint	The percentage of patients who had lost < 15 letters of BCVA compared with their baseline value at 12 months. Visual acuity was measured on the ETDRS scale at an initial distance of 2 metres.
The secondary endpoints included	At 12 months: percentage of patients who gained ≥ 15 letters compared with baseline value. A 24 months: - percentage of patients who lost < 15 letters - percentage of patients who gained ≥ 15 letters, compared with baseline value.
Statistical analysis	At 24 months, the secondary endpoints were analysed by an ITT analysis in patients who were randomised based on their initial treatment group.

Results:

A total of 423 patients were included in this study. 76.9% of patients completed the study in the PDT group and 82.9% in the ranibizumab 0.5 mg group.

96 to 99% of the patients at inclusion had predominantly classic lesions, with a BCVA of between 45 and 47 letters (ETDRS).

- Review of 12 month results:

During this period the patients in the ranibizumab 0.5 mg group were given an average of 12 IVT and those in the PDT group had an average of 2.8 treatments.

The initial objective of this study was to demonstrate non-inferiority of ranibizumab 0.5 mg against verteporfin photodynamic therapy on the change in visual acuity. The results show ranibizumab 0.5 mg to be superior to verteporfin:

- percentage of patients who lost <15 letters BCVA: 96.4% compared with 64.3% (p<0.0001, primary endpoint);
- percentage of patients who gained ≥15 letters BCVA: 40.3% compared with 5.6% (p<0.0001).

Note*:* The difference found between ranibizumab and verteporfin in terms of the percentage of patients who lost less than 15 letters was similar to what was found between ranibizumab and sham injections (approximately 30%). It would have been desirable to have had a fourth placebo arm to confirm the efficacy of verteporfin in this study.

- 24 month results:

During this period, patients in the ranibizumab 0.5 mg group were given an average of 21.3 IVT and those in the PDT group had an average of 3.8 treatments.

Ranibizumab 0.5 mg superiority over PDT was maintained at 24 months:

- percentage of patients who lost <15 letters BCVA: 90.0% compared with 65.7% (p<0.0001);
- percentage of patients who gained ≥15 letters BCVA: 41.0% compared with 6.3% (p<0.0001).
- BCVA improved by an average of 10.7 letters in the ranibizumab 0.5 mg group and deteriorated by an average of 9.8 letters in the group treated initially with verteporfin.

❑ Studies which compared the monthly regimen to other administration regimens

	EXCITE study (Schmidt-Erfurth, 2011)
Primary objective of the study	To demonstrate non-inferiority of the three-monthly ranibizumab retreatment regimen at a dose of 0.3 or 0.5 mg to the monthly retreatment regimen at a dose of 0.3 mg for the maintenance phase.
Method	Double-blind, randomised, phase III study lasting 24 months
Inclusion criteria	Exsudative AMD with any type of CNV.
Treatment groups	▪ ranibizumab 0.3 mg as 3 IVT each month followed by three-monthly IVT (n = 120) ▪ ranibizumab 0.5 mg as 3 IVT each month followed by three-monthly iVT (n = 118) ▪ ranibizumab 0.3 mg as monthly IVT (n = 115) **Note:** the 0.3 mg dose does not comply with the MA.
The study process	The patients were treated for 12 months. The study was intended initially to last for 24 months. This was reduced to 12 months after the amendment to the SPC approving the PRN regimen.
Primary endpoint	Mean change in BCVA measured on the ETDRS scale at 12 months compared with baseline value.
The secondary endpoints included	▪ percentage of patients who lost < 15 letters ▪ percentage of patients who gained ≥ 15 letters
Statistical analysis	The non-inferiority threshold was set at 6.8 ETDRS letters

Results:

A total of 353 patients were included.

The percentages of patients who completed the study were:
- 88.3% in the ranibizumab 0.3 mg group with three-monthly injections,
- 80.5% in the ranibizumab 0.5 mg group with three-monthly injections,
- 89.6% in the ranibizumab 0.3 mg group with monthly injections.

Approximately 80% of patients had occult neovascular lesions or minimally classic lesions. Mean visual acuity pretreatment was 56 to 58 letters.

At 12 months, the average change in BCVA was 4.9 and 3.8 letters in the ranibizumab 0.3 and 0.5 mg group given as three-monthly injections and 8.3 letters in the ranibizumab 0.3 mg group given as monthly injections.
Treatment with three-monthly injections was not demonstrated to be non-inferior to monthly injections of ranibizumab 0.3 mg.

SAILOR study, cohort 1 (Boyer, 2009)
A single-blind, randomised study lasting 12 months which compared ranibizumab at doses of 0.3 mg (n = 1169) and 0.5 mg (n = 1209) administered by a PRN regimen in a first cohort (n=2378): three consecutive monthly injections followed by a 9 month follow-up phase during which the patients were treated based on the following criteria:
- loss of visual acuity > 5 ETDRS letters compared with the highest value from the previous visits
- OR loss of visual acuity > 5 ETDRS letters compared with the highest value in the previous visits and/or increased central retinal thickness > 100 µm compared with the lowest value in previous visits combined with the presence of intra- or subretinal fluid.

In a second cohort, patients (n = 1992) were given a first injection of ranibizumab 0.5 mg on Day 0 and then continued their treatment by a PRN regimen.

The patients who were included had to have exsudative AMD with visible or invisible subfoveal CNV displaying recent signs of disease progression and a BCVA of between 73 and 20 ETDRS letters (approximately 20/40 and 20/400 Snellen equivalent). The eye treated in the study may or may not have been previously treated.
Randomisation was stratified by whether or not the study eye had been treated previously.

The efficacy evaluation was a secondary objective of the study and was evaluated at 3 and 12 months, based in particular on the following criteria:
- mean change in BCVA compared with baseline
- percentage of patients who gained ≥ 15 letters

Results:
As the efficacy endpoints were secondary endpoints and ranibizumab was not compared with a placebo, the results shown below are provided for information purposes. The results from cohort 2 will not be presented, as a large proportion of patients stopped treatment (50% of the total group).
81.7% of patients completed the study in cohort 1. The retreatment criterion was visual acuity and/or optical coherence tomography (OCT) in 81% of patients in both groups.
Approximately 60% of patients in both groups had been treated previously.

The mean change in BCVA after treatment for 12 months compared with baseline was +2.3 letters (ETDRS) in patients who had not been previously treated and in those who had already been treated at inclusion in the study (see table 1).

Table 1: Results for change in visual acuity (SAILOR study)

Endpoints:	**Ranibizumab 0.5 mg Previously untreated patients (n = 490)**	**Ranibizumab 0.5 mg Patients already treated (n = 719)**
Mean BCVA at inclusion (ETDRS)	48.9	50.0
Change from baseline - at 3 months - at 12 months	 +7.0 +2.3	 +5.8 +2.3
% of patients with gain of ≥ 15 letters (ETDRS): - at 3 months - at 12 months	 20.1 19.3	 18.6 16.5

❑ Studies against another VEGF, bevacizumab

Note: bevacizuamb (AVASTIN) does not have Marketing Authorisation in AMD and is marketed as a galenic form which is unsuitable for intravitreal injections.

	CATT study: against bevacizumab (The CATT Research Group, 2011)
Primary objective of the study	American academic non-inferiority study which compared four types of treatment: monthly bevacizumab injections or according to a PRN regimen and ranibizumab as monthly injections or according to a PRN regimen.
Method	Single-blind, randomised, comparative study lasting 24 months.
Inclusion criteria	▪ Patients aged 50 years old or older ▪ primary active AMD with occult or visible subfoveal CNV, never previously treated. ▪ visual acuity between 20/25 and 20/320
Treatment groups	▪ ranibizumab 0.5 mg by monthly injections (n = 301) ▪ bevacizumab 1.25 mg according to monthly injections (n = 286) ▪ ranibizumab 0.5 mg according to a PRN regimen after a 1st injection (n = 298) ▪ bevacizumab 1.25 mg according to a PRN regimen after a 1st injection (n = 300)

The study process	24 month study. After 12 months, patients treated according to a PRN regimen continued their treatment. The patients treated monthly were further randomised into two groups: to continue monthly treatment or to switch to the PRN regimen. The retreatment criteria for the PRN regimen were as follows: ▪ presence of fluid on OCT ▪ decline in visual acuity since the previous examination. ▪ diffusion of dye or increase in size of lesion on fluorescein angiography.
Primary endpoint	Mean change in visual acuity at 12 months.
The secondary endpoints included	▪ percentage of patients who lost < 15 letters ▪ percentage of patients who gained ≥ 15 letters ▪ mean number of intravitreal injections.
Statistical analysis	Non-inferiority study which compared the four treatment groups, two by two using the Bonferroni method with calculations of the 99.2% confidence intervals. The non-inferiority threshold was set at 5 ETDRS letters. **Note:** the analyses were performed on the ITT and not on the per protocol population.

Results:

A total of 1185 patients were included. Data from 23 patients from the same centre were excluded from the analysis on the recommendations of the monitoring committee.
Of the 1161 patients still alive after the first 12 months, the visual acuity scores were available in 95.2%, i.e. in 1105 patients:
- 284 patients in the monthly ranibizumab group
- 265 patients in the monthly bevacizumab group
- 285 patients in the ranibizumab PRN group
- 271 patients in the bevacizumab PRN group.

Mean pretreatment visual acuity was 60 to 61.5 letters.

Primary endpoint:
After 12 months, the mean change in BCVA was:
- +8.5 letters in the monthly ranibizumab group
- +8.0 letters in the monthly bevacizumab group
- +6.8 letters in the ranibizumab PRN group
- +5.9 letters in the bevacizumab PRN group

Bevacizumab was shown to be non-inferior to ranibizumab when given by an equivalent regimen (monthly or according to a PRN regimen).

Ranibizumab was shown to be non-inferior to monthly ranibizumab when given according to a PRN regimen.

Bevacizumab was not shown to be non-inferior to monthly bevacizumab when given according to a PRN regimen.

Secondary endpoints:

At 12 months:
- There was no difference between the groups in the percentage of patients who had lost < 15 letters (91.5 to 95.4%).
- There was no difference between the groups in the percentage of patients who gained ≥ 15 letters (24.9 to 34.2%)
- There were 11.7 and 11.9 intravitreal injections in the ranibizumab and bevacizumab monthly treatment groups and 6.9 and 7.7 in the ranibizumab and bevacizumab PRN treatment groups ($p = 0.003$).

Mean change in BCVA after 24 months:

Because of the further randomisation and increase in the number of treatment groups, these results are only provided for information purposes.

Table 2: results for mean change in visual acuity at 12 and 24 months (CATT study)

Patients re-randomised at 12 months				
24 month results	**Ranibizumab monthly** (n = 134)	**Ranibizumab monthly then PRN** (n = 265)	**Bevacizumab monthly** (n = 285)	**Bevacizumab monthly then PRN** (n = 271)
Mean change in BCVA compared with the 12 month value	-0.3	-1.8	-0.6	-3.6
Patients who stayed on the same treatment for 24 months				
24 month results	**Ranibizumab monthly** (n = 134)	**Bevacizumab monthly** (n = 129)	**Ranibizumab PRN** (n = 264)	**Bevacizumab PRN** (n = 251)
Mean change in BCVA compared with baseline	+8.8	+7.8	+6.7	+5.0

	IVAN study: compared with bevacizumab (Chakravarthy, 2012)
Primary objective of the study	British academic non-inferiority study which compared four types of treatment: bevacizumab by monthly injections or by PRN regimen and ranibizumab by monthly injections or by a PRN regimen.
Method	Single-blind, randomised, comparative study lasting 24 months
Inclusion criteria	▪ Patients 50 years old or older ▪ AMD with newly diagnosed subfoveal CNV confirmed by fluorescein angiography and OCT ▪ visual acuity ≥ 25 ETDRS letters
Treatment groups	▪ ranibizumab 0.5 mg by monthly injections (n = 157) ▪ bevacizumab 1.25 mg by monthly injections (n = 149) ▪ ranibizumab 0.5 mg according to a PRN regimen after 3 consecutive injections (n = 155) ▪ bevacizumab 1.25 mg according to a PRN regimen after 3 consecutive injections (n = 145)
The study process	Patients in all groups were given 3 consecutive monthly injections before randomisation. In the PRN regimen, apart from the 3 initial consecutive injections, the patients repeated a cycle of 3 months of treatment if they: ▪ developed fluid in the retinal lesion or if existing fluid increased. ▪ developed recent blood in the retinal lesion. ▪ or in uncertain cases, if they lost more than 10 letters of visual acuity. ▪ or if the neovascular lesion visible on flurorescein angiography had spread or for a leak of more than 1/4 of the circumference of the lesion. After the 3 months of repeat monthly treatments the patients continued to be treated until they had no further fluid in their retina, which is a sign of active neovascularisation, on OCT examination.
Primary endpoint	Mean change in BCVA measured on the ETDRS scale after treatment for 2 years.
The secondary endpoints included	Mean change in the BCVA measured on the ETDRS scale after treatment for 1 year.
Statistical analysis	The non-inferiority threshold was set at 3.5 ETDRS letters. The interim analysis at 1 year was conducted by grouping the monthly injections and PRN regimen together for each of the active substances.

Results:

A total of 606 patients were randomised. All of the patients were included in the analysis of results. Only the 1-year interim results are available. As a consequence these results are provided for information purposes and no conclusion can be drawn from the comparison between ranibizumab and bevacizumab.
At 1 year, bevacizumab (monthly injections + PRN) was not shown to be non-inferior to ranibizumab (monthly injections + PRN). The difference between the groups was -1.99 letters, 95%CI = [-4.04; 0.06].

❑ Ranibizumab in combination with verteporfin photodynamic therapy (VISUDYNE)

DENALI study: verteporfin + ranibizumab compared with ranibizumab
This was a double-blind, randomised, phase IIIb study which compared for 24 months (reduced subsequently to 12 months following the results of the phase II MONT-BLANC study which demonstrated the non-inferiority combination of verteporfin + ranibizumab compared with ranibizumab alone) in 321 patients suffering from AMD with visible or occult subfoveal CNV. The primary objective of the study was to demonstrate non-inferiority of at least one of the treatment combinations of ranibizumab + verteporfin PTD compared with ranibizumab monotherapy in terms of mean change in BCVA at 12 months compared with baseline. The non-inferiority threshold was set at 7 letters (ETDRS).
The patients were divided into three groups:
- ranibizumab 0.5 mg + PTD with standard fluency verteporfin therapy (50 J/cm^2) (n = 104)
- ranibizumab 0.5 mg + PTD with reduced fluency verteporfin therapy (25 J/cm^2) (n = 105)
- ranibizumab 0.5 mg monotherapy (n = 112)

In the combination groups the patients were treated with verteporfin on D0 and with three monthly intravitreal injections of ranibizumab 0.5 mg. From month 3, the decision to re-treat with verteporfin or ranibizumab was taken by the investigator at the monthly review visits as a function of predetermined criteria based on the OCT, ophthalmoscopic examination, measurement of visual acuity and fluorescein angiography.
The patients in the ranibizumab group were given monthly intravitreal injections throughout the study and had sham PTD.

Results:
Two hundred and eighty-six of the 321 patients randomised (89.1%) completed this study. The results were analysed in the ITT population.
Mean pretreatment corrected visual acuity was 54 letters (ETDRS). Depending on the group 53 to 58% of patients had occult lesions or minimally classic lesions.

Visual acuity improved by 8.1 letters at 12 months with ranibizumab, by 5.3 letters with the PTD standard fluency combination and by 4.4 letters with the PTD reduced fluency combination. Non-inferiority was not demonstrated.

❑ Long-term follow-up studies

HORIZON study (NOVARTIS data)
This was a phase II extension phase of the MARINA and ANCHOR pivotal studies and the FOCUS study (a phase II/II study which evaluated the combination of ranibizumab + verteporfin compared with verteporfin alone), the primary objective being long-term open-label safety follow-up. The efficacy evaluation defined by the mean change in BCVA measured at 4 metres on the ETDRS scale was a secondary endpoint.
Patients who had completed one of the previous studies were included in the extension phase. Patients may or may not have been previously treated with ranibizumab. During the extension phase they were to be treated for a minimum of 24 months with ranibizumab 0.5 mg by a PRN regimen left to the decision of the investigator, although subject to instructions for interrupting and stopping treatment. In the initial studies, the patients treated with ranibizumab had been given monthly injections. The study was kept blind for the initial treatment throughout the follow-up phase.

A total of 853 patients were included. The analyses were performed on patients with available data and based on three patient groups:
- patients treated with ranibizumab from the initial studies.
- patients not initially treated then switched to ranibizumab
- patients who had never been treated with ranibizumab.

Only the data for 614 patients at 1 year and 499 patients at 2 years are available because the study was stopped early after LUCENTIS obtained Marketing Authorisation.
BCVA was 51.6 letters at inclusion in the initial study and 60.5 letters at inclusion in the HORIZON study in patients who had been treated with ranibizumab during the initial studies and in the HORIZON follow-up phase.

In patients treated with ranibizumab from the initial studies:
The mean change in BCVA (ETDRS scale measured at 4 metres) compared with the value at inclusion in the HORIZON study (53.9 letters) was:
- -5.4 letters after follow-up for 1 year (i.e. a total of 3 years of ranibizumab treatment; n = 446)
- -7.5 letters after follow-up for 2 years (i.e. a total of 4 years of ranibizumab treatment; n = 352).

SECURE study (NOVARTIS data)
This study was conducted at the request of the EMA and was a 24 month open-label extension phase of the EXCITE and SUSTAIN studies, the primary objective of which was to evaluate safety of use and long-term safety. Efficacy was evaluated from the mean change in BCVA measured on the ETDRS scale at a distance of 4 metres.
In the initial studies, all of the patients had been treated with ranibizumab, at a dose of 0.3 or 0.5 mg with either, monthly, three-monthly or PRN administration regimens.
In the extension phase, the patients were given ranibizumab at a dose of 0.5 mg by a PRN regimen for 24 months as defined in the SPC. Patients were re-treated if their visual acuity fell by more than 5 letters.

Results:
A total of 234 patients were included. The analyses were performed on patients who had had at least one visual acuity measurement after the initial measurement at inclusion in the follow-up study.

Best mean visual acuity was 55.6 letters at inclusion in the initial study in all patients and 60.7 letters at inclusion in the SECURE study, i.e. an improvement of +5 letters.
After 24 months in the extension phase, the mean change in BCVA compared with baseline in the initial study was +0.4 letters.
However, 41.9% of patients did not have an injection in at least 7 visits although the retreatment criteria had been met.

7.1.2 Diabetic macular oedema

◗ Reminder of previously evaluated data (Transparency Committee opinion of 22 June 2011)

Placebo-controlled study:
The efficacy of ranibizumab 0.5 mg by monthly intravitreal injections (n = 51) was demonstrated against placebo (sham intravitreal injections, n = 49) in a double-blind, randomised, phase II study in patients with visual impairment due to local or diffuse diabetic macular oedema involving the centre of the macula (RESOLVE study), from the mean change in best corrected visual acuity (BCVA) during treatment for 12 months: +6.4 (± 9.2) ETDRS letters with ranibizumab compared with -0.1 (± 9.8) letters with the sham injections (p = 0.0004).

Ranibizumab in combination with laser:
Ranibizumab 0.5 mg monotherapy was compared with the combination of ranibizumab 0.5 mg + laser and to laser alone in a double-blind, randomised, phase III study in 345 patients with focal or

diffuse macular oedema whose BCVA was between 39 and 78 letters (RESTORE study). Ranibizumab was administered by monthly intravitreal injections for 3 months and then for 9 additional months until visual acuity had stabilised (no improvement in BCVA during the last two visits or BCVA ≥ 84 ETDRS letters). After stabilisation, the patients could be re-treated with ranibizumab if required. Laser photocoagulation was given on Day 1 as one or two sessions, 4 weeks apart. The patients could be re-treated with laser at an interval of 3 months if deemed necessary by the investigator.

The mean change in BCVA from 1 to 12 months was 6.1 letters in the ranibizumab group, 5.9 letters in the ranibizumab + laser group and 0.8 letters in the laser only group. The differences between the ranibizumab groups with or without laser and the laser only group were statistically significant ($p < 0.0001$).

Ranibizumab 0.5 mg in combination with either concomitant or deferred laser was compared with laser monotherapy in an independent, double-blind, randomised study (DRCnet) except for the group treated with deferred laser, which included 854 eyes suffering from diabetic macular oedema involving the centre of the macula. The study was initially intended to last for 3 years and was extended to 5 years. Only the 2-year results are available at present. The intravitreal injections were given monthly for 3 months and then monthly for 12 months until stabilisation or from the 6th month depending on the improvement obtained according to the decision of the investigator. Laser photocoagulation was given 3 to 10 days after the first intravitreal injection (concomitant laser) or at least 6 months afterwards (deferred laser). The concomitant laser could be repeated after four months and the deferred laser after 6 months. Patients had to have a BCVA of between 24 and 78 letters at inclusion.

The mean change in BCVA after 1 year compared with baseline (primary endpoint) was statistically greater ($p < 0.001$) in the groups in which ranibizumab was combined with laser than in the laser group (+ sham intravitreal injection), with differences of +5.8 letters (concomitant laser) and +6.0 letters (deferred laser), representing a 1/10 gain.

The percentages of patients with a gain in visual acuity of ≥ 15 letters at 1 year in the ranibizumab + concomitant laser (30%) and ranibizumab + deferred laser groups (28%) was greater than in the laser + sham IVT group (15%; $p < 0.001$ for each comparison).

These values were maintained at 2 years:
- difference compared with the laser + sham IVT group in terms of mean change in BCVA compared with baseline of +5.0 letters (ranibizumab + concomitant laser) and +7.2 letters (ranibizumab + deferred laser)
- The percentage of patients with a gain in BCVA of ≥ 15 letters was 26% in the ranibizumab + concomitant laser group, 29% in the ranibizumab + deferred laser group and 17% in the laser + sham IVT group.

◗ New data

The new data included in this evaluation are:

- 2 year results for the RESTORE study (NOVARTIS data)
- further 2 year results from the DCRnet study.
- REVEAL study which compared ranibizumab in combination with laser (concomitant or deferred) to laser alone.

The ongoing RISE and RIDE studies comparing ranibizumab to sham injections, for which only the 2-year results published as an abstract are available, will not be presented.

❑ Ranibizumab in combination with laser

	RESTORE study: in combination with laser, results of the 2-year extension phase. (Unpublished Novartis data)
Primary objective of the study	To evaluate the long-term safety of ranibizumab in patients who completed the RESTORE study. Efficacy was a secondary objective.
Method	Open-label 2-year study
Inclusion criteria	Patients who completed the RESTORE study, the inclusion criteria for which were as follows: ▪ ≥ 18 years old ▪ type I or II diabetes with HbA1C ≤ 10% ▪ visual impairment due to local or diffuse DME in the eye eligible for laser. ▪ best corrected visual acuity (BCVA) between 39 and 78 ETDRS letters at a distance of 4 metres (i.e. 20/32 to 20/160 Snellen equivalent)
Treatment groups	In the initial study: ▪ ranibizumab 0.5 mg + sham laser ▪ ranibizumab 0.5 mg + laser ▪ laser + sham IVT In the extension study, the patients who were initially included in the laser monotherapy group were also treated with ranibizumab 0.5 mg.
The study process	2-year extension phase, during which the patients continued their initial treatment with the following retreatment methods: ▪ <u>IVT at the initial visit for the extension study if:</u> - the decline in BCVA was due to DME. - the BCVA was unstable or stable but < 84 letters in the last 2 months of the main study. ▪ <u>Treatment discontinued if</u>: - no additional improvement in BCVA on treatment during the last 2 visits. - or BCVA ≥ 84 letters in the last two visits. ▪ <u>Monthly IVT re-started if</u>: decline in BCVA due to the progression of the oedema. Laser if required after at least 3 months consistent with the ETRS recommendations.
Secondary endpoint	Mean change in BCVA measured on the ETDRS scale at 1 year and 2 years compared with baseline in the initial study.

<u>Results:</u>

A total of 240 patients were included in the extension phase: 83 in the ranibizumab + sham laser group, 83 in the ranibizumab + laser group and 74 in the laser + sham IVT group.

The numbers of intravitreal injections given during the 2 years of the studies (initial study + 1st year of the extension) were 11.3 in the ranibizumab 0.5 mg group and 11.0 in the ranibizumab 0.5 mg + laser group (see table 3).

Table 3: Exposure to treatments (RESTORE study)

Mean (SD)	Ranibizumab 0.5 mg n = 83	Ranibizumab 0.5 mg + laser n = 83	Laser + ran 0.5 mg in extn. n = 54	Laser alone in extn. n = 20
Ranibizumab treatment (number of IVT)				
1st extension year	3.9 (3.4)	3.5 (3.4)	5.6 (3.1)	0.0 (0.0)
Over 2 years*	11.3 (5.6)	11.0 (5.6)	-	-
Laser treatment				
1st extension year	0.2 (0.6)	0.1 (0.4)	0.1 (0.3)	0.1 (0.2)

* main study + 1st year of the extension

Review of the 1-year results in the main study:

The mean change in BCVA at 12 months compared with baseline was 6.8 letters for ranibizumab, 6.4 letters for the ranibizumab + laser combination and 0.9 letters for laser alone, i.e. differences compared with laser alone of:

- +6.2 letters (95%CI = [3.6; 8.7]; p < 0.0001) in favour of ranibizumab
- +5.4 letters (95%CI = [2.4; 8.4]); p = 0.0004) in favour of the ranibizumab + laser combination.

The results of the 1st year of the extension phase:

The improvement in mean BCVA at 1 year in the extension phase compared with baseline in the initial study was maintained (i.e. with 2 years of treatment): +7.9 letters with ranibizumab +6.7 letters with the combination of ranibizumab + laser.

	DCRnet Study: in combination with laser, 2-year results (Elman, 2011)
Primary objective of the study	To demonstrate the superiority of ranibizumab 0.5 mg combined with laser compared with laser alone in terms of visual acuity in patients with impaired vision as a result of diabetic macular oedema. This result also included a laser + triamcinolone IVT arm, the results of which will not be described below as use of triamcinolone in this indication is off-label.
Method	Double or single-blind, randomised study lasting 2 years.
Inclusion criteria	▪ ≥ 18 years old ▪ type I or II diabetes ▪ BCVA between 24 and 78 ETDRS letters at a distance of 3 metres (i.e. 20/32 and 20/320 Snellen equivalent). ▪ retinal thickening due to DME involving the centre of the macula and recognised to be the main cause of visual impairment. ▪ Retinal thickness measured by OCT ≥ 250 µm. ▪ both eyes in the same patient could be included in this study. If the right eye was randomised: - into a group other than laser alone, the left eye was assigned to the laser only treatment group. - in the laser only group, if the left eye was randomised into one of the other three groups
Treatment groups	▪ **ranibizumab 0.5 mg IVT + concomitant laser:** Monthly IVT, with a maximum of 13 injections in the 1st year as laser sessions in the 3 to 10 days after IVT. ▪ **ranibizumab 0.5 mg IVT + deferred laser:** Monthly IVT with a maximum of 13 injections in the 1st year and laser sessions more than 6 months after the IVT (these patients were not masked for their treatment). ▪ **triamcinolone 4 mg + concomitant laser** ▪ **laser:** 1 sham monthly IVT + concomitant laser

The study process	intravitreal ranibizumab or sham injections:
	▪ for 12 weeks: 1 monthly IVT.
	▪ weeks 16 to 20: 1 monthly IVT until criteria for success had been achieved = BCVA ≥ 84 letters or CRT ≤ 250 µm and continuation of IVT at the decision of the investigator.
	▪ weeks 24 to 48:
	- success: continue IVT according to the decision of the investigator
	- improvement (improvement in BCVA of ≥ 5 letters or improvement in CRT ≥ 10% since the last injection for ranibizumab or the 1st injection for the sham IVT: further IVT
	- no improvement: IVT given according to the decision of the investigator
	- failure (decline in BCVA of ≥ 10 letters compared with baseline, CRT ≥ 250 µm and complete laser more than 13 weeks previously: IVT according to the decision of the investigator, or alternative treatment.
	▪ after week 52: unblinded
	- stop the sham IVT
	- follow-up every 4 months in the laser + sham IVT group
	- in both groups treated with ranibizumab:
	  - monitor failed eyes every 4 months
	  - for eyes which had not failed: criteria for weeks 24 to 48 applied + the following two factors:
	  1. treatment according to the decision of the investigator including treatments other than the one assigned by randomisation for eyes which failed or met the minimum efficacy criteria, i.e. BCVA ≥ baseline, CRT ≥ 250 µm, DME deemed to be responsible for the impaired VA and laser more than 29 weeks previously)
	  2. successful eyes or no improvement in the two previous visits: doubling of follow-up interval.
	Laser photocoagulation:
	Initial treatment in the 3 to 10 days after IVT (concomitant) or more than 24 weeks after IVT (deferred)
	After week 16:
	- Concomitant laser: within 3 to 10 days after IVT unless:
	  - laser in the previous 13 weeks
	  - previous full laser.
	  - CRT < 250 µm and no oedema around the macula (500 µm around the centre of the macula and no oedema of surface area greater than one papillary disc in an area extending 1 papillary disc from the centre of the macula)
	- Deferred laser: if no improvement in week 24 and following the two previous IVT, laser was repeated until the macular oedema had disappeared or until the full laser had been performed on the decision of the investigator.

Primary endpoint	Mean change in BCVA after 1 year compared with baseline.
Secondary endpoints	Improvement and worsening in BCVA ≥ 15 letters. Change in BCVA at 2 years.

Results:

The 2-year results shown below relate to the 486 eyes in the ranibizumab + laser and laser + sham IVT groups which completed the study. When the results were examined initially by the Transparency Committee, they were based on a population of 381 (patients treated with triamcinolone + laser were excluded).

- Review of 1-year results:

The mean change in BCVA at 1 year compared with baseline was statistically greater ($p < 0.001$) in the groups in which ranibizumab was combined with laser than in the laser group (+ sham intravitreal injection) with differences of +5.8 letters (concomitant laser) and +6.0 letters (deferred laser).

A higher percentage of patients achieved a gain in visual acuity of ≥ 15 letters in the ranibizumab + concomitant laser group (30%) and in the ranibizumab + deferred laser group (28%) than in the laser + sham IVT group (15%; $p < 0.001$ for each comparison).

- 2-year results:

The 2-year results were similar to the 1-year results.

After 2 years, in patients who completed this study (i.e. 486 eyes excluding patients in the triamcinolone + laser group), the mean change in BCVA compared with baseline was statistically greater ($p < 0.001$) in the ranibizumab combined with laser group than in the laser + sham IVT group: +7 letters (ranibizumab + concomitant laser), +9 letters (ranibizumab + deferred laser) compared with +3 letters (laser + sham IVT).

A higher percentage of patients had a gain in visual acuity of ≥ 15 letters in the ranibizumab + concomitant laser group (29%) and in the ranibizumab + deferred laser group (28%) than in the laser + sham IVT group (18%).

Similarly, the percentage of eyes which lost < 15 letters remained stable after 2 years (quantitative data not provided).

	REVEAL study: in combination with laser (Unpublished Novartis data)
Primary objective of the study	To demonstrate superiority of ranibizumab 0.5 mg alone or in combination with laser compared with laser alone in a population of Asian patients with impaired visual acuity due to DME.
Method	Double-blind, randomised, comparative study, lasting 12 months.
Inclusion criteria	▪ age: 18 years or older ▪ type I or II diabetes with HbA1c ≤ 10% ▪ visual impairment due to local or diffuse DME ▪ BCVA between 20/32 and 20/160, Snellen equivalent (i.e. between approximately 78 and 39 ETDRS letters) ▪ eye eligible for laser
Treatment groups	▪ ranibizumab 0.5 mg + sham laser (n = 133) ▪ ranibizumab 0.5 mg + laser (n = 132) ▪ laser + sham IVT (n = 131)
The study process	Ranibizumab treatment: 3 consecutive monthly injections followed by a PRN regimen. The injections were continued until visual acuity was stable or > 84 in 3 successive monthly evaluations. Treatment could then subsequently be restarted if visual acuity fell due to the progression of the DME. The same administration regimen was used for the sham IVT. Laser: treatment on D0, with possible retreatment if necessary at intervals of at least 3 months according to ETDRS recommendations Same regimen for the sham laser.
Primary endpoint	Mean change in BCVA from month 1 to month 12 compared with baseline.

Results:

A total of 396 patients were included. 92.5% of patients completed the study in the ranibizumab + sham laser group, 86.4% in the ranibizumab + laser group and 82.4% in the laser + sham IVT group.

There were an average of 7.8 monthly intravitreal or sham injections during the 12 months of the study in the ranibizumab + sham laser group, 7.0 in the ranibizumab + laser group and 7.4 in the laser + sham IVT group.

There were 1.5 laser sessions in the ranibizumab + sham laser group, 1.5 in the ranibizumab + laser group and 1.9 in the laser + sham IVT group.

The mean changes in BCVA from month 1 to month 12 compared with baseline were:
- +5.9 letters in the ranibizumab + sham laser group ($p < 0.0001$ compared with laser + sham IVT)
- +5.7 letters in the ranibizumab + laser group ($p < 0.0001$ compared with laser + sham IVT)
- +1.4 letters in the laser + sham IVT group

The mean changes in BCVA compared with baseline at 12 months were:
- +6.6 letters in the ranibizumab + sham laser group ($p < 0.0001$ compared with laser + sham IVT)
- +6.4 letters in the ranibizumab + laser group ($p < 0.0001$ compared with laser + sham IVT)
- +1.8 letters in the laser + sham IVT group

7.1.3 Retinal vein occlusion

The company has not submitted new data for this indication since the Transparency Committee opinion of 26 May 2011.

07.2 Safety/adverse effects

7.2.1 Safety data in AMD

SAILOR Safety Study (Boyer, 2009): 1-year follow-up
This 12-month, single-blind, randomised study had the primary objective of ranibizumab safety in a large population of patients suffering from exsudative AMD.

Two cohorts were created for this study:
Cohort 1: patients included were randomised into two groups, ranibizumab, 0.3 and 0.5 mg, administered by a PRN regimen (3 initial consecutive monthly injections followed by a follow-up and retreatment phase if necessary depending on pre-determined criteria).
A total of 2378 patients were included, with 1169 in the ranibizumab 0.3 mg group and 1209 in the 0.5 mg group.
Cohort 2: all of the patients included were treated with an injection of 0.5 mg ranibizumab followed by a PRN regimen with an interval of at least 30 days between two injections.

Approximately 18% of patients in each group dropped out of the study in cohort 1. The main reasons for dropping out of the study were:
- death: 1.7% and 2.3% in the 0.3 and 0.5 mg groups respectively.
- an adverse event: 2.6 and 2.2%
- patient decision: 6.7 and 5.8%
- the decision of the doctor: 3.4 and 2.8%
- alternative treatment started: 2.7 and 3.1%

The patients received an average of 4.6 injections during the 12 months of the study.

Approximately 50% of patients dropped out of the study in cohort 2. The main reasons for dropping out of the study were the patient's decision (29%), alternative treatment being started (5.3%), the doctor's decision (9.4%), death (1.5%) or an adverse event (1.8%).
All of the patients received the initial injection, followed by an average of 3.6 injections during the 12 months of the study.

Serious ocular adverse events occurred in less than 1% of the patients in each of the groups in the two cohorts (see table).

The main non-ocular adverse events related to treatment in cohort 1 were hypertension (9% with 0.3 mg and 10% with 0.5 mg), arterial thromboembolic events (3.8% with 0.3 mg and 4.1% with 0.5 mg) and non-ocular haemorrhage (2.9% with 0.3 mg and 3.1% with 0.5 mg).

These figures were lower in cohort 2: 3% for hypertension, 2.4% for arterial thromboembolic events and 1.4% for non-ocular haemorrhage. It should be noted, however, that half of the patients in this cohort stopped the study.

There were few serious ocular adverse events in the two cohorts (< 1%) (see table 4).

Table 4: Serious ocular adverse events (SAILOR study)

Adverse events,%	Cohort: 1		Cohort 2
	0.3 mg (n = 1169)	0.5 mg (n = 1209)	0.5 mg (n = 1922)
Presumed endophthalmitis*	0.2	0.4	0.1
Uveitis	0.1	0.2	0
Retinal detachment	0.1	0	0.1
Retinal tear	0	0.1	0
Retinal haemorrhage	0.9	0.9	0.3
Detachment of retinal pigment epithelium	0	0.2	0.1
Vitreous haemorrhage	0.3	0.1	0.2
Cataract	0.1	0.1	0.1

*: including 2 cases of uveitis and 1 case of iridocyclitis

The death rates were:
Cohort 1:
- 1.7% (n = 20) in the 0.3 mg group including 1.0% (n = 8) due to a vascular cause
- 2.4% (n = 29) in the 0.5 mg group including 0.9% (n = 11) due to a vascular cause.

Cohort 2: 1.7% (n = 33) including 0.8% (n = 16) for a vascular cause.

SUSTAIN safety study (Holz, 2011): 1-year follow-up

This 12-month non-comparative study had the primary objective of evaluating the safety of ranibizumab at a dose of 0.3 then 0.5 mg (after obtaining Marketing Authorisation) administered according to a PRN regimen after three initial consecutive monthly injections. The safety results shown below are based on the previously untreated study population of 513 patients (18 patients from the ANCHOR study were included in the SUSTAIN study).

88.7% of patients dropped out of the study, mostly because of an adverse event (5.8%) or withdrawal of patient consent (1.9%).

The main ocular adverse events reported were retinal haemorrhage (7.2%), increased intraocular pressure and conjunctival haemorrhage (5.5%).
The non-ocular adverse events were arterial thromboembolic events (3.7%), rhinopharyngitis (3.1%), hypertension (2.9%), back pain (2.7%), headache (2.5%) and influenza (2.5%).
The 19 arterial thromboembolic events included 5 cases of myocardial infarction, 4 cases of angina pectoris, 3 cases of transient ischaemic attack, 2 cases of cerebral infarction, 2 cases of pulmonary embolism, 1 case of acute myocardial infarction, 1 case of cerebrovascular accident, 1 case of acute coronary syndrome, 1 case of retinal artery embolism and 1 case of silent myocardial infarction.
Of the 8 deaths reported, 1 was deemed to be potentially related to the treatment, following an acute myocardial infarction.

HORIZON safety study: 4-year total follow-up period

This study is a 24-month extension phase of the MARINA and ANCHOR pivotal studies and the FOCUS study (a phase I/II study which evaluated the combination of ranibizumab + verteporfin to verteporfin alone), the primary objective of which was open long-term safety monitoring.
Patients who had completed the previous study were included in the extension phase. Patients may or may not have been previously treated with ranibizumab. During the extension phase they were to be treated for a minimum of 24 months with ranibizumab 0.5 mg according to a PRN regimen. In the initial studies, the patients treated with ranibizumab had been given monthly injections.

A total of 853 patients were included in this study. The safety analysis was based on the 790 patients who received at least one injection of ranibizumab either in the initial study or during the extension.

The patients were classified into four groups:

- ranibizumab monotherapy: patients treated with ranibizumab alone or in combination with sham PDT (n = 526)
- ranibizumab + PDT (n = 74)
- cross-over of sham IVT then ranibizumab (n = 116)
- cross-over of sham IVT + PDT then ranibizumab (n = 74)

Only the results of the groups which were exposed for the longest period of time to ranibizumab, i.e. 4 years, are shown below.

The average numbers of IVT received in the initial and extension phases were 28 in ranibizumab monotherapy group and 27 in the ranibizumab + PDT group.

There were few ocular adverse events related to treatment. 3.8% in the ranibizumab monotherapy group and 2.7% in the ranibizumab group + PDT.
In the ranibizumab monotherapy group these were mostly increased intraocular pressure (1.5%, n = 8 including 1 serious case), myodesopsia (1.1%, n = 6) and intraocular inflammation (0.8%, n = 4).
In the ranibizumab + PDT group these were mostly increased intraocular pressure (n = 1), iridocyclitis (n = 1), conjunctival haemorrhage (n = 1) and ocular hyperaemia (n = 1).
One case of non-serious endophthalmitis was reported in the ranibizumab monotherapy group.

The non-ocular adverse events potentially related to VEGF inhibition were reported in the ranibizumab monotherapy and ranibizumab + PDT groups at the following frequencies:
- hypertension: 10.6% and 13.5%
- arterial thromboembolic events: 7.6% and 16.2% (including 9.5% serious cases)
- non-ocular haemorrhage: 6.7% and 4.1% (including 2.1% serious cases).

There were 31 deaths (5.9%) including 9 due to a vascular cause in the ranibizumab monotherapy group and 8 deaths (10.8%) including 2 due to a vascular cause in the the ranibizumab + PDT group.

CATT study (comparison with bevacizumab): 2-year follow-up
In this study, ranibizumab 0.5 mg was compared with bevacizumab 1.25 mg. Each of the substances was administered by IVT either by a monthly administration regimen or PRN from the first injection. After the first year, all of the patients were treated according to the PRN regimen. The proprietary medicinal product currently marketed containing bevacizumab, AVASTIN 25 mg/ml concentrate for solution for infusion, was repackaged in vials under aseptic conditions. In order to evaluate safety, the results were analysed by grouping together patients treated with ranibizumab (n = 599) and those treated with bevacizumab (n = 586).
After 2 years' follow-up the adverse events reported were consistent with those listed in the LUCENTIS SPC and were similar for ranibizumab and bevacizumab except for a higher incidence of gastrointestinal problems and percentage of patients who had at least one serious adverse event with bevacizumab (see table 5).

Table 5: Adverse events (CATT study)

Adverse events (AE), n (%)	Ranibizumab (n = 599)	Bevacizumab (n = 586)
Serious systemic		
Deaths, all causes combined	32 (5.3)	36 (6.1)
Thromboembolic AE	28 (4.7)	29 (5.0)
Non-fatal CVA	8 (1.3)	8 (1.4)
Non-fatal myocardial infarction	9 (1.5)	7 (1.2)
Vascular death	12 (2.0)	14 (2.4)
Venous thromboembolic AE	3 (0.5)	10 (1.7)
Hypertension	3 (0.5)	4 (0.7)
≥ 1 serious AE	190 (31.7)	234 (39.9)
AE previously associated with anti-VEG:		
Yes	45 (7.5)	62 (10.6)
No	170 (28.4)	202 (34.5)
By organ system class (MedDRA)		
Cardiac disorders	47 (7.8)	62 (10.6)
Infections	41 (6.8)	54 (9.2)
Nervous system disorders:	34 (5.7)	36 (6.1)
Injection procedure - related complications	23 (3.8)	35 (6.0)
Benign and malignant tumours	27 (4.5)	22 (3.8)
Gastrointestinal disorders	11 (1.8)	28 (4.8)
Other organ class	81 (13.5)	104 (17.8)
Ocular (eye studied)		
Endophthalmitis	4 (0.7)	7 (1.2)
Pseudo-endophthalmitis	1 (0.2)	1 (0.2)

7.2.2 Safety study in DME

RESTORE study: 2-year total follow-up

The primary objective of this study was to evaluate the long-term safety of ranibizumab, whether or not in combination with laser, in patients suffering from impaired visual acuity due to DME. In the initial 1-year phase the patients were divided into three groups:

- Ranibizumab 0.5 mg + sham laser
- Ranibizumab 0.5 mg + laser
- Laser + sham IVT

In the 2-year extension study the patients initially included in the laser monotherapy group were also treated with ranibizumab 0.5 mg.
The results of the first year of the extension phase are currently available.

The ocular adverse events reported at an incidence of ≥ 5% in the groups treated with ranibizumab since the initial study (ranibizumab monotherapy and ranibizumab + laser) were:

- eye pain: 16.9% and 10.8%
- conjunctival haemorrhage: 9.6% and 10.8%
- conjunctival hyperaemia: 9.6% and 7.2%
- cataract: 6.0% and 12.0%
- foreign body sensation: 6.0% and 8.4%

The ocular adverse events monitored by the RMP were reported at the following incidences:
- traumatic cataract: 12.0 and 20.4%
- ocular inflammation : 2.4% and 1.9%
- increased intraocular pressure: 6.0% and 1.9%
- deterioration in retinal blood flow: 2.4% and 7.4%
- vitreous haemorrhage: 0.6% and 5.6%

No cases of endophthalmitis, retinal tear, retinal detachment or retinal pigment epithelium tear.

The non-ocular adverse events monitored in the RMP were reported at the following incidences:
- hypersensitivity reactions: 12.7% and 11.1%
- hypertension: 12.0% and 9.3%
- non-ocular haemorrhage: 4.8% and 5.6%
- myocardial infarction: 1.2% and 1.9%
- proteinuria: 1.2% and 0%
- other arterial thromboembolic events: 3.0% and 1.9%
- venous thromboembolic events: 1.2% and 1.9%

7.2.3 Pharmacovigilance data

The figures shown are cumulative data from initial marketing until 30 June 2012, which represents an experience of approximately 6 years since initial authorisation was obtained in the United States in June 2006.

By 30 June 2011, in terms of the “identified risks” in the RMP (endophthalmitis, intraocular inflammation, retinal pigment epithelium tear, retinal tear, retinal detachment, transient increase in intraocular pressure, traumatic cataract, intravitreal haemorrhage and hypersensitivity reaction) no change in incidence or severity was seen.

The same applied to the “potential risks” (myocardial infarction, arterial and myocardial thromboembolic events, venous thromboembolic events, hypertension, non-ocular haemorrhage, proteinuria, reduced retinal blood flow, glaucoma and prolonged increase in intraocular pressure).

For the “other risks” (macular hole, vasculitis, depression) there was no information to reveal a link with LUCENTIS.

The number of reports of proteinuria remained low.

The adverse events reported for 71 cases of bilateral treatment were similar to those for unilateral treatment.

Seven of the 20 cases of overdose reported were followed by events involving transient loss of vision or reduced visual acuity, increased intraocular pressure, macular degeneration, eye pain or ocular haemorrhage.
Eleven cases involved injections given by an inappropriate regimen (interval between two injections < 1 month).
Ocular or no events were reported in 9 cases and systemic events were reported in 2 cases: 1 case of systemic embolism occurring 6-9 months after injection in a hypertensive patient and 1 death from multi-organ failure in a patient with a bowel tumour.
There were no new identified risks in the last PSUR (No. 9), from 1st July 2011 to 30 June 2012, in which attributability to treatment with ranibizumab was established and the incidence of adverse events recorded in the RMP was unchanged.

7.2.4 Changes to the SPC (see details in the appendix)

Changes based on data available at 2 years (variation of 27 October 2008):

- Addition of adverse effects classified as common and uncommon:

Eye disorders: **vitreous disorder, subcapsular cataract, injection site haemorrhage, allergic conjunctivitis, eye discharge, photopsia, eyelid pain, hyphaema, iris synechia, corneal deposits, pain at the injection site, irritation at the injection site, abnormal intraocular sensation, retinal pigment epithelium tear.**

Skin disorders: **allergic reactions (rash, urticaria, pruritus, erythema)**

Infections and infestations: **naso-pharyngitis**

Immune system disorders: **hypersensitivity**

Psychiatric disorders: **anxiety**

- Removals:

Eye disorders: Intraocular inflammation, subretinal fibrosis, retinal exsudates, injection site reactions, maculopathy, superficial punctate keratitis (replaced by punctate keratitis), Dellen effect, vitreous disorder, nuclear cataract, closed angle glaucoma,

Skin disorders: lichenoid keratosis

Musculoskeletal disorders: back pain

Infections and infestations: bronchitis

Thoracic respiratory disorders: wheeze, increased upper respiratory tract secretion.

Vascular disorders: hypertension/increased blood pressure

Haematological and lymphatic system disorders: atrial fibrillation

The section on identification of a link between LUCENTIS and thromboembolic events as defined by the "Antiplatelet Trialists' Collaboration" based on the 1-year results was removed.

In the section on anti-VEGF class-related adverse effects, wording was added stating that a low incidence of arterial thromboembolic events was seen in the trials although no major difference was found between the treatment groups.

The "Overdose" section was updated from the pharmacovigilance data following cases seen in the trials and post-marketing, describing the related effects: increased intraocular pressure, temporary blindness, visual impairment, corneal oedema, corneal pain and eye pain.

In the "Special warnings and precautions for use" section, a paragraph was added about the risk of retinal pigment epithelium tear associated with anti-VEGFs (variation of 20 August 2010):
"The risk factors associated with development of a retinal pigment epithelium tear during treatment of neovascular AMD with an anti-VEGF agent include an extensive and/or deep detachment of the retinal pigment epithelium. Caution is required when LUCENTIS is started in patients with these risk factors for a retinal pigment epithelium tear."

In the extensions of indication to DME (variation of 6 January 2011) and retinal venous occlusions (variation of 27 May 2011), it was stated that the safety profile was similar to what is seen in AMD.

Warnings and precautions for use have been added for patients with DME and RVO.
DME:
- potential risk of increased systemic exposure with increased risk of developing hypersensitivity, which cannot be excluded;
- Populations with limited data: DME in patients with type 1 diabetes;
- No data: patients who have previously received intravitreal injections with active systemic infections, proliferative diabetic retinopathy or concomitant eye disorders such as retinal detachment or macular hole, diabetic patients with Hb1c > 12% and those with uncontrolled hypertension, patients with a past history of cerebrovascular accident or transient ischaemic attack.

RVO:
- limited data: patients with a past history of RVO and patients with ischaemic branch or central RVO.
- treatment is not recommended in patients with RVO associated with the clinical signs of ischaemia which have caused an irreversible loss in vision.

A paragraph has also been added to the "Warnings and precautions for use" about the risks of raised intraocular pressure (variation of 27 May 2011):
"Transient rises in intraocular pressure (IOP) have been reported during the 60 minutes following injection of LUCENTIS. Prolonged rises in IOP have also been reported (see section 4.8). Intraocular pressure and perfusion of the head of the optic nerve must be monitored and managed appropriately."

07.3 Usage/prescription data

7.3.1 Observational studies in AMD

The company submitted four observational studies: LUEUR (Novartis data), LUMIERE,[18] Cohen (2009)[19] and Querques (2010).[20]
The LUEUR study was conducted at the request of the Transparency Committee and the CEPS.
The Cohen (2009) and Querques (2010) studies will not be described below as these were single-centre studies.

[18] Querques G, Azrya S, Martinelli D, Berboucha E, Feldman A, Pece A, Coscas G, Soubrane G, Souied EH. Ranibizumab for exudative age-related macular degeneration: 24-month outcomes from a single-centre institutional setting. Br J Ophthalmol. 2010 Mar; 94 (3): 292-6.
[19] Cohen SY, Dubois L, Tadayoni R, Fajnkuchen F, Nghiem-Buffet S, Delahaye-Mazza C, Guiberteau B, Quentel G. Results of one-year's treatment with ranibizumab for exudative age-related macular degeneration in a clinical setting. Am J Ophthalmol. 2009 Sep; 148 (3): 409-13.
[20] Querques G, Azrya S, Martinelli D, Berboucha E, Feldman A, Pece A, Coscas G, Soubrane G, Souied EH. Ranibizumab for exudative age-related macular degeneration: 24-month outcomes from a single-centre institutional setting. Br J Ophthalmol. 2010 Mar; 94 (3): 292-6.

◗ LUEUR study

In order to respond to the study requests by the Transparency Committee (opinion of 28 March 2007) and of CEPS, the company set up a prospective, multi-centre observational study in mainland France on a cohort of patients with neovascular AMD or who were being treated with LUCENTIS regardless of indication. This study involved two sections:

- a cross-over section, which intended to describe the characteristics of patients and their management (1000 to 1100 patients planned for in the protocol, 1042 patients included from July 2008 to June 2009)
- a longitudinal section (total planned follow-up = 4 years) including patients suffering from neovascular AMD and being treated with LUCENTIS or MACUGEN, the primary objective of which was to describe the change in visual acuity at 2 years (500 patients planned, 534 patients included).

The 72 active centres included 1042 patients in the **cross-over section,** 1 of whom was included erroneously (the patient did not meet the inclusion criteria).
One thousand and nineteen (1019) of the 1041 eligible patients (97.9%) were suffering from neovascular AMD and 22 (2.1%) were being treated with LUCENTIS for other diseases (6 cases of diabetic macular oedema, 5 cases of myopathy, 6 central retinal vein occlusions, 2 angioid striae and 3 other indications).

In terms of previous management, 42.9% of the eyes suffering from neovascular AMD have been treated only with LUCENTIS, 24.4% with LUCENTIS combined with other treatments, 15.8% with other treatments excluding LUCENTIS and 19.9% had never been treated.

The decision was taken at the inclusion visit to treat with LUCENTIS in 46.3% of the eyes affected by neovascular AMD, to treat with other treatments than LUCENTIS in 4% and not to treat in 49.7% of eyes. The anti-VEGFs AVASTIN and MACUGEN were prescribed in 2.1% and 0.6% of eyes respectively.

Of the 534 patients included in the **longitudinal section**, 517 were analysed. The reasons for exclusion from the analysis were: complete lack of follow-up in 7 patients (neither a patient questionnaire nor a consultation), no treatment with LUCENTIS during the follow-up in 6 previously untreated patients at inclusion (treatment was planned but not started) and treatment at inclusion with MACUGEN in 4 patients.

The average follow-up in the study of patients analysed was 22.87 ± 4.09 months. Sixteen deaths (3.1%) were reported during the follow-up, 5 patients withdrew their consent and 1 patient was deemed “lost to follow-up” by the doctor. Four hundred and forty-three (443) of the remaining 494 patients (89.7%) had a visit at month 24. There is no information on living or deceased status of the 10.3% of patients who did not have a visit at month 24.

Only 80 of the 517 patients analysed (15.5%) had not previously been treated with LUCENTIS and 50 (9.7%) were similar to those in the pivotal studies (no previous treatment and ETDRS score between 25 and 70 letters before starting LUCENTIS in the treated eye).

Two hundred and six (206) patients (39.8%) had bilateral AMD at inclusion including 75 (36.4% of patients with bilateral disease) who were treated with LUCENTIS in both eyes.

A total of 592 eyes were included in the analysis (“eyes” analysis population), including 90 eyes which had not previously been treated with LUCENTIS and 59 eyes which were similar to those in the pivotal studies.

Patient characteristics at inclusion
62% of the cases were women. Average age at inclusion was 78 years old. 32% were smokers or former smokers. A severe surgically untreated cataract was reported in 8.7% of patients. These characteristics were similar to those in patients not previously treated with LUCENTIS and to those in the pivotal studies.

Mean visual acuity in the eyes included was 55 ± 21 ETDRS letters for all eyes. Although on average the diagnoses have been made more recently (7 months for the previously untreated eyes compared with 16 months for all eyes), the eyes which started LUCENTIS at inclusion had a lower visual acuity (46 ± 20 letters). These findings were similar to the average visual acuities at inclusion into the MARINA (54 ± 13 letters), ANCHOR (47 ± 13 letters) and PIER (54 ± 16 letters) studies. Twenty-six eyes (4.4%) had a visual acuity of < 15 letters at inclusion.

Conditions of use

The conditions for starting LUCENTIS treatment as defined in the Treatment Information Form (TIF) were well respected overall: the majority of eyes which started treatment at inclusion had subfoveal neovascularisation (78%), with a visual acuity of between 25 and 70 ETDRS letters (77%) and all had a lesion of less than 12 papillary diameters.

The recommended induction phase of three injections at least 35 days apart was not carried out in practice. Almost a third of previously untreated patients received at least three injections (31.3%) during the first year of treatment and 7.5% of patients received a single injection. The average time between the first and second induction injections were 54 days (median = 35) and the average time between the 2nd and 3rd induction injection was 100 days (median = 42).

The average number of follow-up consultations was six during the first year of follow-up and four during the second year of follow-up.

Change in visual acuity at 2 years

The percentage treatment success rates (loss of less than 15 letters in 2 years) under real life conditions was 75.8% of the eyes analysed and 76.4% of the eyes previously untreated with LUCENTIS at inclusion compared with 82% in the PIER study (a clinical study with a similar dosage regimen to the SPC). When missing data points are considered as failures (15% missing data points at 2 years), the success rate for all eyes analysed was 66%.

Visual acuity remained stable at 2 years, with a mean change of -0.62 letters (95% CI [-5.51; 4.26]) for the eyes which started LUCENTIS (15% missing data points). A quarter of the eyes previously untreated with LUCENTIS (26%) and 13.5% of the whole population achieved an improvement of more than 15 letters at 2 years.

The logistic regression model investigating for predictive indicators for treatment failure (loss ≥ 15 letters) identified a significant increase in risk of failure with age (5-year age banding centred around 75 years old, OR =1.2 [1.02; 1.41], p = 0.03). Initial visual acuity < 30 (compared with > 30) was associated with fewer failures at 2 years (OR = 0.34 [0.11; 1.04], p = 0.06) (trend, not significant). Maintenance of efficacy of treatment over time (one of the objectives of the study) was not examined; the length of LUCENTIS treatment was not tested in the model.

The patient's mean visual function fell during the 2-year follow-up period of the study (mean VFQ-25 score at inclusion: 75.6 points, average change: -4.83 ± 14.88 points over 2 years (data available for 89.6% of patients)). The EQ-5D score, which is relatively insensitive to small changes in vision, remained stable over the 2-year follow-up period (0.82 at inclusion and 0.79 at 2 years) (data available for 86.7% of patients).

Treatment safety

Six patients previously untreated with LUCENTIS (6.6%) died during the follow-up period. None of the deaths were suspected by the investigator to be due to the treatment with LUCENTIS.

Six serious adverse effects suspected to have been due to LUCENTIS treatment were reported in the study (increased ocular pressure, a herniated iris, trabeculectomy, coronary artery disease, myocardial infarction and pulmonary embolism) in four patients (0.7%). These SAEs resulted in two patient deaths (myocardial infarction and pulmonary embolism).

◗ LUMIERE study[21]

This was a multi-centre, retrospective, observational study examining change in visual acuity in patients suffering from neovascular AMD treated with LUCENTIS under real life conditions in mainland France.

Sixteen centres included 551 analysable patients who had begun treatment and were then treated with LUCENTIS for at least 12 months for neovascular AMD.

This study showed that the average gain in visual acuity after treatment with LUCENTIS for 12 months was 3.2 ± 14.8 letters.

However, fewer than 40% of the patients underwent an induction phase (first three injections every 30 +/- 7 days) and no patients had strict monthly follow-up over the 12 months (i.e. visits carried out every 30 days +/- 7 days). Only 4.4% of patients had “regular” follow-up (visits carried out every 37 +/- 14 days). Each patient was followed up for an average of 8.6 months (± 2.0) including 5.7 ± 1.6 from the third month. Patients received an average of 5.1 ± 2.1 LUCENTIS treatments during the 12 months of this study (including 2.5 ± 1.9 from the third month).

The gain in visual acuity at 12 months was 3.2 ± 14.8 letters and there was no difference depending on whether or not the patient underwent an induction phase. On the other hand, the average 3 month gain in visual acuity was 5.3 ± 11.9 letters and was greater in the group which had an induction phase (6.7 ± 13.1 letters) than in those which did not (4.3 ± 10.9 letters, p = 0.065). 19.6% of patients achieved a gain of 15 or more letters at 12 months.

Like the LUEUR study, this study showed inadequate follow-up of patients and failure to observe the induction phase with three consecutive monthly injections which may explain why the efficacy appears lower than in the clinical studies.

7.3.2 Prescription data

According to IMS data (annual moving cumulative total, August 2012), 22,000 primary care prescriptions were issued for LUCENTIS. In this situation the proprietary medicinal product was prescribed in AMD (66%), for eye and visual investigations (30%) and for retinal vascular occlusions (4%).

[21] Oubraham H, Cohen S-Y, Malbrel C, Mimoun G, Zourdani A. Lumiere: evolution of visual acuity in patients with wet AMD treated with ranibizumab in current practice, ARVO congress, May 2011.

07.4 Summary & discussion

AMD

The clinical study data included in this evaluation are:

- 2-year results of pivotal studies (monthly administration regimen):
  - double-blind, randomised study which compared ranibizumab 0.3 and 0.5 mg to placebo (sham injections) (PIER)
  - double-blind, randomised study which compared ranibizumab 0.3 and 0.5 mg to verteporfin photo-dynamic therapy (PDT) (ANCHOR)
- studies which compared the monthly regimen to other administration regimens:
  - double-blind, randomised, non-inferiority study which compared the monthly regimen to the three-monthly regimen for 24 months (EXCITE)
  - double-blind, randomised, non-inferiority study which compared the monthly regimen to the regimen adjusted according to the change in visual acuity (PRN regimen) after three consecutive monthly injections for 24 months (HARBOR).
  - double-blind, randomised study which compared ranibizumab 0.3 mg to ranibizumab 0.5 mg, to the PRN regimen after three consecutive monthly injections for 24 months (SAILOR).
- studies against another anti-VEGF: bevacizumab
  - single-blind, randomised, non-inferiority study which compared bevacizumab to ranibizumab 0.5 mg by the monthly regimen or PRN after a first injection for 24 months (CATT).
  - double-blind, randomised, non-inferiority study which compared bevacizumab to ranibizumab 0.5 mg by the monthly or PRN regimen after three consecutive monthly injections for 24 months (IVAN).
- double-blind, randomised study which compared the combination of ranibizumab 0.5 mg/verteporfin PDT with ranibizumab 0.5 mg for 12 months (DENALI).
- long-term follow-up studies: extension phases during which all patients were treated with ranibizumab 0.5 mg according to a PRN regimen and in which the efficacy evaluation was a secondary endpoint:
  - 24 month extension study of the MARINA and ANCHOR pivotal studies and the FOCUS study (HORIZON)
  - extension study of the EXCITE and SUSTAIN studies (SECURE):
- observational studies: LUEUR prospective study (requested by the Transparency Committee and CEPS) and the retrospective LUMIERE study.

The initial ANCHOR and MARINA studies evaluated the efficacy of ranibizumab by monthly intravitreal injections. The PIER study evaluated a regimen of three injections each month followed by three-monthly injections. The administration regimen currently approved in the Marketing Authorisation is one which is adapted on an individual case basis depending on changes in visual acuity (PRN regimen). This involves a monthly injection until visual acuity measured in three consecutive monthly evaluations is stable. If there is a further fall in visual acuity due to the neovascular AMD found during a monthly visit the treatment should be restarted using the same regimen. In most of these studies, the doses of ranibizumab evaluated were 0.3 and 0.5 mg. Only the 0.5 mg dose has been retained in the Marketing Authorisation.

The new studies have used the monthly regimen and PRN regimens although these are different from the regimen approved in the Marketing Authorisation. The patients were treated according to the PRN regimen after being given a single injection or after three consecutive monthly injections with variable retreatment criteria between the studies. The current Marketing Authorisation only uses the criterion of a fall in visual acuity due to the AMD. As a result, none of the clinical studies have evaluated the exact dosage regimen approved in the Marketing Authorisation. This is based on modelling from the available data. The model has been validated by simulating the impact of monthly treatment and a retreatment strategy if visual acuity falls by more than five letters and by

comparing these results with the results of the MARINA and ANCHOR clinical studies (monthly treatment) and SUSTAIN study (retreatment strategy). The model predicts that according to the dosage recommended in the first SPC, median visual acuity will reach a peak at month 3 and will then fall by approximately 0.25 letters per month. On the other hand, using the individualised three stage retreatment regimen (induction until stabilisation, follow-up, retreatment), medium visual acuity will increase until month 5 by approximately +6 letters and then fall by approximately 0.003 letters per month.

In its recent recommendations (June 2012), the HAS goes beyond the single criterion of a fall in visual acuity and recommends that one injection be given per month for 3 consecutive months (interval between two injections ≥ 4 weeks) supplemented by a follow-up phase during which the patient should be examined every 4 weeks with:
- measurement of visual acuity by ETDRS;
- fundoscopy and/or retinography;
- optical coherence tomography.

Fluorescence angiography may be performed if necessary.
A repeat injection of ranibizumab is recommended after the first three injections in the following situations:
- persistent signs of activity of the neovascular lesion with or without fall in visual acuity;
- the lesion continues to respond to repeated treatments;
- no contraindication to continuing treatment.

During the follow-up phase, a further injection may be offered if there are no signs of neovascular activity and if previous attempts to discontinue treatment or prolong the interval between repeat injections have resulted in neovascular recurrence.

In the PIER study, ranibizumab 0.3 and 0.5 mg was compared with sham injections with a regimen of three injections each month followed by three-monthly injections. The results appear worse at 12 months than in the studies using the monthly regimen. Whilst the proportion of patients who achieved stable visual acuity was similar to that in the studies using the monthly regimen (in the region of 90%), the percentage of patients with a gain in visual acuity of ≥ 15 ETDRS letters was lower (13% compared with approximately 30-40% with a monthly regimen, with a 9.5% rate achieved from the sham injections in the PIER study and 4.5% in the MARINA study).
After treatment for 12 months the patients in the three groups were switched progressively to a monthly injection regimen of ranibizumab 0.5 mg. At the end of the second period (an additional 1 year) visual acuity remained stable in the group treated initially with 0.5 mg of ranibizumab whereas it fell by 21 letters in the group which initially received sham injections.

In the ANCHOR study, monthly injections of ranibizumab 0.3 and 0.5 mg were compared with verteporfin PDT. After 12 months, ranibizumab 0.5 mg was shown to be superior to verteporfin in terms of the percentage of patients who lost <15 letters (96.4% compared with 64.3%) and in the percentage of patients who gained ≥ 15 letters (40.3% compared with 5.6%).
All of the patients in the verteporfin group were treated with ranibizumab 0.3 mg in the second year of the study although the superiority of ranibizumab 0.5 mg over verteporfin found in year 1 persisted.

In the HARBOR study, which compared two doses of ranibizumab 0.5 mg and 2 mg (non-compliant with the Marketing Authorisation) over 12 months by monthly injections or according to the PRN regimen following three monthly injections, ranibizumab 0.5 mg improved BCVA by + 10.1 letters with monthly injections and by +8.2 letters with the PRN regimen. Non-inferiority was not demonstrated based on the threshold of 4 letters although it was demonstrated in a retrospective analysis with a non-inferiority threshold of 5 letters which is the clinically relevant threshold.

Non-inferiority was demonstrated in the CATT study at 12 months between ranibizumab 0.5 mg by monthly injections and according to the PRN regimen with a non-inferiority threshold of 5 letters (+8.5 letter change in BCVA with monthly injections and +6.8 letters with the PRN regimen).

The PRN regimen following three monthly injections was used with no comparison with the monthly regimen in the SAILOR and SUSTAIN studies. In the SAILOR study in patients treated with 0.5 mg of ranibizumab, after a minor improvement in the region of 6-7 letters at 3 months, BCVA fell returning almost to the baseline (2.3 letters). Similar results were found in the SUSTAIN study with ranibizumab 0.3 mg then 0.5 mg. These results appear to be worse than those in previous studies although no conclusion may be drawn on the effectiveness of the PRN regimen because of the poor methodological quality of the non-comparative studies in which efficacy was not the primary objective.

Overall, the monthly administration regimen was more effective. This regimen, however, is demanding, as it is difficult to administer in practice. Other administration regimens, so-called “as required" or PRN regimens, allowing a smaller number of injections have been evaluated. Overall these regimens have been shown to be effective in stabilising or improving visual acuity. The PRN regimen studied most often is a regimen following three consecutive monthly injections, with varying retreatment criteria between the studies, which could include a fall in visual acuity, OCT examination or fluorescence angiography. The CATT study on ranibizumab 0.5 mg showed the PRN regimen (after an initial injection) to be non-inferior to the monthly regimen.

In view of the off-label use of another anti-VEGF, bevacizumab (of which ranibizumab is a modified fraction), American (CATT) and British (IVAN) academic studies were set up to evaluate the non-inferiority of bevacizumab against ranibizumab. A French study (GEFAL[22]) is also ongoing. The aim of this study is to demonstrate non-inferiority of bevacizumab against ranibizumab in terms of clinical efficacy at 12 months on the visual acuity of patients suffering from subfoveal neovascular AMD. It should be noted that bevacizumab is currently marketed in a galenic form (concentrate for solution for infusion) which is inappropriate for ophthalmological use.

In the CATT study, after 12 months of treatment, bevacizumab 1.25 mg was shown to be non-inferior to ranibizumab 0.5 mg for both monthly administration and the PRN regimen (following the first injection, which is different from the currently recommended regimen) with a non-inferiority threshold of a 5 letter change in BCVA (monthly regimen: +8.5 letters for ranibizumab compared with +8.0 letters for bevacizumab; PRN regimen: +6.8 letters compared with +5.9 letters).

The 24 month results in the IVAN study analysis of the non-inferiority of bevacizumab against ranibizumab on the change in BCVA (primary endpoint) are not yet available.

In the DENALI study in patients suffering from exsudative AMD with visible or occult CNV, the combination of ranibizumab + verteporfin was not shown to be non-inferior to ranibizumab alone. Adding verteporfin to ranibizumab does not appear to improve the efficacy of ranibizumab. This may be explained by the inclusion of patients with occult CNV who have been removed from the Marketing Authorisation indication. In order to draw a conclusion as to the benefit of combining verteporfin with ranibizumab, it would have been desirable to compare the combination with verteporfin alone and with ranibizumab alone.

In its initial opinion, the Transparency Committee had expressed a desire for long-term data in order to confirm that effectiveness was maintained.

The company has submitted two long-term follow-up studies providing a 4-year experience of continued use in the HORIZON study and 3 to 4 years in the SECURE study. The primary objective of these studies was to evaluate the long-term safety. Efficacy was a secondary endpoint. All of the patients in these extension phases were treated with ranibizumab and as a result it is not possible to make a comparison with a placebo or verteporfin (patients from the ANCHOR study).

[22] French Avastin versus Lucentis Evaluation Group

The HORIZON study is a 2-year extension phase of the MARINA, ANCHOR and FOCUS studies which compared the combination of ranibizumab/verteporfin to verteporfin alone for 2 years.

The study was stopped early after Marketing Authorisation was obtained. In patients treated with ranzibizumas in the initial studies, mean BCVA fell by 7.5 letters compared with inclusion in the follow-up study.

The SECURE study conducted at the request of the EMA is a 2-year extension phase of the EXCITE (2 years) and SUSTAIN (1 year) studies. After an improvement in BCVA during the first phase of the studies (+5 letter change), BCVA fell, gradually returning to the baseline value in the initial studies (+0.4 letter difference).

As a result, although the methodology of these studies is sub-optimal (open and follow-up studies with no placebo arm, differences in administration regimens and length of treatment, inadequate patient follow-up, the HORIZON study stopping early), the results of these follow-up phases suggest a reduction in the visual gain from the first years of ranibizumab treatment after treatment for 3 or 4 years.

In order to answer the Transparency Committee and CEPS questions about the treatment conditions for LUCENTIS in real practice and whether efficacy and safety are maintained in the long-term, the company has set up the LUEUR observational study which intends to follow-up patients over 4 years. Currently only the 2-year results are available (primary study endpoint). In real life practice, the efficacy of LUCENTIS appears to be lower than in the clinical studies with a 75.8% proportion of eyes (all eyes analysed) losing fewer than 15 letters at 2 years compared with 82% in the PIER study which used a treatment regimen similar to the SPC.

This figure was higher for eyes previously not treated with LUCENTIS at inclusion in the study (76.4%) and lower for all eyes analysed when missing data are treated as failures (15% missing data points at 2 years), with a figure of 66%. Visual acuity remained stable for 2 years with a mean change of -0.62 letters (95%CI [-5.51; 4.26]) for eyes beginning LUCENTIS treatment (15% missing data). One quarter of the eyes previously untreated with LUCENTIS (26%) and 13.5% of the entire population achieved an improvement of more than 15 letters in 2 years, similar to what was seen in the PIER study (8.5%) during which patients were treated with a 3-monthly regimen after three initial consecutive monthly injections. In the ANCHOR study which used a monthly regimen, the percentage of patients who achieved a gain of ≥ 15 letters was maintained at 40% in patients who were treated with ranibizumab for 2 years.

The results also showed that whilst the treatment initiation conditions described in the Treatment Information Form for LUCENTIS were overall well followed, it appears that monthly patient follow-up was not observed (patients had an average of six follow-up consultations during the first year and five during the second year), reflecting under-monitoring of patients and undoubtedly under-treatment, which may explain why efficacy is lower in real-life practice.

The currently recommended induction phase of three injections at least 35 days apart is not performed in practice. Almost a third of previously untreated patients received at least three injections (31.3%) during the first year of treatment and 7.5% of patients received a single injection. The average time between the first and second induction injection is 54 days (median = 35) and the average time between the second and third induction injection is 100 days (median = 42).

Similar results were found in the LUMIERE retrospective multicentre study carried out in mainland France which included 551 patients treated with LUCENTIS for exsudative AMD for at least 12 months.

This study showed that the average gain in visual acuity after treatment with LUCENTIS for 12 months was 3.2 ± 14.8 letters. 19.6% of patients achieved a gain of 15 or more letters at 12 months. However, fewer than 40% of the patients underwent an induction phase (first three injections every 30 +/- 7 days) and no patients had strict monthly follow-up over the 12 months (i.e. visits carried out every 30 days +/- 7 days). Only 4.4% of patients had “regular” follow-up (visits carried out every 37 +/- 14 days). Each patient was followed up an average of 8.6 times (± 2.0) of

which 5.7 ± 1.6 were from the third month. Patients received an average of 5.1 ± 2.1 LUCENTIS treatments during the 12 months of this study (of which 2.5 ± 1.9 were from the third month).

DME

At the time of the initial registration the company submitted a double-blind, randomised, placebo-controlled phase II study (RESOLVE study) which showed ranibizumab 0.5 mg to be superior to sham injections in patients with visual impairment due to DME after treatment for 12 months. The injections were administered according to a PRN regimen after three consecutive monthly injections with retreatment criteria based on visual acuity, central retinal thickness and the presence of oedema. The mean change in BCVA compared with baseline was +6.4 ETDRS letters for ranibizumab compared with -0.1 letters for sham injections (p = 0004).

Ranibizumab was also found to be effective in combination with laser in this indication in two double-blind, randomised, phase III studies after treatment for 12 months:

- in the RESTORE study, the mean change in BCVA from months 1 to 12 was +6.1 letters for ranibizumab 0.5 mg, +5.9 letters for the ranibizumab + laser combination and 0.8 letters for laser alone (p < 0.0001);
- in the DCRnet study, the mean change in BCVA in the groups in which ranibizumab was combined with laser compared with laser alone was +5.8 letters (combination with concomitant laser) and +6.0 letters (combination with deferred laser). This study needs to be extended to 5 years as the results are now maintained after treatment for 2 years.

In its previous opinion, the Transparency Committee expressed a desire for more long-term data.
In order to respond to the Committee's request, the company has submitted supplementary results at 2 years from the DCRnet study (larger number of patients analysed), the results of the 2-year extension phase of the RESTORE study and a further study in combination with laser (REVEAL study).

In the RESTORE study, patients continued their respective treatments during the 2-year extension phase apart from patients in the laser monotherapy group who were also given ranibizumab. The results of the first extension year (i.e. treatment for 2 years in total) are now available: the mean change in BCVA compared with baseline in the initial study was +7.9 letters with ranibizumab monotherapy and +6.7 letters with the ranibizumab + laser combination.

The 2-year results of the DCRnet study showed that the efficacy of the combination of ranibizumab + concomitant or deferred laser was maintained compared with laser alone.
The mean change in BCVA compared with baseline was statistically greater (p < 0.001) in the ranibizumab combined with laser group than in the laser + sham IVT group: +7 letters (ranibizumab + concomitant laser), +9 letters (ranibizumab + deferred laser) compared with +3 letters (laser + sham IVT).

A higher percentage of patients had a gain in visual acuity of ≥ 15 letters in the ranibizumab + concomitant laser group (29%) and in the ranibizumab + deferred laser group (28%) than in the laser + sham IVT group (18%).
Similarly, the percentage of eyes which lost < 15 letters remained stable after 2 years (figures not supplied).

In the new REVEAL study (unpublished, double-blind, randomised) similar mean changes in BCVA were seen at 1 year compared with the other studies which evaluated the combination of laser with ranibizumab: +6.6 letters for ranibizumab alone, +6.4 letters for ranibizumab in combination with laser and +1.8 letters with laser alone.

Overall, these new data for the treatment of visual impairment due to DME after treatment for 2 years have confirmed the results previously found at 1 year for ranibizumab monotherapy or at 2 years in combination with laser, and have shown that effectiveness is maintained after treatment for 2 years.

Branch and Central RVO
No new data were submitted in this indication.

Safety
Many adverse events have been reported with ranibizumab including ocular effects, particularly those associated with the intravitreal injection, and systemic effects, particularly related to the anti-VEGF class. These have varied in incidence and severity (see SPC). The safety profile of ranibizumab is the same in all indications.

The risk management plan (RMP) stipulates monitoring for a number of ocular adverse effects and effects potentially related to the anti-VEGF class:

- risks identified: endophthalmitis, intraocular inflammations, retinal pigment epithelium tear, retinal tear, retinal detachment, transient increase in intraocular pressure, traumatic cataract, intravitreal haemorrhage and hypersensitivity reactions.
- potential risks: myocardial infarction, arterial and myocardial thromboembolic events, venous thromboembolic events, hypertension, non-ocular haemorrhage, proteinuria, reduced retinal blood flow, glaucoma and prolonged increase in intraocular pressure.

The pharmacovigilance data (5 years' experience post-marketing) have not shown changes in the incidence of these adverse events. In addition, no link has been found between ranibizumab and the arterial thromboembolic events.

No causal relationship has been established with ranibizumab for the other risks monitored in the RMP (macular hole, vasculitis and depression).

In its previous opinions the Committee expressed a desire for long-term safety data.
Safety studies have been conducted in AMD and in DME.

In AMD, the SAILOR and SUSTAIN studies evaluated the safety of treatment with ranibizumab for 1 year according to a monthly and PRN regimen. In the HORIZON study, patients from the MARINA, ANCHOR and FOCUS studies were followed up for 2 additional years, i.e. for a total exposure of 4 years.

The adverse events reported in these studies were consistent with those listed in the SPC. In the HORIZON study which has the longest experience of using ranibizumab there were few ocular adverse effects (3.8%), mostly a rise in intraocular pressure (1.5%), myodesopsia (1.1%) and intraocular inflammation (0.8%).

The adverse events potentially due to VEGF inhibition were: hypertension (10.6%), arterial thromboembolic events (7.6%) and non-ocular haemorrhage (6.7%).
The ATT study compared ranibizumab to bevacizumab over 2 years. The safety profile was similar for both compounds except for an apparently higher percentage of patients who had at least one serious adverse event and gastrointestinal problems with bevacizumab. However, these safety results obtained from a single study and a secondary analysis do not allow a conclusion to be drawn from the comparison between ranibizumab and bevacizumab in terms of safety. The final data from the IVAN study and the data from the GEFAL study will provide additional information on this subject.

In DME, patients in the RESTORE study were included in a 1-year safety follow-up phase after treatment for 1 year. The adverse events reported were consistent with those listed in the SPC.

The "undesirable effects" section of the SPC has been updated in terms of the nature and incidence of adverse effects to incorporate the pharmacovigilance data from the clinical studies and the marketing of LUCENTIS.

The following adverse effects have been added: vitreous disorder, subcapsular cataract, haemorrhage at the injection site, allergic conjunctivitis, eye discharge, photopsia, eyelid pain, hyphaema, iris synechiae, corneal deposits, pain at the injection site, irritation at the injection site,

abnormal intraocular sensation, retinal pigment epithelium tear, allergic skin reactions (rash, urticaria, pruritus, erythema, nasopharyngitis, hypersensitivity, anxiety).

Endophthalmitis was a potentially significant risk when the product was first marketed, as it is linked to the injection procedure which not all ophthalmologists had mastered, and it has a serious outcome as it may lead to loss of the eye. It is now considered to be an uncommon adverse effect.

Warnings and precautions for use have been added:

- for all indications: transient prolonged rise in intraocular pressure
- for AMD: risk factors for pigment epithelium tear during treatment with anti-VEGF
- for DME:
  - risk of hypersensitivity due to the potential risk of increased systemic exposure
  - populations with limited data
  - populations with no data
- for RVO:
- populations with limited data
- treatment not recommended in ischaemic forms of the disease.

08 THERAPEUTIC USE

AMD

According to the latest HAS recommendations (June 2012) on the management of AMD,[23] intravitreal anti-VEGF treatment should be started as soon as the diagnosis of exsudative AMD with subfoveal choroidal neovascularisation is made (< 10 days) regardless of the initial visual acuity.

Photodynamic therapy (PDT) with verteporfin (VISUDYNE) is no longer the first line treatment for exsudative AMD with predominantly classic subfoveal choroidal neovascularisation. It can be used in situations of contraindications or failure to respond to anti-VEGFs and in some clinical forms of the disease in combination with anti-VEGFs (for example, polypoidal vasculopathy). VISUDYNE is no longer indicated in exsudative AMD with occult choroidal neovascularisation.

Currently, pegaptanib (MACUGEN) and ranibizumab (LUCENTIS) are the two anti-VEGFs which have Marketing Authorisation in France for the indication "treatment of neovascular (wet, exsudative) AMD". Bevacizumab (AVASTIN) is used outside of its Marketing Authorisation (off-label).
Although pegaptanib and ranibizumab have not been compared in a clinical study, pegaptanib appears to be less effective than ranibizumab in terms of the percentage of patients with a gain in visual acuity of 15 letters or more. In practice, pegaptanib is not widely prescribed.

LUCENTIS is a first-line treatment for impaired visual acuity due to subfoveal exsudative AMD.
The HAS recommends that one injection is given per month for 3 consecutive months (with an interval of ≥ 4 weeks between two injections) supplemented by a follow-up phase during which it is recommended to carry out the following examinations every 4 weeks:
- measurement of visual acuity by ETDRS;
- fundoscopy and/or retinography;
- optical coherence tomography.

Fluorescence angiography may be performed if necessary.

A repeat injection of ranibizumab is recommended after the first three injections in the following situations:
- persistent signs of activity of the neovascular lesion with or without a fall in visual acuity;
- the lesion continues to respond to repeated treatments;
- no contraindication to continuing treatment.

During the follow-up phase a further injection may be offered in the absence of signs of neovascular activity if previous attempts to stop treatment or extend the reinjection interval have led to neovascular recurrences.

[23] Age-related macular degeneration: diagnostic and therapeutic management. HAS (June 2012). http://www.has-sante.fr/portail/jcms/c_1311607/diagnostic-et-prise-en-charge-de-la-dmla

DME

Diabetic macular oedema is a complication of diabetic retinopathy. Maintaining glycaemic[24] and blood pressure[25] control helps to reduce the risk of developing macular oedema.

Laser photocoagulation is the only treatment which has been shown to be effective in reducing the impairment in visual acuity as a result of diabetic macular oedema. It does not achieve a gain in visual acuity.
There are two laser photocoagulation techniques for diabetic macular oedema:

- photocoagulation directed towards the local lesions responsible for the oedema (micro-aneurysm and/or specific blood vessels)
- non-confluent perifoveal "staggered row" photocoagulation (so-called "grid" photocoagulation) to treat diffuse macular oedema.

Laser therapy is effective in focal forms of disease.
If the lesions are close to the centre of the macula, the expected benefits of this treatment must be balanced against the possible complications of paracentral scotomas, accidental foveal impact and neovascularisation developing from a photocoagulation scar. Because of these side effects the number of retreatments must be limited.

According to the ETDRS recommendations,[26] all patients with clinically significant macular oedema must be treated by laser regardless of their visual acuity to limit the progression of the macular oedema.
Clinically significant oedemas are defined by one of the following three criteria:

- retinal thickening and/or exsudates reaching the centre of the macula
- retinal thickening and/or exsudates located less than 500 µm from the centre of the macula but not reaching the macula.
- retinal thickening of a surface area of 1 papillary diameter (PD) or more located at least in part less than 1 PD from the centre of the macula.

Surgical vitrectomy is indicated for the rare cases of tractional macular oedema caused by contraction of the thickened condensed premacular hyaloid membrane.

In the absence of long-term data on the use of ranibizumab monotherapy and because of the demanding treatment regimen which requires monthly injections until visual acuity has stabilised in three consecutive monthly evaluations on treatment, laser photocoagulation therapy remains the reference treatment.
Ranibizumab is reserved for patients who cannot be treated with laser, i.e. diffuse forms of the disease or leaks close to the centre of the macula. Ranibizumab treatment must be started when visual acuity is 5/10, in the same way as for laser photocoagulation, and only if diabetic management has been optimised.
In the absences of specific data, LUCENTIS is not recommended in diabetic macular oedema with focal and diffuse components.
The place of ranibizumab remains to be established in diabetic macular oedema with focal and diffuse components.

[24] DCCT – The diabetes control and complications trial research group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-86.

[25] UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317: 703-13.

[26] Early Treatment Diabetic Retinopathy Study Report Number 1: Photocoagulation for diabetic macular edema, Early Treatment Diabetic Retinopathy Study Research Group Arch. Ophthalmol 1985; 103 (12): 1796-1806.

Branch and Central RVO

Two main forms of retinal vein occlusion can be distinguished: an ischaemic form which has a poor visual prognosis and a well perfused form (so-called oedematous) which has a better prognosis.

The aim of treating oedematous retinal vein occlusion is to facilitate restoration of normal retinal venous circulation to avoid development of an ischaemic form of the disease and to prevent or treat macular complications, particularly cystoid macular oedema.

The aim of treating mixed or ischaemic venous occlusion is to prevent or treat neovascular complications.

Intravitreal implantation of dexamethasone (OZURDEX) has Marketing Authorisation to treat adult patients with macular oedema following branch or central retinal vein occlusion. It is a first-line treatment.

Various medicines are used systemically off-label but have not been evaluated in clinical studies.
Triamcinolone retard (KENACORT retard) is used off-label by intravitreal injection. Its formulation is not suitable for the intravitreal route and contains a preservative which may cause local pseudo-endophthalmitis reactions. The other complications are cataract, almost invariably after the two injections and ocular hypertonia.

Other treatments are used:

- Grid laser photocoagulation in oedematous forms of the disease and panretinal photocoagulation in ischaemic forms of the disease are less than 3 months old.
- Surgical treatments of macular oedema: vitrectomy, radical optical neurotomy, chorioretinal venous anastamoses, arteriovenous adventitial sheathotomy. These treatments have not been evaluated in a clinical study.

Like OZURDEX, LUCENTIS is a first-line treatment for visual impairment due to macular oedema secondary to branch or central retinal vein occlusion. In the absence of directly comparable data between LUCENTIS and OZURDEX, the choice of either of these medicines is made taking account of their specific efficacy, patient characteristics, contraindications, potential adverse effects and follow-up requirements. As a result, patient age, the patient's ability to travel to be given the monthly injections for LUCENTIS, the presence of a lens and existence of glaucoma as a result of the increased risk of raised intraocular pressure and cataract with OZURDEX are major factors to take into account when one or other of these treatments is started.
A fluorescein angiogram is recommended before treatment is started in order to exclude ischaemic forms of the disease, which are not indications for LUCENTIS. The oedematous form of the disease may progress towards the ischaemic form on treatment. This should be monitored.

The treatment should be stopped if no improvement in visual acuity occurs following three consecutive monthly injections.

09 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all of the above information and following a debate and vote, the Committee has drawn the following conclusions:

09.1 Actual benefit

AMD

Age-related macular degeneration (AMD) is the leading cause of blindness in France in patients over 50 years old. The severe forms of AMD which are responsible for the largest number of cases of severe reduction in visual acuity include the exsudative or neovascular forms.

This proprietary medicinal product is a curative therapy for the consequences of the disease.

The efficacy and safety of LUCENTIS have been studied in trials which have only included patients with AMD and subfoveal choroidal neovascularisation (CNV). The efficacy/adverse effects ratio for this medicinal product in these patients is considered to be high.

Ranibizumab is a first-line therapy.

There are alternative, less effective, medical treatments (MACUGEN, VISUDYNE).

- Public health benefit:
  The public health burden of subfoveal exsudative AMD is moderate.
  Improvement in the management of AMD is a public health need (GTNDO priority).
  In light of the available data and in view of the existing treatments, LUCENTIS is expected to have a moderate impact on AMD-related morbidity mostly in terms of maintaining visual acuity.
  The results of the observational LUEUR study have confirmed the efficacy (loss of less than 15 ETDRS letters) at 2 years for LUCENTIS in AMD in usual practice.
  The proprietary medicinal product LUCENTIS provides an additional response to the identified public health need.
  As a result LUCENTIS is expected to have a public health benefit. This benefit is **moderate.**

In view of this information, the Committee expresses the opinion that:

The actual benefit of LUCENTIS 10 mg/ml remains substantial in the treatment of exsudative age-related macular degeneration (AMD) with subfoveal choroidal neovascularisation.

DME

Diabetic macular oedema is a complication of diabetic retinopathy. It is asymptomatic but progresses gradually towards poor sight and blindness which is a disability and causes a marked deterioration in quality of life.

This proprietary medicinal product is a curative therapy for the reduction in visual acuity due to diabetic macular oedema.

The efficacy/adverse effects ratio is high.

Laser photocoagulation is the reference treatment for visual impairment due to diabetic macular oedema. In the absence of long-term data and because of the demanding treatment regimen requiring monthly injections until visual acuity has stabilised over three consecutive monthly evaluations on treatment, LUCENTIS should be restricted to patients who cannot be treated with laser, i..e those with diffuse macular oedema or leaks close to the centre of the macula.

Ranibizumab treatment can be started when visual acuity is 5/10 or under and whose diabetic management has been optimised.

An alternative treatment exists: laser photocoagulation for local disease.

- Public health benefit:

  Diabetic retinopathy is a major cause of poor sight and the leading cause of blindness in people under 60 years old in the general population in all industrialised countries.[27,28] Diabetic macular oedema (DME) is the leading cause of visual impairment in diabetic patients. Approximately 5% of diabetic patients are estimated to develop macular oedema.[29] There are limited epidemiological data available on the prevalence of DME in France.

  The burden of macular oedema is due to the visual impairment and to the incapacities and deterioration in quality of life which it causes. It can also have significant psychosocial or even occupational consequences, which are particularly significant in young patients. The public health burden of DME is considered to be moderate.

  Reducing the frequency and severity of the complications of diabetes, improving the screening and treatment of systemic diseases causing ophthalmological complications and improving quality of life in people suffering from chronic diseases are established public health priorities (objectives 55 and 66 of the 9 August 2004 Public Health Policy Law, Improvement Plan for quality of life of people suffering from chronic disease 2007-2011).

  In the light of the available data, the proprietary medicinal product LUCENTIS is expected to have a minor impact compared with laser photocoagulation on the morbidity of DME (mostly in terms of improving visual acuity) and on the quality of life of patients who are treated with it. However, this impact is considered to be moderate in the sub-population of patients who cannot receive laser treatment.
  However, it is not clear whether the trial results can be extrapolated to clinical practice because of:
  - doubts about maintaining the long-term efficacy in a population suffering from a chronic disease such as diabetes;
  - lack of knowledge about the optimum number of intravitreal injections, the need for frequent reinjections and questions about the retreatment criteria;
  - insufficient data in poorly controlled diabetic patients.

  It would also be expected to have an impact on organisation of care because of the very regular follow-up visits for patients who are restricted by their mobility.

  Despite all of this, the proprietary medicinal product LUCENTIS should provide an additional response to the identified public health need.

  As a result, LUCENTIS is expected to have a public health benefit in this indication. This benefit is **low**.

In view of this information, the Committee is of the opinion that:

- **The actual benefit of LUCENTIS 10 mg/ml remains <u>substantial</u> in patients with visual impairment of 5/10 or less as a result of diabetic macular oedema in diffuse forms of the disease or with leaks close to the centre of the macula in whom diabetic care has been optimised.**
- **It remains <u>insufficient</u> in the other situations.**

[27] Porta M, Bandello F. Diabetic retinopathy. A clinical update. Diabetologia 2002;45(12):1617-34.
[28] Frank RN. Diabetic retinopathy. N Engl J Med 2004;350(1):48-58.
[29] Delcourt C, Massin P, Rosilio M. Epidemiology of diabetic retinopathy: expected *vs* reported prevalence of cases in the French Population. Diabetes Metab 2009; 35 (6): 431-8.

Branch and Central RVO

Retinal vein occlusion is an eye disease affecting the retina, and at its centre, the macula, which is responsible for fine vision. It causes a delay in the circulation, together with infiltration and oedema of the macula which is responsible for a fall in visual acuity.
The visual prognosis depends on the clinical form of the retinal vein occlusion: two main forms are distinguished, an ischaemic form which has a poor visual prognosis and a well perfused form (so-called oedematous) which has a better prognosis.

These proprietary medicinal products intended as symptomatic treatments.

The efficacy/adverse effects ratio is high.

This proprietary medicinal product is a first-line therapy.

There is a treatment alternative (OZURDEX).

- Public health benefit:
  The public health burden of retinal vein occlusion is low.
  A reduction in visual impairment is a public health need (GTNDO priority).
  In light of the available data, LUCENTIS is expected to have a moderate short term impact on the morbidity of these diseases, mostly in terms of maintaining visual acuity.
  In the absence of available data, the impact of LUCENTIS on quality of life and organisation of care cannot be quantified.
  It is debatable whether the study results can be extrapolated to clinical practice particularly because of uncertainty about the management methods (particularly the recommended angiography before treatment), the number of optimal injections and the criteria for retreatment.
  The proprietary medicinal product LUCENTIS may however provide a partial response to the identified public health need.
  As a result, LUCENTIS is expected to have a public health benefit in this indication. This benefit is **low**.

In view of this information, the Committee is of the opinion that:

The actual benefit of LUCENTIS 10 mg/ml remains substantial in the treatment of visual impairment due to macular oedema secondary to branch or central RVO

09.2 Improvement in actual benefit (IAB)

- **AMD:**

In light of the data submitted, the Committee deems that the substantial improvement in actual benefit (IAB II) of LUCENTIS 10 mg/ml is maintained for the management of patients suffering from exsudative AMD with subfoveal choroidal neovascularisation.

- **DME:**

In light of the data submitted, the Committee deems that the minor improvement in actual benefit (IAB IV) for LUCENTIS 10 mg/ml is maintained in the treatment strategy for visual impairment due to diabetic macular oedema in diffuse forms of the disease or with leaks close to the centre of the macula in patients whose visual acuity is 5/10 or less and in whom diabetic care has been optimised.

- **Branch RVO and central RVO:**

In view of the absence of new data, the Committee considers that the minor improvement in actual benefit (IAB IV) for LUCENTIS 10 mg/ml compared with OZURDEX is maintained in the treatment of visual impairment due to macular oedema secondary to branch or central retinal vein occlusion.

010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Transparency Committee recommends continued inclusion on the list of medicines refundable by the National Health Insurance in the following indications:

- **The treatment of exsudative age-related macular degeneration (AMD) with subfoveal choroidal neovascularisation.**
- **Treatment of visual impairment due to diabetic macular oedema (DME) in patients with visual impairment of 5/10 or less due to diabetic macular oedema, either diffuse disease or with leaks close to the centre of the macula in whom diabetes management has been optimised.**
- **Treatment of visual impairment due to macular oedema secondary to branch or central retinal vein occlusion (RVO).**

Proposed reimbursement rate: 65%

Packaging

On 28 February 2008, the Committee approved registration of a new packaging in a vial of 0.23 ml of solution containing 2.3 mg of ranibizumab to replace the initial packaging in a vial of 0.3 ml of solution containing 3 mg of ranibizumab.
However, the Committee is of the opinion that the packaging in a vial of 0.23 ml is still not appropriate for the prescription conditions, which require removal of 0.05 ml, and reiterates its recommendation that the packaging be made more suitable, such as a prefilled syringe.

Specific requests relating to reimbursement

Exception drug status

Request for data

The Committee is awaiting the results of the observational studies requested previously in the indications for treatment of visual impairment due to DME and visual impairment secondary to branch or central RVO.

APPENDIX 1: Amendments to the SPC of LUCENTIS 10 mg/ml solution for injection since the 22 January 2007

Text highlighted in yellow: additional text
Text ~~struck through~~: deleted text
Text highlighted in green: changes in incidence of adverse effects

	Initial version of 22 January 2007	Amendment of 2 September 2011
1. NAME OF THE MEDICINAL PRODUCT	LUCENTIS 10 mg/ml solution for injection	LUCENTIS 10 mg/ml solution for injection
2. QUALITATIVE AND QUANTITATIVE COMPOSITION	One ml contains 10 mg of ranibizumab. Each vial contains ~~3.0~~ mg of ranibizumab in ~~0.3~~ ml solution. Ranibizumab is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology. For the list of excipients, see section 6.1.	One ml contains 10 mg of ranibizumab. Each vial contains 2.3 mg of ranibizumab in 0.23 ml of solution. Ranibizumab is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology. For the list of excipients, see section 6.1.
3. PHARMACEUTICAL FORM	Solution for injection Sterile aqueous solution, clear and colourless to pale yellow in colour.	Solution for injection Sterile aqueous solution, clear and colourless to pale yellow in colour.
4.1 Therapeutic indications	LUCENTIS is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) (see section 5.1).	LUCENTIS is indicated in adults for: • the treatment of neovascular (wet) age-related macular degeneration (AMD) (see section 5.1). • the treatment of visual impairment due to diabetic macular oedema (DME) (see section 5.1). • the treatment of visual impairment due to macular oedema secondary to branch or central retinal vein occlusion (RVO) (see section 5.1).
4.2 Posology and method of administration	Single use vial for intravitreal use only. LUCENTIS must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose for LUCENTIS is 0.5 mg ~~(0.05 ml).~~ ~~LUCENTIS treatment is started with an induction phase with 1 injection per month for 3 consecutive months followed by a maintenance phase during which patients' visual acuity should be monitored once per month. If the patient loses more than 5 letters (ETDRS scale or equivalent on a line on the Snellen chart), LUCENTIS must be administered. The interval between two doses should not be shorter than 1 month.~~	Single use vial for intravitreal use only. LUCENTIS must be administered by a qualified ophthalmologist experienced in intravitreal injections. Treatment of wet AMD In neovascular (wet) AMD, the recommended dose for LUCENTIS is 0.5 mg, given monthly as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. Treatment is given monthly and continued until maximum visual acuity is achieved, i.e. the patient's visual acuity is stable for three consecutive monthly evaluations performed while on ranibizumab treatment Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly evaluations (implying a minimum of two

		injections). The interval between two doses should not be shorter than 1 month. Treatment of visual impairment due to either DME or macular oedema secondary to retinal vein occlusion (RVO) (see section 5.1) The recommended dose for LUCENTIS is 0.5 mg, given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. Treatment is given monthly and continued until maximum visual acuity is achieved, i.e. the patient's visual acuity is stable for three consecutive monthly evaluations performed while on ranibizumab treatment. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to DME or to macular oedema secondary to RVO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly evaluations (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month. LUCENTIS and laser photocoagulation in DME and in macular oedema secondary to BRVO Data are available on concomitant administration of LUCENTIS and laser photocoagulation (see section 5.1). If both treatments are given on the same day, LUCENTIS should be administered at least 30 minutes after laser photocoagulation. LUCENTIS can be administered in patients who have received previous laser photocoagulation. Method of administration As applies to all parenteral medicines, LUCENTIS should be inspected visually for particulate matter and discoloration prior to administration. Before treatment, the patient should be instructed to self-administer anti-bacterial drops (four times daily for 3 days before and following each injection). The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section 4.4). The periocular skin, eyelid and ocular surface

	As applies to all parenteral medicines, LUCENTIS should be inspected visually for particulate matter and discoloration prior to administration. Before treatment, the patient should be instructed to self-administer anti-bacterial drops (four times daily for 3 days before and following each injection). The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section 4.4). The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and the broad-spectrum topical microbiocide should be administered prior to the injection. ~~Before withdrawing the contents of the bottle, the external part of the rubber bottle stopper must be disinfected. The 5 µm filter-needle must be fixed onto the 1 ml syringe. All of the contents of the LUCENTIS vial must be removed keeping the bottle straight. The filter-needle must be discarded after removing the contents of the vial and must not be used for the intravitreal injection. The needle must be replaced by the sterile needle to administer the intravitreal injection. Excess solution must be expressed until the end of the plunger reaches the line showing 0.05 ml on the syringe.~~ The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml is then delivered; a different scleral site should be used for subsequent injections. <u>Special populations</u> *Hepatic impairment* LUCENTIS has not been studied in patients with hepatic impairment. However, no special considerations are needed in this population. *Renal impairment* Dose adjustment is not needed in patients with renal impairment (see section 5.2). ~~*Children and adolescents*~~	should be disinfected and adequate anaesthesia and the broad-spectrum topical microbiocide should be administered prior to the injection. For information on preparation of LUCENTIS, see section 6.6. The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml is then delivered; a different scleral site should be used for subsequent injections. <u>Special populations</u> *Hepatic impairment* LUCENTIS has not been studied in patients with hepatic impairment. However, no special considerations are needed in this population. *Renal impairment* Dose adjustment is not needed in patients with renal impairment (see section 5.2). *Paediatric population* LUCENTIS must not be used in children and adolescents because of a lack of information about the safety and efficacy in this patient subpopulation. *Elderly* No dose adjustment is required in the elderly. There is limited experience in patients older than 75 years with DME. *Ethnicity* Experience with treatment is limited in groups other than Caucasians.

	LUCENTIS must not be used in children and adolescents because of a lack of information about the safety and efficacy in this patient subpopulation. *Elderly* No dose adjustment is required in the elderly. *Ethnicity* Experience with treatment is limited in groups other than Caucasians.	
4.3 Contraindications	Hypersensitivity to the active substance or to any of the excipients. Patients with active or suspected ocular or periocular infections. Patients with active severe ocular inflammation.	Hypersensitivity to the active substance or to any of the excipients. Patients with active or suspected ocular or periocular infections. Patients with active severe ocular inflammation.
4.4 Special warnings and precautions for use	Treatment with LUCENTIS is for intravitreous injection only. Intravitreous injections including those with LUCENTIS have been associated with endophthalmitis; intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering LUCENTIS. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above-mentioned events without delay. Increases in intraocular pressure have been seen within 60 minutes of injection of LUCENTIS (see section 4.8). ~~As a result~~, both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. The safety and efficacy of LUCENTIS therapy administered to both eyes concurrently have not been studied. If bilateral treatment is performed at the same time this could lead to an increase in systemic exposure, which could increase the risk of systemic adverse effects. As with all therapeutic proteins, there is a potential for immunogenicity with LUCENTIS. Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation. ~~LUCENTIS has not been studied in patients who have previously~~	Treatment with LUCENTIS is for intravitreous injection only. Intravitreous injections including those with LUCENTIS have been associated with endophthalmitis; intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering LUCENTIS. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above-mentioned events without delay. Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of LUCENTIS. Sustained IOP increases have also been identified (see section 4.8). Intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately. The safety and efficacy of LUCENTIS therapy administered to both eyes concurrently have not been studied. If bilateral treatment is performed at the same time this could lead to an increase in systemic exposure, which could increase the risk of systemic adverse effects. As with all therapeutic proteins, there is a potential for immunogenicity with LUCENTIS. Since there is a potential for an increased systemic exposure in subjects with DME, an increased risk for developing hypersensitivity in this population cannot be excluded. Patients should also be instructed if an intraocular inflammation increases in severity which may be a clinical sign

	~~received intravitreal injections.~~ LUCENTIS should not be administered concurrently with other anti-VEGF (systemic or ocular). The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of: • a decrease in best corrected visual acuity (BCVA) of ≥ 30 letters compared with the last evaluation of visual acuity; • an intraocular pressure of ≥ 30 mmHg; • a retinal tear; • a subretinal haemorrhage involving the centre of the fovea or if the size of the haemorrhage is ≥ 50% of the total lesion area. • performed or planned intraocular surgery within the previous or next 28 days. Treatment should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.	attributable to intraocular antibody formation. LUCENTIS should not be administered concurrently with other anti-VEGF (vascular endothelial growth factor) (systemic or ocular). The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of: • a decrease in best corrected visual acuity (BCVA) of ≥ 30 letters compared with the last evaluation of visual acuity; • an intraocular pressure of ≥ 30 mmHg; • a retinal tear; • a subretinal haemorrhage involving the centre of the fovea or if the size of the haemorrhage is ≥ 50% of the total lesion area. • performed or planned intraocular surgery within the previous or next 28 days. Risk factors associated with the development of a retinal pigment epithelium tear after anti-VEGF therapy for wet AMD include a large and/or high pigment epithelial retinal detachment. Caution is required when LUCENTIS is started in patients with these risk factors for a retinal pigment epithelium tears. Treatment should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes. There is only limited experience in the treatment of subjects with DME due to type 1 diabetes. LUCENTIS has not been studied in patients who have previously received intravitreal injections, in patients with active systemic infections, proliferative diabetic retinopathy or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with LUCENTIS in diabetic patients with an HbA1c level over 12% and uncontrolled hypertension. There are limited data on safety in the treatment of DME and macular oedema due to RVO in patients with prior history of stroke or transient ischaemic attacks. Since there is a potential risk of arterial thromboembolic events following intravitreal use of VEGF (vascular endothelial growth factor) inhibitors caution should be exercised when treating such patients (see section 4.8). There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischaemic branch RVO and central RVO (CRVO) In patients with RVO presenting with clinical signs of irreversible ischaemic visual function loss, treatment is not recommended.

4.5 Interaction with other medicinal products and other forms of interactions	No specific interaction studies have been performed. For use of LUCENTIS in combination with verteporfin photodynamic therapy (PDT), see section 5.1.	No specific interaction studies have been performed. For use of LUCENTIS in neovascular AMD in combination with verteporfin photodynamic therapy (PDT), see section 5.1. For adjunctive use of laser photocoagulation and LUCENTIS in DME and BRVO, see sections 4.2 and 5.1.
4.6 Pregnancy and lactation	Pregnancy For ranibizumab, no data on exposed pregnancies are available. ~~No studies have been conducted in animals.~~ The systemic exposure to ranibizumab is expected to be very low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/foetotoxic. Therefore, ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. Women of child-bearing potential Women of child-bearing potential should use effective contraception during treatment. Breast-feeding ~~It is unknown whether LUCENTIS is excreted into breast milk.~~ Breast-feeding is not recommended during the use of LUCENTIS.	Women of child-bearing potential/contraception in females Women of child-bearing potential should use effective contraception during treatment. Pregnancy For ranibizumab, no clinical data on exposed pregnancies are available. Studies in Cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development (see section 5.3). The systemic exposure to ranibizumab is expected to be very low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/foetotoxic. Therefore, ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. For women who wish to become pregnant and who have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child. Breast-feeding It is unknown whether LUCENTIS is excreted into human milk. Breast-feeding is not recommended during the use of LUCENTIS.
4.7 Effects on ability to drive and use machines	The LUCENTIS treatment procedure may induce temporary visual disturbances which may affect the ability to drive or use machines (see section 4.8). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.	The LUCENTIS treatment procedure may induce temporary visual disturbances which may affect the ability to drive or use machines (see section 4.8). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

4.8 Undesirable effects	~~A total of 1,323 patients have been included in three phase III studies. A total of 859 patients were exposed to LUCENTIS for at least 12 months and 452 were exposed for 24 months. 9,200 LUCENTIS injections were administered during the first year of treatment and more than 13,000 injections if the second year of study FVF2598g (MARINA)) is included. 440 patients were treated at the recommended dose of 0.5 mg.~~ The serious adverse events related to the injection procedure ~~which occurred in < 0.1%of intravitreal injections~~ included endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see section 4.4). The other serious ocular adverse reactions occurring in patients treated with LUCENTIS, ~~which occurred in < 1% of patients,~~ included intraocular inflammation and increased intraocular pressure (see section 4.4). The adverse events listed below occurred at a higher rate (at least ~~3~~%) points in patients receiving treatment with LUCENTIS 0.5 mg than in those receiving a control treatment (sham or verteporfin PDT) in the three controlled phase III studies, FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER). These were therefore considered potential adverse drug reactions. The safety data described below also include all adverse events suspected of being at least potentially due to the injection procedure or to the drug in the 440 patients (from the three studies combined) treated with 0.5 mg.	Population with neovascular AMD The safety evaluation in neovascular AMD involved a total of 1,315 patients in the three phase III studies with 24 months exposure to LUCENTIS and 440 patients were treated at the recommended dose of 0.5 mg. The serious adverse events related to the injection procedure included endophthalmitis, rhegmatogenous retinal detachment, retinal tears and iatrogenic traumatic cataracts (see section 4.4). The other serious adverse events occurring in patients treated with LUCENTIS included intraocular inflammation and increased intraocular pressure (see section 4.4). The adverse events listed below occurred at a higher rate (at least 2%) in patients treated with LUCENTIS 0.5 mg than in those receiving control treatment (sham or verteporfin PDT) in the three controlled phase III studies FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER) in neovascular AMD. These were therefore considered potential adverse drug reactions. The safety data described below also include all adverse effects (in at least 0.5% points of patients) suspected to be at least potentially related to the injection procedure or medicinal product in 440 patients suffering from neovascular AMD (three studies combined) treated with 0.5 mg. DME population The safety of LUCENTIS was studied in a one year sham-controlled study (RESOLVE) and in a one year laser-controlled study (RESTORE) conducted respectively in 102 and 235 ranibizumab treated patients with visual impairment due to DME (see section 5.1). Only the event of “urinary tract infection” was classed in the “common” frequency category in the table of adverse effects below; otherwise ocular and non-ocular events in the RESOLVE and RESTORE studies were reported with a frequency and severity similar to those seen in the wet AMD studies. RVO population The safety of LUCENTIS was studied in two 12 month studies (BRAVO and CRUISE) conducted in 264 and 261 ranibizumab-treated patients with visual impairment due to macular

	The adverse reactions are listed by system organ class and frequency using the following convention: (very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000) and very rare (< 1/10 000), not known (cannot be estimated from the available data). Within in each frequency grouping, adverse reactions are presented in order of decreasing seriousness. ~~**Cardiac disorders:**~~ ~~*Uncommon*~~ ~~Atrial fibrillation~~ **Nervous system disorders:** *Very common* Headaches: **Eye disorders** *Very common* Conjunctival haemorrhage, eye pain, vitreous floaters, retinal haemorrhage, increase in ocular pressure, vitreous detachment~~, intraocular inflammation~~, eye irritation, cataract, foreign body sensation in the eye, visual disturbance, blepharitis~~, subretinal fibrosis,~~ ocular hyperaemia, visual disturbance/reduced visual acuity, dry eye, hyalitis. *Common* Eye discomfort, conjunctival, hyperaemia, opacification of the posterior capsule, ~~retinal exsudates~~, ~~reactions at the injection site,~~ increased tear secretion, eye pruritus, conjunctivitis, ~~maculopathy~~, retinal pigment epithelium detachment. *Uncommon* Retinal degeneration, iritis, iridocyclitis, punctate keratitis ~~superficial~~, keratopathy, ~~dellen effect,~~	oedema secondary to branch RVO and central RVO respectively, (see section 5.1). Ocular and non-ocular events in the BRAVO and CRUISE studies were reported with frequency and severity similar to those seen in the wet AMD studies. The adverse reactions are listed by system organ class and frequency using the following convention: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. **Infections and infestations** *Very common* Naso-pharyngitis *Common* Urinary tract infection* **Blood and lymphatic system disorders** *Common* Anaemia **Immune system disorders:** *Common* Hypersensitivity **Psychiatric disorders** *Common* Anxiety **Nervous system disorders:** *Very common* Headaches: **Ocular disorders** *Very common* Vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritus. *Common* Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous

	corneal striae, retinal disorder~~, vitreous disorder,~~ photophobia, ~~nuclear cataract,~~ Tyndall effect in the anterior chamber, corneal abrasion, ~~closed angle glaucoma,~~ vitreous haemorrhage, uveitis, endophthalmitis, retinal detachment, retinal tear, ocular haemorrhage, eyelid oedema, eyelid irritation, blindness, corneal oedema, hypopyon **Respiratory, thoracic and mediastinal disorders** *Uncommon* Cough~~, wheeze, Increased upper respiratory tract secretions~~ **Gastrointestinal disorders** *Common* Nausea **Skin and subcutaneous tissue disorders:** ~~*Uncommon* Lichenoid keratosis~~ **Musculoskeletal and connective tissue disorders** *Common* Arthralgia~~, back pain~~ **Infections and infestations** *Common* ~~Bronchitis,~~ anaemia ~~**Vascular disorders:**~~ ~~*Very common* Hypertension increased arterial blood pressure~~	haemorrhage, vitreous disorder, uveitis iritis, iridocyclitis, cataract, subcapsular cataract, posterior capsule opacification, punctate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eye oedema, eyelid pain, conjunctival hyperaemia *Uncommon* Blindness, endophthalmitis, hypopyon, hyphaema, keratopathy, iris adhesion, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation. **Respiratory, thoracic and mediastinal disorders** *Common* Cough **Gastrointestinal disorders** *Common* Nausea **Skin and subcutaneous tissue disorders:** *Common* Allergic reactions (rash, urticaria, pruritus, erythema) **Musculoskeletal and connective tissue disorders** *Very common* Arthralgia **Investigations** *Very common* Intraocular pressure increased * observed only in DME population **Adverse effects listed by class**: in the phase III neovascular AMD studies, the overall frequency of non-ocular haemorrhages, an adverse event potentially related to systemic VEGF (vascular endothelial growth factor) was slightly increased in ranibizumab-treated patients. However, there was no consistent pattern amongst the different haemorrhages. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors A low incidence rate of arterial thromboembolic events was observed in the LUCENTIS clinical trials in patients with

	~~A link between arterial thromboembolic events as defined by the Antiplatelet Trialists' Collaboration, including vascular deaths, non-fatal myocardial infarctions, non-fatal ischaemic cerebrovascular accidents and non-fatal cerebrovascular accidents and systemic exposure to very potent VEGF (vascular endothelial growth factor) inhibitors has been identified. When the 1 year data from the three phase III studies (MARINA, ANCHOR and PIER) were combined, the overall incidence of arterial thromboembolic events was higher in patients treated with LUCENTIS 0.5 mg (2.5%) than in patients in the control group (1.1%). During the second year of the MARINA study, however, the incidence of arterial thromboembolic events was similar in patients treated with LUCENTIS 0.5 mg (2.6%) and in patients in the control group (3.2%).~~	AMD, DME and RVO and there were no major differences between the groups treated with ranibizumab compared with the control.
4.9 Overdose	~~As LUCENTIS must be administered by a qualified ophthalmologist experienced in intravitreal injections the risk of overdose is very low. Only 2 cases of accidental overdose have been reported in clinical trials. One patient was given 1.2 mg of LUCENTIS instead of the intended dose at randomisation (0.3 mg) whereas the second patient was treated with 2.0 mg instead of 0.5 mg. No adverse effects were associated with these overdoses except for slight transient increases in intraocular pressure.~~ In the event of overdose, intraocular pressure must be monitored and treated, if deemed necessary by the attending ophthalmologist.	Cases of accidental overdose have been reported from the clinical studies in wet AMD and post-marketing data. Adverse reactions associated with these cases were a rise in intraocular pressure, transient blindness, reduced visual acuity, corneal oedema, corneal pain and eye pain. In the event of overdose, intraocular pressure must be monitored and treated, if deemed necessary by the attending ophthalmologist.
5.1 Pharmacodynamic properties	Pharmacotherapeutic group: other ophthalmologicals, ATC code: S01LA04 Ranibizumab is a humanised, recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$), therefore preventing binding of VEGF-A to the receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration. In wet AMP, the clinical safety and efficacy of LUCENTIS have been evaluated in three randomised, double-masked, sham- or	Pharmacotherapeutic class: anti-neovascularisation agents, ATC code: S01LA04 Ranibizumab is a humanised, recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$), therefore preventing binding of VEGF-A to the receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO. Treatment of wet DME In wet AMP, the clinical safety and efficacy of LUCENTIS have been evaluated in three randomised, double-masked, sham- or

active-controlled studies in patients with neovascular AMD. A total of 1323 patients (879 active and 444 sham injections) were enrolled in these studies.

In study FVF2598g (MARINA), in patients with minimally classic or occult with no classic choroidal neovascularisation (CNV) received monthly intravitreal injections of LUCENTIS 0.3 mg or 0.5 mg or sham injections. A total of 716 patients were included in this study (sham injection, 238; LUCENTIS 0.3 mg, 238; LUCENTIS 0.5 mg, 240). ~~Patients were followed up for 24 months.~~

In study FVF2587g (ANCHOR), in patients with predominantly classic choroidal neovascularisation (CNV) received either: 1) intravitreal monthly injections of 0.3 mg LUCENTIS and sham PDT; 2) monthly intravitreal injections of LUCENTIS 0.5 mg and sham PDT; or 3) intravitreal sham injections and active verteporfin PDT. Sham or active verteporfin PDT was administered with an initial injection of LUCENTIS then every 3 months if fluorescein angiography showed persistence or recurrence of vascular diffusion. A total of 423 patients were included in this study (sham injection, 143; LUCENTIS 0.3 mg, 140; LUCENTIS 0.5 mg, 140). Patients were followed up for 12 months.

~~In both studies the primary efficacy endpoint was the proportion of patients who maintained vision defined as losing <15 letters of visual acuity at 12 months compared with baseline. Almost all patients treated with LUCENTIS (approximately 95%) preserved their visual acuity. 34 to 40% of LUCENTIS treated patients experienced a clinically significant improvement in the vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not influence the results significantly. Generally, the patients with low visual acuity (< 20/200) when treatment was started benefited from treatment. Conversely, wet AMD which evolved into lesions with subretinal fibrosis and advanced geographical atrophy did not appear to respond to LUCTENTIS treatment. The detailed results are shown in the table below.~~

Table 1 Outcomes at Month 12 and Month 24 in study FVF2598g (MARINA)

Table 1 Outcomes at Month 12 and Month 24 in study FVF2598g (Marina)

Outcome measure	Month	Sham (n=238)	Lucentis 0.5 mg
Loss of <15 letters in visual acuity (%)[a]	Month 12	62%	95%
	Month 24	53%	90%

active-controlled studies of 24 months duration in patients with neovascular AMD. A total of 1323 patients (879 active and 444 sham injections) were enrolled in these studies.

In study FVF2598g (MARINA), 716 patients with minimally classic or occult with no classic choroidal neovascularisation (CNV) AMD received monthly intravitreal injections of LUCENTIS 0.3 mg (n=238), 0.5 mg (n=240) or sham injections (n=238).

In study FVF2587g (ANCHOR), 423 patients with predominantly classic choroidal neovascularisation (CNV) received either: 1) monthly intravitreal injections of LUCENTIS 0.3 mg and sham PDT (n=140); 2) monthly intravitreal injections of LUCENTIS 0.5 mg and sham PDT (n=140); or 3) sham intravitreal injections and active verteporfin PDT (n=143). Sham or active verteporfin PDT was given with the initial LUCENTIS injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of vascular diffusion.

Key outcome measures are summarised in Tables 1 and 2 and Figure 1.

Table 1 Outcomes at Month 12 and Month 24 in study FVF2598g (MARINA)

Gain of ≥ 15 letters in visual acuity (%)[a]	Month 12	5%	34%
	Month 24	4%	33%
Mean change in visual acuity (letters) (SD)[a]	Month 12	-10.5 (16.6)	+7.2 (14.4)
	Month 24	-14.9 (18.7)	+6.6 (16.5)

[a]p<0.01

Table 2 Outcomes at Month 12 and Month 24 in study FVF2587g (ANCHOR)

Outcome measure	Verteporfin PDT (n=143)	Lucentis 0.5 mg (n=140)
Loss of <15 letters in visual acuity (%}a	64%	96%
Gain of ≥ 15 letters in visual acuity (%)a	6%	40%
Mean change in visual acuity (letters) (SD)a	-9.5 (16.4)	+11.3 (14.6)

[a]p<0.01

Figure 1 **Mean change in visual acuity from baseline to Month 24 months in study FVF2598g (MARINA) ~~and at 12 months~~ in study FVF2587g (ANCHOR).**

Study FVF2598g

Outcome measure	Month	Sham (n=238)	Lucentis 0.5 mg (n=240)
Loss of <15 letters in visual acuity (%)[a] (maintenance of vision, primary endpoint)	Month 12	62%	95%
	Month 24	53%	90%
Gain of ≥15 letters in visual acuity (%)[a]	Month 12	5%	34%
	Month 24	4%	33%
Mean change in visual acuity (letters) (SD)[a]	Month 12	-10.5 (16.6)	+7.2 (14.4)
	Month 24	-14.9 (18.7)	+6.6 (16.5)

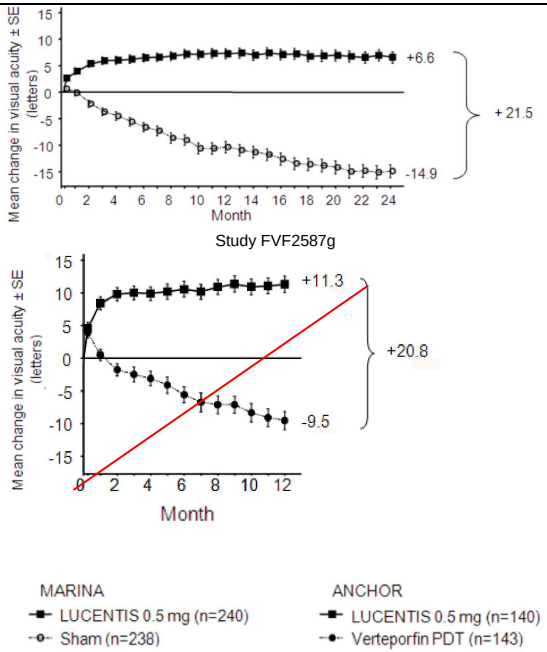
[a] p<0.01

Table 2 Outcomes at Month 12 and Month 24 in study FVF2587g (ANCHOR)

Outcome measure	Month	Verteporfin PDT (n=143)	Lucentis 0.5 mg (n=140)
Loss of <15 letters in visual acuity (%)[a] (maintenance of vision, primary endpoint)	Month 12	64%	96%
	Month 24	66%	90%
Gain of ≥15 letters in visual acuity (%)[a]	Month 12	6%	40%
	Month 24	6%	41%
Mean change in visual acuity (letters) (SD)[a]	Month 12	-9.5 (16.4)	+11.3 (14.6)
	Month 24	-9.8 (17.6)	+10.7 (16.5)

[a] p<0.01

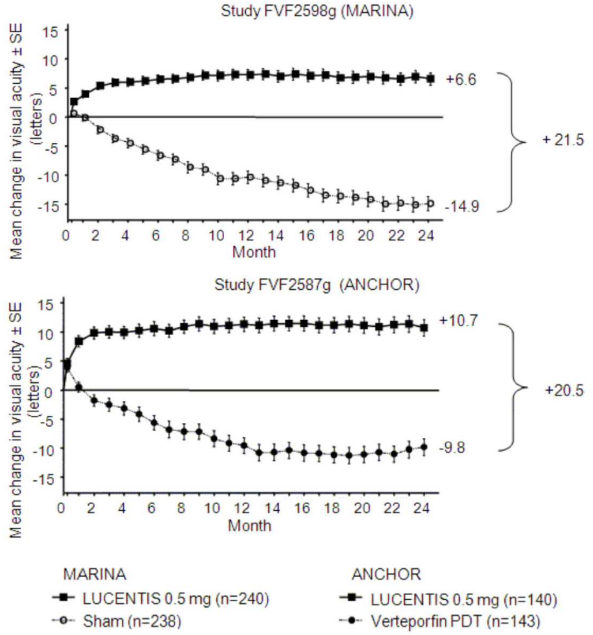
Figure 1 Mean change in visual acuity at 24 months in study FVF2598g (MARINA) and in study FVF2587g (ANCHOR), compared with baseline visual acuity.



~~Overall, patients in the LUCENTIS treated groups had scarcely identifiable increase in their CNV lesions. At month 12, the mean change in total surface area of the CNV lesions was 0.1-0.3 papillary surface areas for LUCENTIS compared with 2.3-2.6 disc surface areas for the control groups.~~

The use of LUCENTIS beyond ~~24~~ months has not been studied.

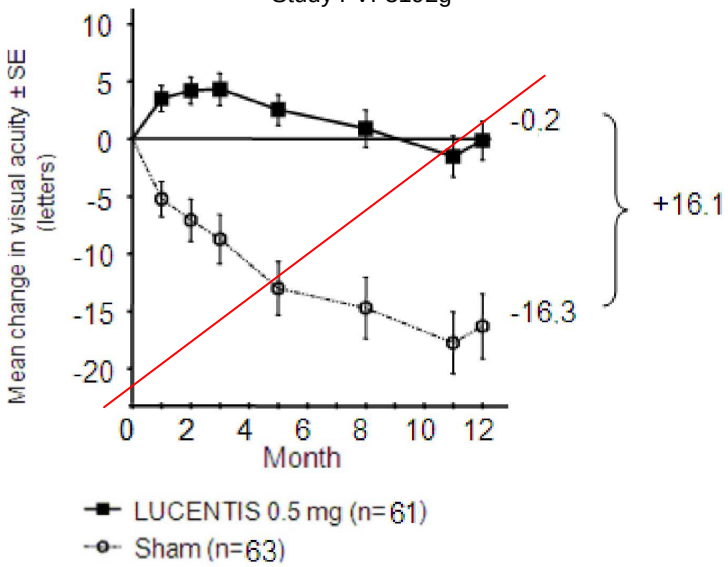
Study FVF3192g (PIER) was a ~~two-year~~ randomised, double-masked, sham-controlled study designed to evaluate the safety and efficacy of LUCENTIS in 184 patients with all forms of neovascular AMD (~~79% of patients had "minority classic" occult AMD, 21% had "classical" CNV).~~ ~~Data are available until the end of month 12.~~ Patients receive LUCENTIS 0.3 mg or 0.5 mg or sham injections once a month for 3 consecutive doses followed by a dose administered once every 3 months. ~~In total, 184 patients were included in this study (LUCENTIS 0.3 mg, 60; LUCENTIS 0.5 mg, 61; sham injections, 63); 171 (93%) patients completed the 12 months of this study. The patients treated with LUCENTIS in the PIER study received an average of 6 treatments out of the possible 6 treatments between day 0 and 12 months.~~



Results from both trials indicated that continued ranibizumab therapy may also be of benefit in patients who lost ≥ 15 letters of best-corrected visual acuity (BCVA) in the first year of treatment.

The use of LUCENTIS beyond 36 months has not been studied.

Study FVF3192g (PIER) was a randomised, double-masked, sham-controlled study designed to evaluate the safety and efficacy of LUCENTIS in 184 patients with all forms of neovascular AMD. Patients received LUCENTIS 0.3 mg (n=60) or 0.5 mg (n=61) intravitreal injections or sham (n=63) injections once a month for 3 consecutive doses followed by a dose administered once every 3 months. From Month 14 of the study, sham-treated patients were allowed to cross over to received LUCENTIS and from Month 19 more frequent treatments were possible. Patients treated with LUCENTIS in PIER received a mean of 10 total injections.

	The primary efficacy endpoint in the PIER study was mean change in visual acuity at 12 months compared with baseline (~~see Figure 2~~). After an initial increase in visual acuity (following monthly dosing) ~~on average, patients' visual acuity declined with quarterly dosing returning to baseline at month 12. In the PIER study almost all patients treated with LUCENTIS (90%) preserved their visual acuity at month 12.~~ **~~Figure 2 Mean change in visual acuity at 12 months in stud FVF3192g (PIER) compared with baseline visual acuity~~** Study FVF3192g  ~~Preliminary~~ data from an open label study (PROTECT), ~~in~~ which the safety of ~~administration~~ of verteporfin PDT and LUCENTIS 0.5 mg on the same day was evaluated, showed ~~that~~ the incidence of intraocular inflammation ~~after the initial dual therapy was low~~ (2 out of 32 patients, ~~6.3%).~~ In both the MARINA and ANCHOR studies the improvement in visual acuity seen with LUCENTIS 0.5 mg at 12 months with ~~resulted in~~ patient reported benefits. These were estimated using ~~these three subscales~~ the National Eye Institute visual function questionnaire (VFQ-25) ~~which were pre-specified, secondary efficacy endpoints (close vision activities, distance vision activities and vision related dependency). On average, the three scores~~	The primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline. After an initial increase in visual acuity (following monthly dosing), on average, patients' visual acuity declined with quarterly dosing returning to baseline at Month 12 and this effect was maintained in most ranibizumab treated patients (82%) at Month 24. Data from a limited number of subjects that crossed over to receive LUCENTIS after more than one year of sham treatment suggested that early initiation of treatment may be associated with a better preservation of visual acuity. Data from an open label study (PROTECT), during which the safety of administration of verteporfin PDT and LUCENTIS 0.5 mg given on the same day was evaluated in 32 patiennts followed up for 9 months, showed an incidence of intraocular inflammation after initial treatment of 6.3% (2 out of 32 patients). In both the MARINA and ANCHOR studies, the improvement in visual acuity seen with LUCENTIS 0.5 mg at 12 months was accompanied by patient-reported benefits as measured by the National Eye Institute Visual Function Questionnaire (VFQ-25) scores. The differences between LUCENTIS 0.5 mg and the two control groups were evaluated with p-values ranging from 0.009 to < 0.0001. Treatment of visual impairment due to DME The efficacy and safety of LUCENTIS have been evaluated in two

~~improved in the MARINA study in patients treated with LUCENTIS and deteriorated in the control group receiving the sham injections. In the ANCHOR study in patients receiving verteporfin PDT the mean scores for close or distance vision activities improved in a smaller proportion of patients whereas visual dependency increased. All~~ the differences between the LUCENTIS 0.5 mg and the two control groups ~~were statistically significant and clinically relevant~~, with p-values of between 0.009 and < 0.0001~~. In the MARINA study the differences were greater at 24 months compared with treatment with sham injections (*p* < 0.0001 for the three subscales).~~

randomised, double-masked, sham- or active-controlled studies of 12 months duration in patients with visual impairment due to diabetic macular oedema. A total of 496 patients (336 active and 160 control control) were enrolled in these studies. The majority had type 2 diabetes; 28 ranibizumab treated patients had type I diabetes.

In the phase II study D2201 (RESOLVE), 151 patients were treated with ranibizumab (6 mg/ml, n = 51, 10 mg/ml, n = 51) or sham injections (n = 49) by monthly intravitreal injections until pre-defined treatments stopping criteria were met. The initial ranibizumab dose (0.3 mg or 0.5 mg) could be doubled at any time during the study after the first injection. Laser photocoagulation was allowed as rescue treatment from month 3 in both treatment arms. The study had two parts: an exploratory part (the first 42 patients analysed at Month 6) and a confirmatory part (the remaining 109 patients analysed at Month 12).

Key outcome measures from the confirmatory part of the study (2/3 of patients) are summarised in table 3.

Table 3 Outcomes at Month 12 in study D2201 (RESOLVE) - Overall study population

Outcome measure	Ranibizumab pooled (n=102)	Sham (n=49)
Mean average change in BCVA from Month 1 to Month 12 compared to baseline[a] (letters) (SD) (primary endpoint)	+7.8 (7.72)	-0.1 (9.77)
Mean change in BCVA at Month 12[a] (letters) (SD)	+10.3 (9.14)	-1.4 (14.16)
Gain of ≥10 letters in BCVA (%) at Month 12[a]	60.8	18.4
Gain of ≥15 letters in BCVA (%) at Month 12	32.4	10.2
p-value	0.0043	

[a]p<0.0001

In phase III study D2301 (RESTORE), 345 patients with visual impairment due to macular oedema were randomised to receive either intravitreal injection of ranibizumab 0.5 mg as monotherapy and sham laser photocoagulation (n=116), combined ranibizumab 0.5 mg and laser photocoagulation (n=118), or sham injection and lase photocoagulation (n=111). Treatment with ranibizumab was started with monthly intravitreal injections and continued until visual acuity was stable for at least three consecutive monthly evaluations.

The treatment was reinitiated when a reduction in BCVA due to DME progression was observed. Laser photocoagulation was administered at baseline on the same day, at least 30 minutes before injection of ranibizumab and then as needed based on ETDRS criteria.

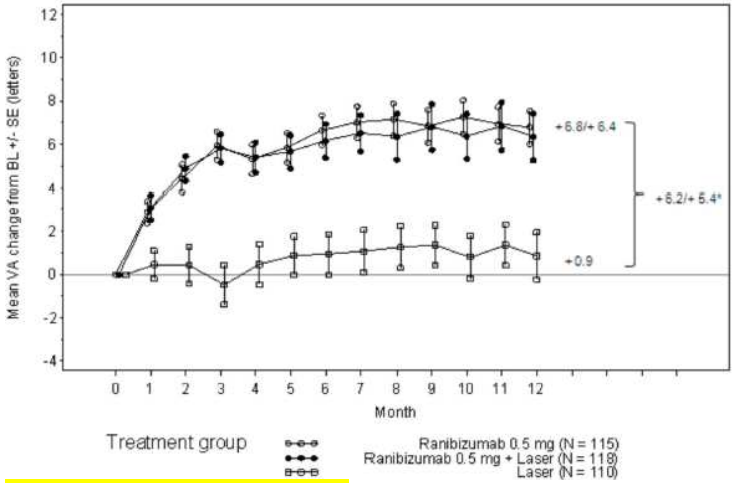
Key outcome measures are summarised in table 4 and figure 2.

Table 4 Outcomes at Month 12 in study D2301 (RESTORE)

Outcome measure compared to baseline	Ranibizumab 0.5 mg n=115	Ranibizumab 0.5 mg + Laser n=118	Laser n=110
Mean average change in BCVA from Month 1 to Month 12[a] (±SD)	6.1 (6.4)	5.9 (7.9)	0.8 (8.6)
Gain of ≥10 letters or BCVA ≥84[a] (%)	37.4	43.2	15.5
Gain of ≥15 letters or BCVA ≥84 (%)	22.6	22.9	8.2
p-value	0.0032	0.0021	

[a]p<0.0001

Figure 2 Mean change in visual acuity from baseline over time in study D2301 (RESTORE)



SE = standard error of the mean
* Difference in least square means, $p < 0.0001/0.0004$, based on two-sided, stratified, Cochran-Mantel-Haenszel test)

This effect was consistent in most sub-groups. However, subjects with a fairly good baseline BCVA (> 73 letters) together with macular oedema with central retinal thickness of < 300 µm did not appear to benefit from treatment with ranibizumab compared with laser photocoagulation.

The improvement in visual acuity seen with LUCENTIS 0.5 mg at 12 months was accompanied by patient-reported benefits with regards to most vision-related functions as measured by the National Eye Institute Visual Function questionnaire (VFQ-25) scores. For other subscales of this questionnaire, no treatment differences could be established. The difference between LUCENTIS 0.5 mg and the control group was demonstrated with p-values of 0.0137 (ranibizumab mono) and 0.0041 (ranibizumab+laser) for the VFQ-25 composite score.

In both studies, the improvement in vision was accompanied by a continuous decrease in the macular oedema as measured by central retinal thickness (CRT).

Treatment of visual impairment due to macular oedema secondary to RVO
The clinical safety and efficacy of LUCENTIS in patients with visual impairment due to macular oedema secondary to RVO have been evaluated in the randomised, double-masked, controlled studies

BRAVO and CRUISE that recruited subjects with BRVO (n = 397) and CRVO (n = 392) respectively. In both studies subjects received either 0.3 mg or 0.5 mg intravitreal ranibizumab or sham injections. After 6 months, patients in the sham-control arms were crossed over to 0.5 mg ranibizumab. In BRAVO, laser photocoagulation as rescue was allowed in all arms from Month three.

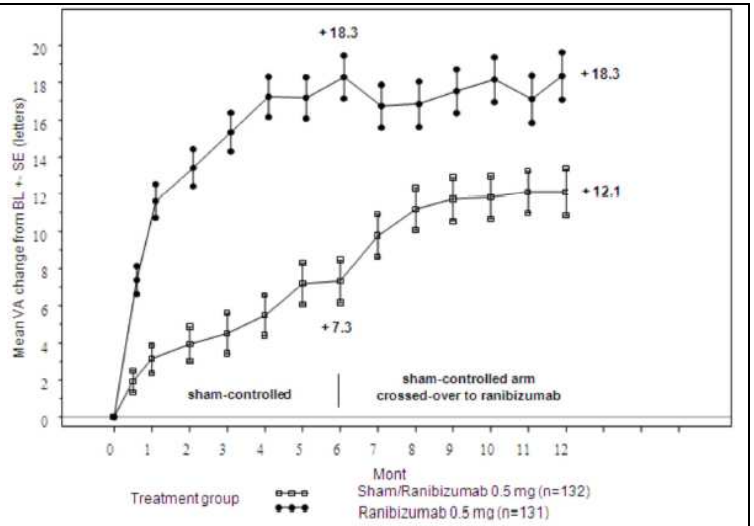
Key outcome measures from BRAVO and CRUISE are summarised in tables 5 and 6 and figures 3 and 4.

Table 5 Outcomes at Month 6 and 12 (BRAVO)

	Sham/Lucentis 0.5 mg (n=132)	Lucentis 0.5 mg (n=131)
Mean change in visual acuity at Month 6[a] (letters) (SD) (primary endpoint)	7.3 (13.0)	18.3 (13.2)
Mean change in BCVA at Month 12 (letters) (SD)	12.1 (14.4)	18.3 (14.6)
Gain of ≥15 letters in visual acuity at Month 6[a] (%)	28.8	61.1
Gain of ≥15 letters in visual acuity at Month 12 (%)	43.9	60.3
Proportion (%) receiving laser rescue over 12 months	61.4	34.4

[a]p<0.0001

Figure 3 Mean change from baseline BCVA over time to Month 6 and Month 12 (BRAVO)



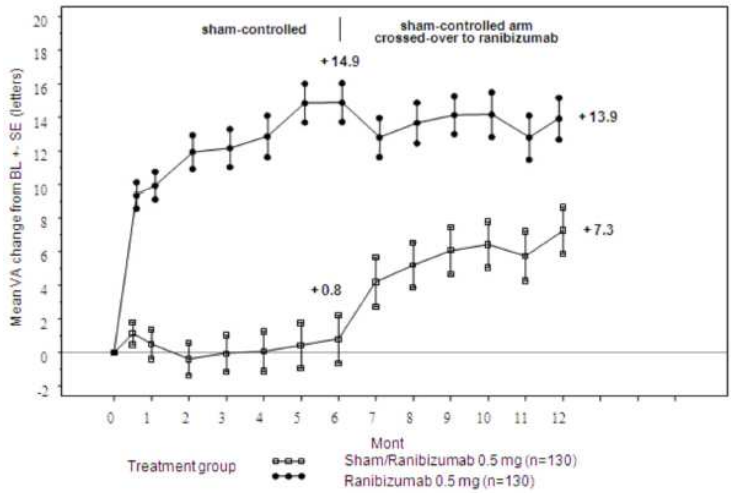
BL=baseline; SE=standard error of mean

Table 6 Outcomes at Month 6 and 12 (CRUISE)

	Sham/Lucentis 0.5 mg (n=130)	Lucentis 0.5 mg (n=130)
Mean change in visual acuity at Month 6[a] (letters) (SD) (primary endpoint)	0.8 (16.2)	14.9 (13.2)
Mean change in BCVA at Month 12 (letters) (SD)	7.3 (15.9)	13.9 (14.2)
Gain of ≥15 letters in visual acuity at Month 6[a] (%)	16.9	47.7
Gain of ≥15 letters in visual acuity at Month 12 (%)	33.1	50.8

[a]p<0.0001

Figure 4 Mean change from baseline BCVA over time to Month 6 and Month 12 (CRUISE)



BL=baseline; SE=standard error of mean

In both studies, the improvement in vision was accompanied by a continuous and significant reduction in macular oedema as measured by central retinal thickness.

In patients with BRVO (BRAVO and extension study HORIZON): After 2 years, subjects that were treated with sham in the first 6 months and subsequently crossed over to ranibizumab treatment had achieved comparable gains in VA (□15 letters) compared with subjects that were treated with ranibizumab from study start (□16 letters). However, the number of patients completing 2 years was limited and in HORIZON only quarterly monitoring visits were scheduled. Therefore there is currently insufficient evidence to conclude on recommendations as to when ranibizumab treatment should be initiated in patients with BRVO.

In patients with CRVO (CRUISE and extension study HORIZON): After 2 years, subjects that were treated with sham in the first 6 months and subsequently crossed over to ranibizumab treatment did not achieve comparable gains in VA (□6 letters) compared with subjects that were treated with ranibizumab from the study start (□12 letters).

The improvement in visual acuity observed with ranibizumab treatment at 6 and 12 months was accompanied by patient-reported benefits as measured by the National Eye Institute Visual Function questionnaire (VFQ-25) subscales related to near and distance

		activity. The difference between LUCENTIS 0.5 mg and the control group was evaluated at Month 6 with p-values of 0.02 and 0.0002. *Paediatric population* The safety and efficacy of ranibizumab have not yet been studied in paediatric patients. The European Medicines Agency has waived the obligation to submit the results of studies with LUCENTIS in all sub-sets of the paediatric population in neovascular AMD, visual impairment due to diabetic macular oedema and visual impairment due to macular oedema secondary to retinal vein occlusion (see section 4.2 for information on paediatric use).
5.2 Pharmacokinetic properties	Following monthly intravitreal administration of LUCENTIS to patients with neovascular AMD, serum concentrations of ranibizumab are generally low with maximum levels (C_{max}) generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (11-27 ng/ml, as evaluated in an *in vitro* cellular proliferation assay). C_{max} was dose-proportional over the dose range of 0.05 to 1.0 mg/eye. Based on an analysis of population pharmacokinetics and disappearance of ranibizumab from serum for patients treated with the 0.5 mg dose, the average vitreous elimination half-life of ranibizumab is approximately ~~10~~ days. Upon monthly intravitreal administration of LUCENTIS 0.5 mg/eye, the serum ranibizumab C_{max} attained approximately 1 day after dosing is predicted to generally range between 0.79 and 2.90 ng/ml and C_{min} is predicted to generally range between 0.07 and 0.49 ng/ml. Serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal ranibizumab concentrations. Patients with renal impairment: No formal studies have been conducted to examine the pharmacokinetics of LUCENTIS in patients with renal impairment. In a population pharmacokinetic analysis, 68% (136 of 200) of patients had renal impairment (46.5% mild [50-80 ml/min], 20% moderate [30-50 ml/min] and 1.5% severe [< 30 ml/min]). Systemic clearance was slightly lower but this was	Following monthly intravitreal administration of LUCENTIS to patients with neovascular AMD, serum concentrations of ranibizumab are generally low with maximum levels (C_{max}) generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (11-27 ng/ml, as evaluated in an *in vitro* cellular proliferation assay). C_{max} was dose-proportional over the dose range of 0.05 to 1.0 mg/eye. Serum concentrations in a limited number of DME patients indicate that a slightly higher systemic exposure cannot be excluded compared with those observed in neovascular AMD patients. Serum ranibizumab concentrations in RVO patients were similar or slightly higher compared with those observed in neovascular AMD patients. Based on an analysis of population pharmacokinetics and disappearance of ranibizumab from the serum for patients with neovascular AMD treated with the 0.5 mg dose, the average vitreous elimination half-life of ranibizumab is approximately 9 days. Upon monthly intravitreal administration of LUCENTIS 0.5 mg/eye, the serum ranibizumab C_{max} attained approximately 1 day after dosing is predicted to generally range between 0.79 and 2.90 ng/ml and C_{min} is predicted to generally range between 0.07 and 0.49 ng/ml. Serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal ranibizumab concentrations. Patients with renal impairment: No formal studies have been conducted to examine the pharmacokinetics of LUCENTIS in patients with renal impairment. In a population pharmacokinetic analysis of neovascular AMD patients, 68% (136 of 200) of patients had renal impairment (46.5% mild [50-80 ml/min], 20% moderate [30-50 ml/min] and 1.5% severe [< 30 ml/min]). In RVO patients, 48.2% (253/525) had renal impairment (36.4% mild, 9.5% moderate and 2.3% severe). Systemic clearance was slightly lower but this

	not clinically significant. Hepatic impairment: No formal studies have been conducted to examine the pharmacokinetics of LUCENTIS in patients with hepatic impairment.	was not clinically significant. Hepatic impairment: No formal studies have been conducted to examine the pharmacokinetics of LUCENTIS in patients with hepatic impairment.
5.3 Preclinical safety data	Bilateral, intravitreal administration of ranibizumab to cynomolgus monkeys at doses between 0.25 mg/eye and 2.0 mg/eye once every 2 weeks for up to 26 weeks resulted in dose-dependent ocular effects. Intraocularly, there were dose-dependent increases in anterior chamber flare and cells with a peak 2 days after the injection. The severity of the inflammatory response generally diminished with subsequent injections or during recovery. In the posterior segment there were vitreal cell infiltration and floaters which also tend to be dose-dependent and generally persisted to the end of the treatment period. In the 26-week study the severity of the vitreous inflammation increased with the number of injections. However, evidence of reversibility was observed after recovery. The nature and timing of the posterior segment inflammation is suggestive of an immune-mediated antibody response, which may be clinically irrelevant. Cataract formation was observed in some animals after a relatively long period of intense inflammation, suggesting that the lens changes were secondary to severe inflammation. A transient increase in post-dose intraocular pressure was observed following intravitreal injections irrespective of dose. Microscopic ocular changes were related to inflammation and did not indicate degenerative processes. Granulomatous inflammatory changes were noted in the optic disc of some eyes. These posterior segment changes diminished and in some cases resolved during the recovery period. Following intravitreal administration, no signs of systemic toxicity were detected. The serum and vitreous antibodies to ranibizumab were found in a subset of treated animals. No carcinogenicity or mutagenicity data are available ~~or reproductive or developmental toxicity.~~	Bilateral, intravitreal administration of ranibizumab to cynomolgus monkeys at doses between 0.25 mg/eye and 2.0 mg/eye once every 2 weeks for up to 26 weeks resulted in dose-dependent ocular effects. Intraocularly, there were dose-dependent increases in anterior chamber flare and cells with a peak 2 days after the injection. The severity of the inflammatory response generally diminished with subsequent injections or during recovery.. In the posterior segment there were vitreal cell infiltration and floaters which also tend to be dose-dependent and generally persisted to the end of the treatment period. In the 26-week study the severity of the vitreous inflammation increased with the number of injections. However, evidence of reversibility was observed after recovery. The nature and timing of the posterior segment inflammation is suggestive of an immune-mediated antibody response, which may be clinically irrelevant. Cataract formation was observed in some animals after a relatively long period of intense inflammation, suggesting that the lens changes were secondary to severe inflammation. A transient increase in post-dose intraocular pressure was observed following intravitreal injections irrespective of dose. Microscopic ocular changes were related to inflammation and did not indicate degenerative processes. Granulomatous inflammatory changes were noted in the optic disc of some eyes. These posterior segment changes diminished and in some cases resolved during the recovery period. Following intravitreal administration, no signs of systemic toxicity were detected. The serum and vitreous antibodies to ranibizumab were found in a subset of treated animals. No carcinogenicity or mutagenicity data are available. In pregnant monkeys, intravitreal ranibizumab treatment resulting in maximum systemic exposures of 0.9-7 -fold a worst case clinical exposure did not elicit developmental toxicity or teratogenicity and had no effect on weight or structure of the placenta, although, based

		on its pharmacological effect ranibizumab should be regarded as potentially teratogenic and/or embryo-foetotoxic. The absence of ranibizumab-mediated effects on embryo-foetal development is plausibly related mainly to the inability of the Fab fragment to cross the placenta. Nevertheless, a case was described with high maternal ranibizumab serum levels and presence of ranibizumab in foetal serum, suggesting that the anti-ranibizumab activity acted as (Fc region containing) carrier protein for ranibizumab, thereby decreasing its maternal serum clearance and enabling its placental transfer. As the embryo-foetal development investigations were performed in healthy pregnant animals and disease (such as diabetes) may modify the permeability of the placenta towards a Fab fragment, this study should be interpreted with caution.
6.1 List of excipients	α,α-trehalose dihydrate Histidine hydrochloride monohydrate Histidine Polysorbate 20 Water for injections	α,α-trehalose dihydrate Histidine hydrochloride monohydrate Histidine Polysorbate 20 Water for injections
6.2 Incompatibilities	In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.	In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
6.3 Shelf life	~~18 months~~	3 years.
6.4 Special precautions for storage	Store in a refrigerator (2℃ - 8℃). Do not freeze. Keep the vial in the outer carton in order to protect from light.	Store in a refrigerator (2℃ - 8℃). Do not freeze. Keep the vial in the outer carton in order to protect from light.
6.5 Nature and contents of container	~~0.3~~ ml of solution in a vial (type I glass) with a stopper (chlorobutyl rubber), 1 filter needle, 1 injection needle and 1 syringe (polypropylene). ~~Pack~~ containing 1 vial.	0.23 ml of solution in a vial (type I glass) with a stopper (chlorobutyl rubber), 1 filter needle, 1 injection needle and 1 syringe (polypropylene). ~~Carton~~ containing 1 vial.
6.6 Special precautions for disposal and other handling	Vials for single use only.	Vials for single use only. To prepare LUCENTIS for intravitreal injection, please adhere to the following instructions: 1. Before withdrawing the contents of the bottle, the external part of the rubber bottle stopper must be disinfected. 2. Assemble the 5 µm filter needle (provided in the carton) onto the 1 ml syringe (provided in the carton) using aseptic technique. Push the tip of the filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial. 3. Withdraw all of the liquid from the vial keeping the vial in an upright position, slightly inclined to ease complete withdrawal. 4. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

	Any unused product or waste material should be disposed of in accordance with local requirements.	5. Leave the filter needle in the vial and disconnect the syringe from the filter needle. The filter needle should be discarded after withdrawal of the vial contents and should not be used for the intravitreal injection. 6. Aseptically and firmly assemble the injection needle (provided in the carton) onto the syringe. 7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe. Note: Grip at the yellow hub of the injection needle while removing the cap. 8. Carefully expel the air from the syringe and adjust the dose to the 0.05 ml mark on the syringe. The syringe is ready for injection. Note: Do not wipe the injection needle. Do not pull back on the plunger. Any unused product or waste material should be disposed of in accordance with local requirements.
7. MARKETING AUTHORISATION HOLDER	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex, RH12 5AB United Kingdom	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex, RH12 5AB United Kingdom
8. MARKETING AUTHORISATION NUMBER(S)	EU/1/06/374/001	EU/1/06/374/001
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION	22.01.2007	22.01.2007
10. DATE OF REVISION OF THE TEXT		

APPENDIX 2

OPINION OF GROUP
PUBLIC HEALTH BENEFIT AND POST-MARKETING STUDIES
ON THE RESULTS OF THE CROSS-OVER STUDY (December 2009)
AND 2-YEAR FOLLOW-UP (September 2012)
OF THE POST-MARKETING - LUCENTIS STUDY

PROTOCOL: LUEUR study: Study of LUCENTIS under real life conditions of use
VERSION: Interim Reports: Results of the cross-over study
2-year results (September 2012)

PROPRIETARY MEDICINAL PRODUCT: LUCENTIS
COMPANY: Novartis

1 Reminder of background and study request

LUCENTIS obtained European Marketing Authorisation on 22 January 2007 in the treatment of neovascular (wet) age-related macular degeneration (AMD). On 28 March 2007, the Transparency Committee approved inclusion on the list of medicines refundable by National Health Insurance and approved fro hospital use for LUCENTIS in this indication with a substantial AB in exsudative subfoveal AMD with a moderate expected public health benefit and a substantial IAB (level II). The Transparency Committee did not make a recommendation for the AB in extra-foveal AMD in the absence of efficacy data.

The Transparency Committee requested a study in its opinion of 28/03/2007. The wording reads:
"The Transparency Committee would like data on the follow-up of patients suffering from AMD treated with LUCENTIS in France. The purpose of this is to record the following information under actual treatment conditions:

- the conditions for starting treatment (characteristics of patients treated, previous treatments, concomitant treatments, etc.).
- the conditions of use for the proprietary medicinal product, particularly the dosage regimen (dosage and frequency of injections) and the methods used to monitor visual acuity,
- the impact of the treatment on the medium- and long-term change in visual acuity and on quality of life and avoidance of disability in these patients.
- the impact of safety on continuing the treatment,
- the predictive factors for response to treatment."

In its amendment of 24/05/2007 the **CEPS** reiterated its request for a study:
"The company undertakes to carry out a pharmaco-epidemiological study, also containing a medico-economic analysis, allowing the role and impact of LUCENTIS in the treatment of AMD in France to be evaluated, in particular taking account of orthoptic rehabilitation and visual aids. This study should provide an evaluation of the impact of the treatment on the medium- and long-term-change in visual acuity and on quality of life and avoidance of disability in these patients.
The conditions for starting treatment (characteristics of treated patients, previous treatments, concomitant treatments, etc.) the conditions of use of these treatments, particularly the dosage regimen (dosage and frequency of injections) and the methods to follow-up visual acuity, the impact of continuing treatment on safety and predictive factors for response to treatment should be identified. The size of the study, endpoints to measure impact and the follow-up period will be established by an independent scientific committee, the composition of which will be communicated to the Ministry of Health.
A detailed synopsis of the study must be provided to the Directorate-General for Health 4 months after signature of this amendment. The study must have started between now and the first quarter of 2008, an interim report submitted to the TC and to CEPS at 2 years and the final report within 5 years of signature of this amendment. Pursuant to the framework agreement, the Transparency Committee opinion will be obtained."

2 Summary of studies proposed in response to the request for studies

In order to respond to the study requests the company set up a prospective, multi-centre observational study in mainland France on a cohort of patients with wet AMD or who were being treated with LUCENTIS, regardless of indication. This study involved two sections:

- a cross-over section, intended to describe the characteristics of patients and their management (1000 to 1100 patients intended in the protocol, 1042 patients included from July 2008 to June 2009)
- a longitudinal section (total intended follow-up = 4 years) including patients suffering from wet AMD and being treated with LUCENTIS or MACUGEN, (pegaptanib, another anti-VEGF indicated in AMD), the primary objective of which was to describe the change in visual acuity at 2 years (500 patients intended, 534 patients included). The primary endpoint was the percentage of patients treated with LUCENTIS with successful treatment at 24 months. Treatment success was defined as a loss of visual acuity of < 15 letters compared with inclusion (according to the ETDRS scale).

A cost-effectiveness model has been proposed in order to evaluate the place of LUCENTIS (ranibizumab) in the treatment of neovascular AMD in France from real-life data from the LUEUR and OPV (VISUDYNE) studies. This model should initially include real-life data from MACUGEN. However, in view of the limited number of patients treated with MACUGEN in the LUEUR study (n=6), these data have not been included in the model.

This report shows the results of the cross-over study and the 2-year longitudinal study.

3 Characteristics of doctors taking part in the study and national representivity

Out of a total of 303 doctors identified, 97 (32%) agreed to take part in the study. 72 (74%) of these were active (including at least 1 patient) in the cross-over study, of which 67 (93% of active doctors in the cross-over study) were also active in the longitudinal study.

Twenty-one of the 72 doctors active in the study practised in hospital (29.2%), 38 (52.8%) in self-employed practices and 13 (18.1%) had mixed practices.
Most of the investigators were average prescribers (44.4%), treating between 15 and 29 patients per month with LUCENTIS or high prescribers (29.2%), treating over 30 patients.
Most of the investigating centres were in the South-East region (23.6%), Paris region (19.4%), or West (15.3%) or Centre-West (15.3%) regions.
The average number of patients included per centre was 14 and none of the 72 active centres recruited more than 40 patients, consistent with the protocol.

Representivity of the active centres compared with national data:

- fewer GP surgeries (58.3% compared with 65.9%), more non-university hospital hospitals (25% compared with 16.6%),
- more average prescribers (44.4% compared with 32.8%) or high prescribers (19.4% compared with 14.6%),
- same geographical distribution.

4 Main results of the transverse subgroup study

4.1. Patient characteristics at inclusion

The 72 active centres included 1042 patients, 1 of whom was included erroneously (the patient did not meet the inclusion criteria).
One thousand and nineteen (1019) of the 1041 eligible patients (97.9%) were suffering from neovascular AMD and 22 (2.1%) were being treated with LUCENTIS for other diseases (6 cases of diabetic macular oedema, 5 cases of myopathy, 6 central retinal vein occlusions, 2 angioid striae and 3 other indications).

More of the 1019 patients suffering from neovascular AMD were women (62.3%), with an average age of 78.7 years. The AMD also affected the contralateral eye in 37.9% of patients.
The analysis by eye revealed that 40.7% of eyes suffering from neovascular AMD had visible new vessels, 52.8% had occult new vessels and 6.5% had both types of new vessels.
Vessels were mostly located in the subfoveal area (84.6% of eyes) and more occasionally juxtafoveal (13.2%) or extrafoveal (2.2%).
The ETDRS score at inclusion of the eyes suffering from AMD was 49.1 (+/- 24.2) letters (median=55). The diagnosis of AMD had been made an average of almost 2 years previously (median = 1 year).

4.2. Description of prescription and management methods

4.2.1. Previous management

The proportion of eyes suffering from neovascular AMD treated only with LUCENTIS was 42.9%, in 24.4% of eyes LUCENTIS was combined with other treatments, in 15.8% of eyes the patients were receiving other treatments excluding LUCENTIS and 19.9% of eyes had never been treated.[30]
The per patient analysis showed that 44.2% of patients were only treated with LUCENTIS, 36.6% with LUCENTIS combined with other treatments, 8% with other treatments excluding LUCENTIS and 11.2% had never been treated. Almost half of the patients had received one previous treatment and slightly over a quarter of them had received two previous treatments.
The most common previous treatments were: LUCENTIS (80.8%), VISUDYNE (33.8%), AVASTIN (9.9%) or laser (8.4%).
Previous treatments differed between patients suffering from unilateral and bilateral AMD. More patients with unilateral disease have been treated with LUCENTIS alone (53.4%) than patients with bilateral disease (29%) and on the other hand fewer have been treated with LUCENTIS in combination (25.9% compared with 54.1%).

In terms of orthoptic management, a visual impairment assessment[31] was performed in 11.4% of patients, orthoptic rehabilitation sessions in 5.6% of patients and optical aids had been purchased by 17.2%.

[30] Nutritional supplements were not deemed to be treatments for AMD.
[31] Visual impairment assessments are generally only considered late in the process, when the VA has become particularly poor and has stabilised.

4.2.2. Treatment at inclusion

The decision was taken at the inclusion visit to treat with LUCENTIS in 46.3% of the eyes affected by neovascular AMD, to treat with other treatments than LUCENTIS in 4% and not to treat in 49.7% of eyes.
The anti-VEG, AVASTIN and MACUGEN were prescribed in 2.1% and 0.6% of eyes.
The per patient analysis revealed the following distribution:

- 602 patients treated with LUCENTIS
- 28 patients treated with AVASTIN
- 27 patients treated with PDT with VISUDYNE
- 9 patients treated with MACUGEN

5 Main results of the longitudinal subgroup study

5.1. Population of patients included and analysed

Of the 534 patients included in the longitudinal part, 517 were analysed. The reasons for exclusion from the analysis were: complete lack of follow-up in 7 patients (neither a patient questionnaire nor a consultation), no treatment with LUCENTIS during the follow-up in 6 previously untreated patients at inclusion (treatment was planned but not started) and treatment at inclusion with MACUGEN in 4 patients.

The average follow-up time of patients analysed in the study (taking account of visits to the study ophthalmologists and telephone interviews) was 22.87 ± 4.09 months (min = 2, max = 33, Q1 = 23, median = 24, Q3 = 25, DM = 7). Sixteen deaths (3.1%) were reported during the follow-up, 5 patients withdrew their consent and 1 patient was deemed “lost to follow-up” by the doctor. Four hundred and forty-three (443) of the remaining 494 patients (89.7%) had a visit at month 24. The average time between inclusion and the M24 visit was 23.92 ± 1.19 months.

There is no information on the living or deceased status of the 10.3% of patients who did not have a visit at month 24.

Eighty (80) of the 517 patients analysed (15.5%) had not previously been treated with LUCENTIS and 50 (9.7%) were similar to those in the pivotal studies (no previous treatment and ETDRS score between 25 and 70 letters before starting LUCENTIS in the treated eye).

Two hundred and six (206) patients (39.8%) had bilateral AMD at inclusion, of which 75 (36.4% of patients with bilateral disease) were treated with LUCENTIS in both eyes.

A total of 592 eyes were included in the analysis (“eyes” analysis population), including 90 eyes which had not previously been treated with LUCENTIS and 59 eyes which were similar to those in the pivotal studies.

5.2. Patient and eye characteristics at inclusion

5.2.1. Patient characteristics

Sixty-two per cent of patients treated with LUCENTIS were women. Average age at inclusion was 78 years old. Thirty-two per cent of the 490 patients whose smoking status was known were smokers or former smokers. A severe surgically untreated cataract was reported in 8.7% of patients. These characteristics were similar to those in patients not previously treated with LUCENTIS and to those in the pivotal studies.

5.2.2. Characteristics of the neovascular AMD at inclusion and previous treatments

The diagnosis of AMD had been made an average of 16.2 ± 25.1 months previously in the “eyes” analysis population, 7.3 ± 16.5 months in the previously untreated eyes and 3.6 ± 12.4 months for eyes similar to those in the pivotal studies.

The eyes previously untreated with LUCENTIS and those similar to the pivotal studies had fewer occult new vessels than those in the “eyes” analysis population: 37.8% and 40.7% respectively compared with 52.1%.

Most of the new vessels were subfoveal (75 to 82%), occasionally juxtafoveal (16 to 22%) but rarely extrafoveal (2 to 3%). Fibrous lesions and haematomas were reported in 19.4% and 12.2% of eyes in the “eyes” analysis population.

The average size of the lesion was 1.80 ± 1.54 papillary diameters in the “eyes” analysis population, 1.58 ± 1.21 papillary diameter in the eyes previously untreated with LUCENTIS and 1.42 ± 1.11 papillary diameter in the eyes similar to the pivotal studies. These figures were relatively similar to the average size of the lesions in the ANCHOR study (1.79 pap. diameter) but well below the average sizes of the lesions found in the MARINA study (4.5 pap diam) and the PIER study (4.04 papillary diameters).
Most of the eyes (85%) had been treated with LUCENTIS before they were included in the study. Fewer than 10% of the eyes beginning treatment with LUCENTIS at inclusion had been treated with VISUDYNE before beginning LUCENTIS treatment.
The average length of LUCENTIS treatment at inclusion was 8.1 ± 6.3 months (missing data points (MD) = 90, min = 0, Q1 = 3, median = 7, Q3 = 12, max = 33) (mean including previously untreated patients). The previously treated eyes had received an average of 3.7 ± 2.4 injections (MD = 2, min = 1, Q1 = 2, median = 3, Q3 = 4, max = 16).

5.2.3. Visual acuity at inclusion

Mean visual acuity in the eyes included was 55 ± 21 ETDRS letters for all eyes (DM=1). Although on average the diagnoses had been made more recently (7 months for the previously untreated eyes compared with 16 months for all eyes), the eyes which started LUCENTIS at inclusion had a lower visual acuity (46 ± 20 letters). These findings were similar to the average visual acuities at inclusion into the MARINA (54 ± 13 letters), ANCHOR (47 ± 13 letters) and PIER (54 ± 16 letters) studies.
Twenty-six eyes (4.4%) had a visual acuity of < 15 letters at inclusion.
Almost half of the 206 patients with bilateral disease, were poor sighted, (corrected visual acuity (47.3%) between 20 and 65 ETDRS letters in both eyes) and one patient was blind (legally blind, corrected VA < 20 ETDRS in both eyes).
The average composite functional VA score (VFQ-25) was 75.58 ± 19.03 in the 500 patients in the “patients” analysis population.

5.2.4. Functional status and living conditions of patients at inclusion

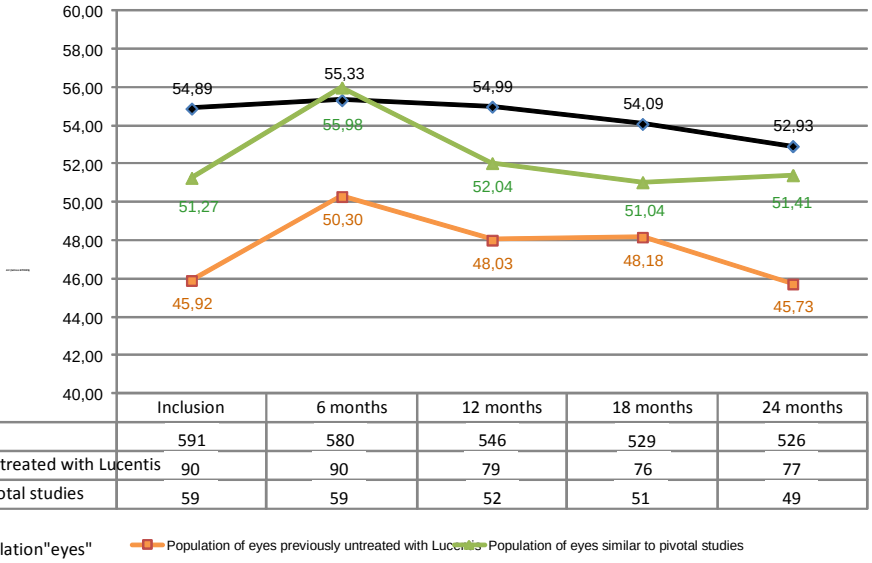
The patients’ disability has resulted in loss of independence in 7.2% of patients in the “eyes” analysis population and in 11.3% of the patients previously untreated with LUCENTIS.

The average total EQ-5D score at inclusion was 0.82 ± 0.17 for the 498 patients in the “patients” analysis population which is equivalent to the score generally seen in the population of this age.
Almost a third of patients (31%) had used a magnification system (optical or electronic) at inclusion.

The majority of patients were living in normal accommodation (98.2%). A slightly higher proportion of the patients previously untreated with LUCENTIS (4.0%) and patients similar to those in the pivotal studies (4.1%) were living in institutions compared with the “patient” analysis population (1.2%).

5.3. Change in visual acuity at 2 years

The average change in visual acuity in all of the eyes for which data were available (92% at 1 year and 89% at 2 years) was -1.2 letters (95%CI [-2.5; 0.2]) at 1 year and -3.4 letters (95%CI [-4.9; 1.7]) at 2 years.
For all previously untreated eyes for which data were available (88% at 1 year and 86% at 2 years), the average change in visual acuity was 1.3 letters (95%IC [-3.1; 5.9]) at 1 year and -0.6 letters (95%IC [-5.5; 4.3]) at 2 years.



Numbers	Inclusion	6 months	12 months	18 months	24 months
Analysis population"eyes"	591	580	546	529	526
Population of eyes previously untreated with Lucentis	90	90	79	76	77
Population of eyes similar to pivotal studies	59	59	52	51	49

Treatment success at 2 years, the primary endpoint of the study, was defined as a loss of visual acuity of fewer than 15 letters compared with inclusion. This endpoint was only defined for eyes which could lose 15 letters. Eyes in which visual acuity at inclusion was below 15 letters were therefore excluded from this analysis and deemed to be missing data in order to avoid overestimating the proportion of treatment successes.
On average in this study, treatment success at 2 years was 76% for both the group of eyes with available data (n=505, 14.7% missing data points) and for the subgroup population of eyes previously untreated with LUCENTIS at inclusion with available data (n=72, 20% missing data points).
A sensitivity analysis was carried out using missing data points at month 24 and the falls in visual acuity in patients with visual acuity < 15 letters at inclusion being defined as treatment failures and the improvement of visual acuity in patients with visual acuity of < 15 letters at inclusion as treatment successes. Treatment success in this situation of maximum bias was 66.2% for all eyes (results not available for previously untreated eyes).
In the MARINA and ANCHOR studies on patients previously untreated with LUCENTIS who received one monthly injection of LUCENTIS during the study, the success rates were 90.0% and 89.9% respectively at 2 years in the LUCENTIS group, 52.9% in the placebo group of the MARINA study and 65.7% in the VISUDYNE group (verteporfin) (treatment changed to LUCENTIS in 35% of patients at 18 months).
In the PIER study on patients previously untreated with LUCENTIS who received a monthly injection during the first 3 months followed by an injection of LUCENTIS every 3 months during the study (dosage regimen closer to the SPC), the success rate was 82% at 2 years in the LUCENTIS group and 41.3% in the Placebo group (treatment changed to LUCENTIS from 14 months in 60% of patients).

Almost half of the eyes (44.2%) gained at least 5 letters at 2 years in eyes previously untreated with LUCENTIS at inclusion. A quarter of the eyes previously untreated with LUCENTIS (26%) and 13.5% of the whole population achieved an improvement of more than 15 letters at 2 years.

A logistic regression model investigating for predictive factors for treatment failure (≥15 letters) was carried out in the “eyes” analysis population. A random effect was included in the model to take account of differences in measurement of visual acuity by centre.

A significant increase in risk of failure was found with age (5 year age band either side of 75 years old, OR = 1.2 95% CI [1.02; 1.41], p = 0.03). The estimated odds ratio for initial visual acuity was 0.34 (95% CI [0.11; 1.04], p = 0.06) showing an insignificant trend in favour of fewer treatment failures in patients with initial visual acuity < 30 letters. The other factors were not significant (number of follow-up consultations, eyes previously treated with an anti-VEGF at inclusion).

Maintenance of efficacy of treatment over time (one of the objectives of the study) was not examined; the length of LUCENTIS treatment was not tested in the model.

An investigation for predictive factors for treatment failure (loss ≥ 15 letters) was also performed in a subgroup population of eyes previously untreated with LUCENTIS (n = 72). The factors which were significantly associated with a risk of treatment failure at 2 years were the same as in the overall population: increased risk with age (age based around 75 years old, OR = 1.71 95%CI [1.02; 1.41] by 5 year increase, p = 0.04) and for initial high VA (VA at inclusion based around 55 letters, OR = 1.71 95% CI [1.02; 1.41] per 5 letter increase, p = 0.002)). An insignificant trend for reduced risk of failure with increasing number of injections was found (OR = 0.77 95% CI [0.54; 1] per additional injection, p = 0.10). The impact of following guidelines on the treatment induction phase (first three injections given with a period of ≤ 35 days between the injections) on the risk of failure was not tested in the model.

5.4. Conditions of use of LUCENTIS during the 2-year follow-up period.

5.4.1. Observation of conditions for starting treatment

The conditions for starting LUCENTIS treatment as defined in the Treatment Information Form (TIF) were well respected overall: the majority of eyes which started treatment at inclusion had subfoveal neovascularisation (78%), with a visual acuity of between 25 and 70 ETDRS letters (77%) and all had a lesion of less than 12 papillary diameters.
In addition, the dose (0.5 mg) was observed for almost all of the injections given (96.3%).
On the other hand, fewer than a quarter of previously untreated patients received the recommended induction phase of three injections of LUCENTIS at least 35 days apart. Almost a third of previously untreated patients (25 out of 80 eyes, 31.3%) and a quarter of eyes similar to those in the pivotal studies (14 out of 54 eyes, 26%) received at least three injections during the first follow-up year. One previously untreated patient out of five received a total of fewer than three injections of LUCENTIS over 2 years (15 out of the 72 patients followed up at 2 years).
The average time between the first and second induction injections was 54 ± 65 days (median = 35; min-max = 12-353) and the average time between the second and third induction injections was 100 ± 112 days (median = 42; min-max = 27-532).

Overall, patients were not re-treated routinely in the induction phase (36.6% routine injections). This was not due to an observed loss in visual acuity in the maintenance phase (5.4% due to a fall in VA) as recommended in the SPC. The decision to re-treat was mostly based on the results of OCT (42% in the induction phase and 66% in the maintenance phase).
The average number of follow-up consultations was 6.1 ± 3.4 during the first year of follow-up and 4.9 ± 3.5 during the second year of follow-up.
In terms of the recommended post-injection investigations, intraocular pressure was measured after 44.8% of injections; fundoscopy was performed after 59.9% of injections and an anterior segment examination after 51.6% of injections.
These findings reveal under-treatment and under-monitoring of patients during treatment with LUCENTIS under real life conditions compared with what is recommended in the LUCENTIS SPC.
12.1% of the 140 patients with bilateral disease in whom both eyes were treated with LUCENTIS received simultaneous treatment for both eyes

5.4.2. Frequency of LUCENTIS injections during follow-up

The average number of injections of LUCENTIS during the first 2 years of follow-up was 5.1 ± 4.3 injections (min = 0, Q1 = 2, median = 4, Q3 = 8, max = 21) in all eyes with 2 years follow-up and 5.0 ± 3.4 (min = 1, Q1 = 3, median = 4, Q3 = 6, max = 21) in previously untreated eyes followed up at 2 years.
Fifty-four patients (76 eyes (12.8%)) received no treatment for the AMD (neither LUCENTIS nor other treatment) during follow-up. The average follow-up time in these patients in the study was 22.6 ± 5.0 months (MD = 4, median = 24, min-max = 2-27). The average change in VA at 2 years (33% of missing data points) was -2 ± 11 ETDRS letters (min = -34, Q1 = -6, median = 0, Q3 = 3, max = 15).

5.4.3. Other treatments for AMD received during follow-up.

During the 2 year follow-up the main treatment of AMD other than LUCENTIS given to patients was VISUDYNE (9.0% of eyes), often used in combination with LUCENTIS (7.4% of eyes). Eleven eyes (1.9%) received at least one injection of MACUGEN during the follow-up period and 13 eyes (2.2%) received at least one injection of AVASTIN.

5.5. Change in functional vision (VFQ-25) and the EQ-5D utility score over 2 years

The patient's mean visual function fell during the 2-year follow-up period of the study (mean VFQ-25 score at inclusion: 75.6 points, average change: -4.83 ± 14.88 points over 2 years (data available for 89.6% of patients). The EQ-5D score, which is relatively insensitive to small changes in vision, remained stable over the 2-year follow-up period (0.82 at inclusion and 0.79 at 2 years) (data available for 86.7% of patients).

5.6. Safety of LUCENTIS

As defined in the study protocol, only serious adverse events suspected of being related to medical treatment of AMD had to be reported by the study investigators.
This record of serious adverse events was supplemented by routine recording of every death occurring in patients included in the LUEUR study, together with every pigment epithelial detachment even declared as non-serious by the investigator as required in the LUCENTIS risk management plan (RMP) and as requested by the EMA and FDA. If a patient was not contacted during these annual telephone contacts, the CRO then contacted the investigator in order to establish the patients' clinical and living or deceased status. Where applicable, the CRO contacted the general practitioner, the patient's family or even patient's council offices of their place of birth in order to obtain this information.
Some deaths were therefore recorded in the study although they were not suspected as being related to treatment for the AMD.
Some investigators reported serious adverse events which were not suspected of being related to medical treatment for the AMD. These serious adverse events were presented in the study report although they were not recorded routinely or exhaustively.

For all of the patients eligible for follow-up (whether or not included in the analysis population, n = 534), 33 serious adverse events (SAEs) were reported in 24 patients during the 2-year follow-up, including 17 deaths.
Six of the SAEs which occurred in four patients were suspected by the investigator of being related to LUCENTIS treatment (increased ocular pressure, iris hernia, trabeculectomy, coronary artery disease, myocardial infarction and pulmonary embolism). These SAEs resulted in two patient deaths (myocardial infarction and pulmonary embolism).
A total of 0.7% of eligible patients had at least one SAE suspected of being related to LUCENTIS treatment.

In terms of patients previously untreated with LUCENTIS and eligible for follow-up: seven of these patients (7.7%) developed at least one SAE during the 2-year follow-up, including six deaths. None of the SAEs declared which occurred in patients previously untreated with LUCENTIS was suspected by the investigator of being related to LUCENTIS treatment.
The seven SAEs were as follows:

- one eye disorder: pigment epithelium tear (26 days after the last injection).
- one nervous system disorder: death due to a cerebrovascular accident (92-year-old woman, date of last recorded injection = 11 months before the SAE).
- one tumour disorder: death from hepatocellular carcinoma.
- four deaths with no information (time since last injection = 16 days, 6 months and 18 months).

Most of the non-serious AEs suspected of being related to treatment (23) were SAEs listed in the SPC for substances used during treatment except for 2 AEs suspected of being relating to LUCENTIS (bilateral madarosis and central corneal ulcer) and one AE suspected of being related to the use of Kenacort (myodesopsia).

The LUCENTIS injections were stopped in one patient following a serious event (iris hernia) suspected of being promoted by intravitreal injections of LUCENTIS.

6 Conclusion

A large majority of the 592 eyes included in this study (517 patients) were previously treated with LUCENTIS (85%): 90 previously untreated eyes and 502 previously treated eyes. The diagnosis of AMD had been made an average of 16 months previously.
The percentage treatment success rates (loss of less than 15 letters in 2 years) under real life conditions was 75.8% of the eyes analysed and 76.4% of the eyes starting LUCENTIS at inclusion compared with 82% in the PIER study (a clinical study with a similar dosage regimen to the SPC). If missing data points are considered as failures (15% missing data points at 2 years), the success rate for all eyes analysed was 66%.
Visual acuity remained stable at 2 years, with a mean change of -0.62 letters (95%CI [-5.51; 4.26]) for the eyes which started LUCENTIS (15% missing data points). A quarter of the eyes previously untreated with LUCENTIS (26%) and 13.5% of the whole population achieved an improvement of more than 15 letters at 2 years.

The conditions for starting LUCENTIS treatment as defined in the Treatment Information Form (TIF) were well respected overall: the majority of eyes which started treatment at inclusion had subfoveal neovascularisation (78%), with a visual acuity of between 25 and 70 ETDRS letters (77%) and all had a lesion of less than 12 papillary diameters.
The recommended induction phase of three injections at least 35 days apart was not given in practice. Almost a third of previously untreated patients received at least three injections (31.3%) during the first year of treatment and 7.5% of patients received a single injection. The average time between the first and second induction injections was 54 days (median = 35) and the average time between the second and third induction injection was 100 days (median = 42).
The average number of follow-up consultations was six during the first year of follow-up and five during the second year of follow-up.
In terms of treatment safety, six serious adverse effects likely to have been due to LUCENTIS treatment were reported in the study (increased ocular pressure, a herniated iris, trabeculectomy, coronary artery disease, myocardial infarction and pulmonary embolism) in four patients (0.7%). These SAEs resulted in two patient deaths (myocardial infarction and pulmonary embolism).