EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Lucentis

ranibizumab

Procedure no: EMEA/H/C/000715/P46/070

Note

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

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Abbreviations

AE	adverse event
BCVA	best corrected visual acuity
CNV	choroidal neovascularisation
CSC	central serous chorioretinopathy
CSFT	central subfield thickness
DME	diabetic macular oedema
ETDRS	Early Treatment Diabetic Retinopathy Study
IOP	intraocular pressure
ME	macular edema
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire – 25
OCT	optical coherence tomography
PIP	paediatric investigation plan
PM	pathological myopia
RVO	retinal vein occlusion
SAE	serious adverse event
VA	visual acuity
VEGF	vascular endothelial growth factor
wAMD	(wet) age related macular degeneration

Introduction

On 24 February 2016, the MAH submitted a completed study that included paediatric patients for Lucentis, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

Study CRFB002G2302 (PROMETHEUS, EudraCT No. 2012-005418-20), "A 12-month, randomized, double-masked, sham-controlled, multicenter study to evaluate the efficacy and safety of 0.5 mg ranibizumab intravitreal injections in patients with visual impairment due to vascular endothelial growth factor (VEGF) driven macular edema (ME)" is part of a clinical development program in the adult population. Since some ocular conditions that cause ME in adults can also occur in the paediatric population, during the conceptual discussion of the Lucentis Paediatric Investigation plan (PIP) with CHMP, before the PIP waiver was granted on 06 August 2014 [EMEA-000527-PIP03-13], it was agreed that the study should be open also for the inclusion of paediatric patients ≥12 years of age.

1.2. Information on the pharmaceutical formulation used in the study

Lucentis 10 mg/ml ranibizumab solution for injection as the currently marketed formulation in the EU has been used. The formulation contains:

- Trehalose 10% (w/v) (provides an isotonic solution) for the intravitreal injection of ranibizumab.
- Histidine HCl 10 mM (buffer)
- Polysorbate 20, 0.01% w/v (surfactant to minimize the risk of aggregation).

During review of PIP [EMEA-000527-PIP03-13], the formulation working group concluded that "the formulation is already optimized so there is no concern for its intravitreal injection to the pediatric population."

1.3. Clinical aspects

1.3.1. Introduction

Ranibizumab is a recombinant humanised IgG1 κ isotype monoclonal antibody fragment (Fab) that selectively binds and neutralises vascular endothelial growth factor (VEGF)-A. Binding of VEGF-A to its receptors triggers angiogenesis and neovascularisation by promoting vascular endothelial cell proliferation/ migration and an increased vascular permeability resulting in leakage. The neutralisation of VEGF results in a reduced vascular leakage.

Lucentis (ranibizumab), was approved for the treatment of neovascular (wet) age related macular degeneration (wAMD) in 2007, for the treatment of visual impairment due to diabetic macular oedema (DME), retinal vein occlusion (RVO) in 2011 and for choroidal neovascularisation (CNV) secondary to pathologic myopia (PM) in 2013. Vascular leakage occurs in CNV that lead to exudation of intra- and subretinal fluids with subsequent atrophic changes (e.g. wAMD and PM) as well as in macular oedema

(DME and RVO). Subsequently, vision is impaired. The objective of the current procedure is to report a summary of the data obtained in adolescent patients from study CRFB002G2302.

The MAH submitted a final report for:

- Study CRFB002G2302 (PROMETHEUS, EudraCT No. 2012-005418-20), "A 12-month, randomized, double-masked, sham-controlled, multicenter study to evaluate the efficacy and safety of 0.5 mg ranibizumab intravitreal injections in patients with visual impairment due to vascular endothelial growth factor (VEGF) driven macular edema (ME)".

1.3.2. Clinical study

Study CRFB002G2302 (PROMETHEUS, EudraCT No. 2012-005418-20):
"A 12-month, randomized, double-masked, sham-controlled, multicenter study to evaluate the efficacy and safety of 0.5 mg ranibizumab intravitreal injections in patients with visual impairment due to vascular endothelial growth factor (VEGF) driven macular edema (ME)"

Description

Methods

This was a randomized, double-masked, sham-controlled, multicenter study of ranibizumab in adult patients, with a non-randomized, open-label ranibizumab-treated cohort of adolescent patients. At Month 2, all adult patients assigned to the sham group were switched to individualized ranibizumab open-label treatment. Thus, as of Month 2, both adult and adolescent patients received open-label individualized ranibizumab intravitreal injections based on evidence of disease activity.

Evidence of disease activity (eg, visual acuity impairment, intra-/sub-retinal fluid, cysts or leakage) was assessed clinically or based on imaging and functional testing. All assessments had equal weight for decision making. Study design components including all study procedures and assessments for adult and adolescent patients were presented in the 6-month CSR for completeness. This final CSR includes the results up to the Month 12 for adults and adolescent patients.

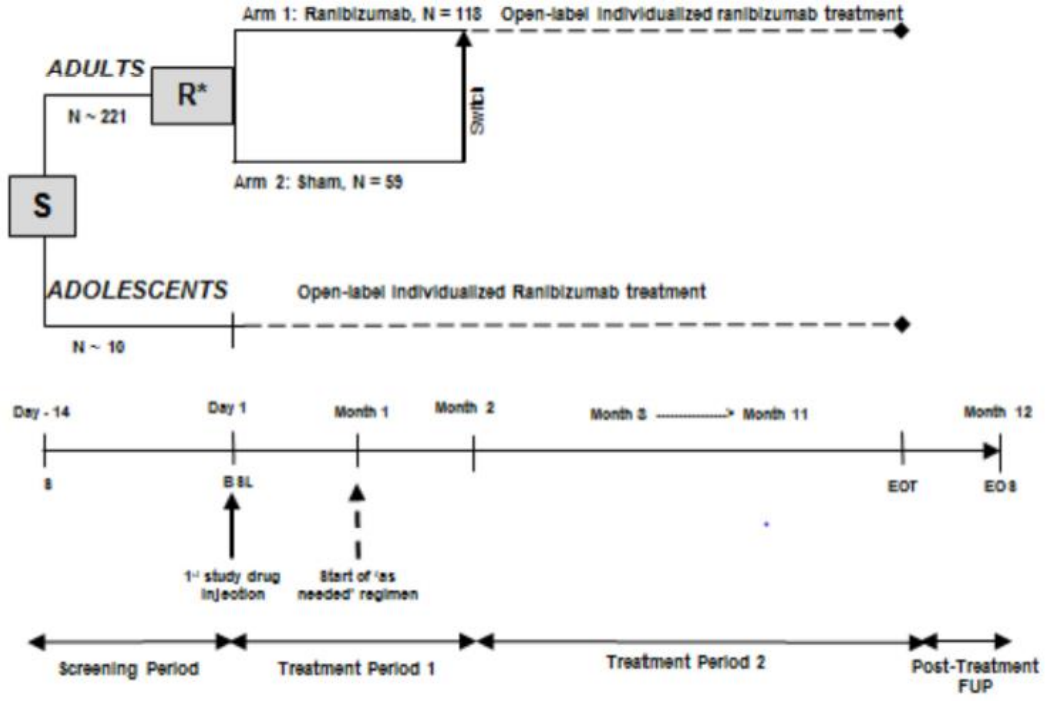
Objective(s)

The primary objective of this study was to demonstrate that an individualized regimen of intravitreal injection of ranibizumab 0.5 mg has superior efficacy compared to sham treatment in adult patients with visual impairment due to ME. The primary objective was assessed by the best-correct visual acuity (BCVA) change from baseline to Month 2 (letters in Early Treatment Diabetic Retinopathy Study (ETDRA) charts).

The primary objective in the adolescent patients was to describe the efficacy and safety of ranibizumab in adolescent patients by assessing the same efficacy and safety objectives as chosen for adult patients where applicable and depending on the number of adolescent patients enrolled.

Study design

For an outline of the study, see below figure.



S = screening; R* = randomization at 2:1, including stratification by type of underlying ocular pathophysiologic mechanisms; BSL = baseline; EOT = end of treatment; EOS = end of study

Study population /Sample size

The main inclusion criteria were as follows:

- Written informed consent (from adult patients and parents/guardians of adolescent patients) and written assent (from adolescents patients only) was to be obtained before any assessment was performed
- Male or female patients ≥ 18 years of age (adults) and male or female patients ≥ 12 and < 18 years (adolescents)
- Diagnosis of active ME secondary to any causes (for adult patients: except DME, wAMD and RVO) that was primary, chronic (ie, ME was present for > 3 months) or recurrent
- BCVA was to be between ≥ 24 and ≤ 83 letters tested at 4 meters starting distance using
- Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity (VA) charts (approximate Snellen chart equivalents of 20/25 and 20/320)
- Visual loss in the study eye was to be mainly due to the presence of any eligible types of ME (for adult patients: non-DME, non-AMD, and non-RVO) based on ocular clinical, as well as FA and OCT findings

Main exclusion criteria were as follows:

- Any type of advanced, severe or unstable systemic disease or its treatment, that could interfere with primary and/or secondary outcome evaluations

- Active malignancies
- Uncontrolled systemic inflammation or infection
- Uncontrolled blood pressure defined as systolic value of ≥ 160 mmHg or diastolic value of ≥ 100 mmHg
- History of stroke less than 6 months prior to screening

The study population was planned to consist of approximately 177 patients.

Treatments

All eligible adolescent patients were treated in an open-label manner with a ranibizumab 0.5 mg intravitreal injection at baseline, followed by an individualized treatment regimen based on evidence of disease activity (judged clinically or based on morphology/imaging) as assessed by the investigator at each individual visit.

Eligible adult patients were randomized at 2:1 ratio to receive ranibizumab or sham injection until Month 2. At Month 2, all adult patients (in both sham and ranibizumab arms) could receive ranibizumab open-label treatment. Thus, as of Month 2, both adult and adolescent patients received open-label individualized ranibizumab intravitreal injections based on evidence of disease activity.

Evidence of disease activity (e.g., visual acuity (VA) impairment, intra-/sub-retinal fluid, cysts or leakage) was assessed clinically or based on imaging and functional testing.

Outcomes/endpoints

The assessments performed for activity of ranibizumab on retinal structure and visual function were BCVA with ETDRS-like chart at 4 meters.

- The primary endpoint was the mean change in BCVA from baseline to Month 2.
- Secondary evaluations of BCVA included evaluations of mean changes at various time points (e.g. 6 and 12 months) and responder analyses (e.g. proportion of patients gaining or loosing ≥ 5, 10 or 15 letters in BCVA).

Changes in retinal structures including the oedema (e.g. as central subfield thickness, CSFT) were conducted with optical coherence tomography (OCT), colour fundus photography, and fluorescein angiography.

Health-related quality of life was assessed using the National Eye Institute Visual Function Questionnaire – 25 (NEI-VFQ-25).

Safety assessments consisted of collecting all AEs, SAEs, ophthalmic examinations, intraocular pressure, vital signs, and laboratory parameters.

No pharmacokinetic data were generated.

Statistical Methods

Data for adult and adolescent patients are presented separately. Data for adult patients were analysed and listed. Data for adolescent patients were listed only due to the small number.

The last assessment collected just prior to start of treatment was considered to be the baseline value. All assessments performed after the first study treatment were considered to be post-baseline.

Results

Recruitment/ Number analysed

Overall, 178 adult and 3 adolescent patients were recruited.

The 3 adolescent patients finalised the 12-month treatment period.

For comparison, in the adult population, 106/118 (89.8%) and 50/60 (83.3%) in the ranibizumab and sham treatment arms, respectively finalised the 12 month treatment period. Discontinuations were mainly due to physician's decision or lost to follow up (ranibizumab group) or due to withdrew consent (sham group).

Baseline data

The baseline demographics and disease characteristics for the paediatric patients are summarised in the below table.

Table1 Demographics and baseline aetiology in the adolescent patients

Patient no	**2042-20001**	**2076-20001**	**2171-20001**
Country	France	Italy	Turkey
Age	14	14	16
Gender	M	F	F
Baseline aetiology	Miscellaneous: pre-papillary benign tumour	Idiopathic	Miscellaneous: retinitis pigmentosa
BCVA (letters)	71	40	62
CSFT (µm)	351	539	466

As retinitis pigmentosa was prohibited ocular disorders in the study eye, patient 2171-20001 was recorded as a protocol deviation related to the inclusion criteria.

For comparison, the adult population was in average 63 years old, somewhat more males (62%) and the majority were Caucasians. The mean baseline BCVA was 65 letters and the mean CSFT was 466 µm. Baseline aetiologies were as follows: Inflammatory/Post-uveitis (12%), Pseudophakic/Aphakic (33%), CSC (14%), Idiopathic Retinopathy/Retinochoroidopathy (29%) and Miscellaneous (12%).

The exposure in the study eye of the three adolescent patients is presented in **Table 2**.

Table 2 Exposure of study medication in the study eye

	2042-20001	2076-20001	2171-20001
Treatment received at	Baseline and each month from Month 1 to Month 11	Baseline, Months 1, 2, 5, 6, 7, 9	Baseline, Months 1, 2, 4, 6, 7, 9, 11

Patients 2042-20001 and 2076-20001 did not receive any treatment in the fellow eye while patient 2171-20001 received a total of 7 injections in the fellow eye.

Efficacy results

The visual function outcome measure, BCVA and a key anatomical endpoint, Central subfield thickness (CSFT, measured by the optical coherence tomography (OCT)) of the study eye from the three adolescent patients are presented in **Table 3**.

Table3 Observed BCVA and CSFT at baseline, Months 2, 6 and 12

		Baseline	Month 2	Month 6	Month 12
2042-20001 pre- papillary benign tumour	**BCVA (letters)**	71	64	70	61
	CSFT (μm)	351	492	629	759
2076-20001 Idiopathic	**BCVA (letters)**	40	85	75	85
	CSFT (μm)	539	268	358	344
2171-20001 retinitis pigmentosa	**BCVA (letters)**	62	64	70	70*
	CSFT (μm)	466	298	345	354

* A 5 letter improvement was reported in the patient's treated fellow eye.

In the adult population, at month 2, 6 and 12, the mean changes in BCVA were 5.7, 6.4 and 7.5 letters, respectively in the ranibizumab treatment arm. The corresponding figures at months 2, 6 and 12 were 2.9, 4.5 and 5.8 letters in the sham treatment arm (note that subjects in the sham treatment arm crossed over to receive ranibizumab from month 2).

Safety results

Adolescent population

No patient died. No serious adverse events (SAEs), no severe adverse events (AEs) and no AEs suspected to be related to study drug were reported. No clinically notable abnormal vital signs were identified. No ocular AEs were reported. There were no patients with Intraocular pressure (IOP) of 30 mmHg or greater in the study eye at any time post-baseline.

Two episodes of epilepsy were reported for patient 2042-20001. Both events were of mild intensity, resolved without any action to the study medication and the investigator evaluated both events as not suspected to be related to the injection or medication. The reported non-ocular AE of epilepsy was consistent with the medical history of the patient (tuberous sclerosis, epilepsy and surgery for benign brain tumour).

Adult population

The most common ocular AEs were conjunctival haemorrhage (39.5%), eye pain (8.5%) and visual acuity reduced (5.6%). The most common non-ocular AEs were nasopharyngitis (53.1%), hypertension (7.9%) and influenza (4.5%). Three patients died during the 12-month study period, one patient in the sham arm died due to a brain stem stroke and basilar artery thrombosis (up to Month 2) and two patients in the ranibizumab treatment arm died due to a cardio-respiratory arrest and a cerebral haemorrhage. None of the deaths was considered by the investigator to be related to study treatment. A total of 3 patients experienced ocular SAEs in the ranibizumab treatment eye up to Month 12; one event each of endophthalmitis (related to injection), worsening of glaucoma (not suspected related) and conjunctivitis allergic (not suspected related).

1.3.3. Discussion on clinical aspects

Three adolescent patients with different diagnoses (macular oedema secondary to pre-papillary benign tumour, idiopathic macular oedema and retinitis pigmentosa) were included in Study CRFB002G2302. During the 12 months of the study, they received 7 – 12 injections. A 45 and 8 letter improvement in BCVA was observed in the two subjects with idiopathic oedema and retinitis pigmentosa, respectively while the subject with a pre-papillary benign tumour lost 10 letters over the course of the study. The efficacy data from the three adolescent patients are too limited to draw any conclusions.

With regards to safety, the narratives provided for the three patients did not report any related AEs, but again, the number of patients is too limited to draw any conclusions with regards to potential differences in the AE profile between the paediatric and the adult population.

However, with regards to adolescent patients, the eye is fully developed and it would not be expected that the efficacy or the ocular AE profile would differ from that in the adult population.

2. CHMP overall conclusion and recommendation

Overall conclusion

The paediatric data has been submitted in accordance with article 46 of regulation (EC) No 1901/2006. The data are too limited to draw any conclusions and no regulatory action is requested.

Recommendation

Fulfilled: No regulatory action required.

Additional clarifications requested: Not applicable.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies Not applicable.

Clinical studies

Product Name: Lucentis Active substance: ranibizumab

Study title	Study number	Date of completion	Date of submission of final study report
A 12-month, randomized, double-masked, sham-controlled, multicenter study to evaluate the efficacy and safety of 0.5 mg ranibizumab intravitreal injections in patients with visual impairment due to vascular endothelial growth factor (VEGF) driven macular edema (ME)	CRFB002G2302	09 September 2015	24 February 2016