Name of sponsor IOBA – University of Valladolid	Individual Study Table Referring to Part of the Dossier **Volume:** Not applicable **Page:** Not applicable	***(For National Authority Use Only)***
Name of Finished Product: Avastin®		
Name of Active Ingredient: Bevacizumab		

Title of the study

Safety and Effectiveness of Bevacizumab Intravitreal Injections in the Treatment of Macular Edema Secondary to Retinal Vein Occlusion (EBOVER).

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Publication (reference)

Studied period (years)

Date of first enrolment: 23/04/2009
Date of last completed: 29/06/2012

Phase of development

Phase III Trial

Objetives

Main efficacy objetives:

To determine if Bevacizumab (Avastin®) intravitreal injection allows improvement of Best corrected visual acuity versus sham injection.

To determine if Bevacizumab (Avastin®) intravitreal injection allows a significant decrease of retinal thickness at the fovea versus sham injection.

Secondary efficacy objectives:

To determine if treated patients converted less frequently to ischemic forms and/or neovascularization development than the patients with sham injection.

Secondary safety and tolerability objectives.

Assessment of the possible complications of Bevacizumab (Avastin®) intravitreal injections as treatment for macular foveal edema secondary to Retinal Vein Occlusion.

Methodology

Phase III multicenter, parallel, randomized with masked evaluation trial.

Number of patients (planned and analysed)

A total of 103 patients of both genders were included with ages ≥ 18 years old with central edema secondary to retinal vein occlusion.

Diagnosis and main criteria for inclusion

Inclusion Criteria:

1. Patient male or female 18 years old or more

Patients with best corrected visual acuity loss within the last 6 months of evolution, caused by the macular edema as stated by investigator´s judgement. Best corrected visual acuity tested by ETDRS within 20/40 and 20/400 in the study eye.

2. Signed Informed consent.
3. Signed Data Protection Consent.
4. Negative pregnancy test before entering the study for childbearing potential women, who must commit to use a medically accepted contraceptive method for the whole study.
5. Foveal macular edema secondary to Retinal Vein Occlusion confirmed by Fluorescein angiography and Optical Coherence Tomography, with a subcentral field thickness of at least 250 microns.
6. Macular Subcentral field assessed by Ocular coherence tomography of at least 250 microns thick.
7. No presence of eye opacities that may prevent fundus exploration. No condition that may prevent correct eye dilation.
8. No known allergy to fluorescein.
9. Only an eye per patient will be included in the study, even if both eyes have the pathology.

Exclusion Criteria:

1. Macular edema secondary to any other condition such as: diabetes retinopathy, hypertension, juxta foveal telangiectasia, ...
2. Any previous treatment for macular edema such as photocoagulation, vitrectomy, triamcinolone, radial optic neurotomy in the study eye.
3. Any ocular illness that may be associated to increased/high levels of VEGF (Age related macular degeneration, Diabetes retinopathy, Uveitis, ...)
4. Systemical illnesses that may be associated to increased/high levels of VEGF (e.g. tumors).
5. Medical history of brain vascular episodes, stroke, angor pectoris or myocardial infarct within 3 months before study inclusion.
6. Pregnancy or nursing.
7. Known or suspected hypersensitivity to Bevacizumab, his excipients or any related molecule.
8. Uncontrolled hypertension refractory to medical treatment.
9. Participation in any other trial or study within the last 3 months (minerals and vitamins excluded) or treatment with anti-VEGF in the non-study eye within the previous 3 months.

10. Tractional maculopathy and/or epiretinal membrane assessed by Ocular Coherence Tomography.
11. Media opacities that don´t allow correct eye exploration and fundus examination or photographs.
12. Cataract surgery / YAG capsulotomy within the previous 6 months.
13. Filtration surgery.
14. Previous medical history of ocular illnesses as: viral infections, inflammatory pathology, serous central choroidopathy, retinal detachment or any other illness that may have an influence in visual acuity.
15. Presence of foveal atrophy, severe pigmentary changes, dense sub foveal hemorrhages, confluent sub foveal hard exudates or any other condition that may influence functional recovery of the macular edema.
16. Cataract that may be responsible for additional visual acuity loss of more than 2/10.
17. Medically uncontrolled intraocular pressure higher than 25 mm Hg.
18. External ocular illnesses active at inclusion as: conjunctivitis, blepharitis, eye sore, ...

Test product, dose and mode of administration, batch number:

Generic Denomination: Bevacizumab
Commercial trade name: Avastin®
Pharmaceutical form: Concentrate for solution perfusion.
Route of administration: Ocular
Samples manufactured by: Genentech/Roche

Duration of treatment:

Maximum Treatment time for every patient was 12 months with monthly injections. Number of total injections may differ depending on progression of the disease, lost-to-follow, unacceptable toxicity or death.

Reference therapy, dose and mode of administration, batch number:

Not applicable. Sham procedure does not include any therapy, only method of administration is simulated.

Criteria for evaluation:

Efficacy

Treatment efficacy was evaluated with Best Corrected Visual Acuity (BCVA) and macular thickness assessed with Optical Coherence Tomography (OCT).

Safety

Safety assessment of investigational product was performed by clinical exploration, adverse event and serious adverse events, changes in concomitant medication and complementary ophthalmic examinations which included: ocular tonometry, Indocyanine-Green Angiography, Fluorescein Angiography, Optical coherence tomography, slit lamp examination and fundus examination.

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Statistical methods:

Two different samples were defined for efficacy analysis: Intention to Treat (ITT) sample and Per Protocol (PP) sample, together with a Safety Sample.

Safety sample

Safety simple included all patients that entered the study and had at least one study medication injection.

Intention to Treat (ITT) Sample

ITT simple included all randomized patients that received treatment during the load phase (3 injections in 3 months) and who at least had a baseline value and a post treatment before month 6 and a post treatment value after month 6 of the principal study variables: best corrected visual acuity and optical coherence tomography).

For the evaluation of missing values, the last observation carried forward (LOCF) method was used.

Per protocol (PP) Sample

Per protocol sample included the patients that met all inclusion criteria, that were randomized, treated as per protocol, that completed the study having all principal efficacy assessments in every visit and with no major protocol violations.

Categorical variables were described as absolute and relative frequencies. For continuous variables mean, standard deviation, median, minimum and maximum (including total number of valid values) were used.

For quantitative variables and 2 or more independent groups comparation non parametrical Kruskal-Wallis was used (taking into account the required assumptions for the test).

For the comparison of two or more matched groups, non-parametrical Wilcoxon test was used, following the required assumptions for the use of the test.

For the comparison of categorical variables Chi-Square test was used, unless exact test had to be used if necessary.

All statistics were done with SAS for Windows Version 9.3. Bilateral test with 0,05 significance was used.

Primary efficacy endpoint analysis

Mean change in best corrected visual acuity was calculated as the difference between final and baseline values.

Mean change in macular thickness assessed by Optical coherence tomography was calculated as the difference between final and baseline values.

Secondary efficacy endpoins analysis

Percentage of patients with ischemia at 6 and 12 months.

Percentage of patients with neovascularization at 6 and 12 months.

Secondary safety and tolerability endpoints analysis

Total number of adverse events (AE) and percentage of patients with AE.

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SUMMARY - CONCLUSIONS

Efficacy results

Bevacizumab has demonstrated its efficacy versus placebo in the treatment of macular edema secondary to retinal vein occlusion taking into account the main study variables: changes in Best Corrected Visual Acuity (BCVA) and foveal thickness.

Statistically significant differences were found in BCVA changes in both ITT and PP in favor of Bevacizumab.

Differences regarding foveal thickness assessed by OCT were also found in favor of Bevacizumab versus placebo.

Safety results

Reported adverse events were comparable within both arms. No unexpected serious adverse events were reported. A death not related to study medication was reported, together with 12 serious adverse events, none related to study medication.

CONCLUSION:

Bevacizumab showed efficacy versus placebo in patients with macular edema secondary to retinal vein occlusion. Both groups shared the same safety profiles.

However, due to the small sample size we consider a new study with a greater number of patients and with greater follow-up period should be performed in order to obtain confirmatory efficacy and safety results of intravitreal injections of bevacizumab in macular edema secondary to retinal vein occlusion.

Date of the report: 13- May-2014 (Final Report). 18-Dec-2019 (This report)