Title: Effectiveness and safety of two intravitreal combination therapies versus the Macugen® monotherapy for the therapy of diabetic retino and maculopathy - a single center, randomized, prospective phase II study

EudraCT-Nr.: 2009-009909-25

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Study Site: Department of Retina and Vitreous Surgery, Center for Ophthalmology, Johann Wolfgang Goethe University Hospital, Haus 1, Theodor-Stern-Kai 7, 60590 Frankfurt am Main

Reason for Study: comparison of the efficacy of anti-VEGF monotherapy (Macugen) vs. a combination therapy of anti-VEGF and cortisone administration.

Start Date: 2009-05-05

Completion Date: 2011-10-24 (prematurely ended)

Subject disposition

- **Number of subjects screened:** 70
- **Number of subjects started:** 32
- **Total number of study eyes:** 46
- **Number of subjects completed**: study ended prematurely
- **Gender**
    - Female: n=14
    - Male: n= 18
- **Average age of participants:** 63.8 years ± 11.7 years

Study Design: A monocentric, randomized, clinical prospective study in patients with diabetic retinopathy, which compared three groups. A maximum of 120 patients should be randomized 1: 1: 1 into the 3 therapy arms (monotherapy, with vitrectomy or vitrectomy and administration of triamcinolone).

Study Arms:

1. Group 1, monotherapy group
    a. 14 eyes, 6 women, 7 men (1 man with two study eyes)
2. Group 2, Macugen & triamcinolone treatment group
    a. 16 eyes, 6 women, 9 men (1 man with two study eyes)
3. Group 3, Macugen & core PPV treatment group
    a. 16 eyes, 9 women (1 woman with two study eyes), 6 men

Main Target criterion: The primary target criterion was the proof of the clinical effectiveness (central visual acuity according to EDTRS) of the interaction of VEGF inhibitor monotherapy without and with limited vitrectomy versus a combination therapy of anti-VEGF and cortisone administration in the treatment of diabetic retinopathy.

Secondary Target criteria: Secondary target criteria were the development of the macular thickness and the degree of retinal proliferation, as well as the analysis of the objective and subjective visual quality and the occurrence of adverse clinical events after 56 weeks.

a) The change in macular thickness in pm in optical coherence tomography (OCT)
b) The change in the degree of proliferation in fluorescence angiography (FLA)
c) The change in objective and subjective quality of vision during the clinical examination
d) The occurrence of undesirable events in the context of the clinical ophthalmological examination

Inclusion Criteria:

- Moderate to severe non-proliferative cystic diabetic macular edema
- Age of 18 years
- Existing declaration of consent for participation in the study

Exclusion Criteria:

- Relevant exclusion diagnoses:
    - History of GRID central retinal laser photocoagulation
    - History of chronic, diffuse or macular edema with vitreoretinal traction
    - History of anti-VEGF, steroid within the last 6 months
    - History of vitrectomy and / or (core) vitrectomy
    - A history of acute or chronic illness that reduces visual acuity alone, such as intraocular inflammation, radiation of the head or neck, corneal pathologies, significant cataract or probable cataract within the next 10 months, myopia greater than 8 diopters, axis length> 26mm
    - Internal history of >3 severe hypoglycemic episodes within the last 3 months, HbAlc> 13%, >2 episodes of severe ketoacidosis within the last 12 months, severe coronary artery disease with postoperative status, uncontrolled arterial hypertension (treated blood pressure > 155mmHg or diastolic > 95mmHg), cerebral apoplexy within the last 12 months before study inclusion
- Any other illness for which the study is impossible or poses a risk for the patient (e.g. psychiatric illness)
- Incapacitated patients
- Pregnancy or lack of contraceptive protection in childbearing age
- Breastfeeding
- Contraindications to the administration of the test medication
- Participation in another clinical trial or participated in a study with a drug 4 weeks prior to participation in this trial.

Study Medication: Macugen® is a potent VEGF inhibitor that can lead to regression of retinal neovascularization and a reduction in retinal thickness, which can subsequently be accompanied by stabilization or improvement of vision. Macugen® 0.3 mg solution for injection is supplied as a pre-filled syringe for single use with a nominal volume of 90 microliters with 1.65 mg pegaptanib sodium, accordingly 0.3 mg of the free acid of the oligonucleotide is made available.

The cortisone preparation Triamhexal®, which is intravitreally injected and has a very effective anti-edematous effect on macular edema, is also used. Triamhexal® is purchased from the Center for Ophthalmology in a dosage of 40 mg as a suspension for injection from Hexal AG and is stored in the storage rooms of the operating room at room temperature, protected from light and frost. When used as study medication, the corresponding batch is documented in the study medication folder for each patient and treatment day. 0.2ml (filtered = 8mg) is drawn up from the 1ml injection suspension (= 40mg) under hygienic standard conditions with a cannula.

Ethics: The study was planned and carried out in accordance with the standards of Good Clinical Practice (GCP) and the Declaration of Helsinki (as amended).

Premature End of Study: The study ended prematurely in agreement with Pfizer on October 17, 2011**.** This warns that on the one hand it has been very difficult since the start of the study to attract adequate patients according to inclusion criteria. It was made significantly more difficult**,** however, in mid-2011, as the competitor product Ranibizumab from Novartis was approved in Germany for the treatment of diabetic macular edema**.** The fact that the expected gain in visual acuity would have been higher than the treatment with Pegaptanib led to fewer patients being referred to our center and those who were had to be informed about the matter according to GCP. As a result, Pfizer stopped licensing Pegaptanib and no longer sold the product in Germany. The study was stopped from the point in time mentioned above and the patients were taken into regular care at the clinic, depending on the point in time of treatment. We are aware that the early termination of the study led to a weakening of the results of the more primary investigation parameters. However, the associated adverse events listed below were not dependent on the study medication pegaptanib, so we do not assume any added value in this regard if the study had been continued.

Results:

- **Primary endpoint: visual acuity**
    - The initial visual acuity was 74 ETDRS letters (± 18 letters) in group 1 and in last examination 68 letters (± 23). In group 2 the starting visual acuity was 71 (± 21), which was confirmed at the last time with 71 (± 23) letters. Group 3 showed a change from 65 (± 21) to 71 (± 21) letters. The differences were not significant in terms of change over time or over the individual groups.

- **Secondary endpoints**
    - There were no significant correlations between the left and right eyes regarding the difference between the first and the last examination time for all target variables (visual acuity, volume of the macula, thickness of the foveola).
    - There was also no statistical trend, which might have resulted in the superiority of one versus another therapy if the calculated number of study patients had been reached (despite the premature discontinuation).
    - When considering the influence of the macular edema configuration on the four target variables, it is evident that the diffuse cystic edema and the ischemic edema are inferior to focal or non-ischemic edema. It also shows

that the duration of diabetes (p=0.0439) and diastolic blood pressure (p= 0413) were slightly significant influencing factors for visual acuity.

Adverse Events:

There was no systemic adverse event noted, that was suspected to be related to the study or one of the treatment arms:

- In Group 1: Peripheral artery disease, hypoglycemia, coronary heart disease and a bicycle accident with hospitalization were noted as systemic adverse events.
- In Group 2: coronary heart disease, death of unknown reason, and coronary heart disease was documented as systemic adverse events.
- In Group 3: coronary heart disease was noted as systemic adverse event.

The following ophthalmological adverse events were assessed by the investigators as unlikely to be related to the study medication or one of the therapy groups:

- In Group 1: 2 cases of ocular hypertension, vitreous bleeding
- In Group 3: 2 cases of ocular hypertension, vitreous bleeding

One ophthalmological adverse event was assessed by the investigators as not suspected to be related to the study medication or one of the therapy groups:

- Group 2: 1 case of a retinal detachment