Appendix 3:

Statistical analysis

The systemic AIR of drug-related AEs was calculated as number of events per person year and presented together with 95% CI. The systemic AIR of AESI/drug-related AEs was defined as the number of systemic events of special interest/drug-related events that occurred during the patient's time at risk divided by the patient's time at risk throughout the observation period. The ocular AIR of drug-related AEs were calculated as number of events per eye year and presented together with 95% CI. The ocular AIR of AESI/drug-related AEs was defined as the number of ocular events of special interest/drug-related events that occurred during the treated eye's time at risk divided by the treated eye's time at risk throughout the observation period.

$$IR = \frac{n}{T} = \frac{n}{\sum t_i}$$

$$95\%CI = \left(IR - 1.96\sqrt{n/T^2}, IR + 1.96\sqrt{n/T^2}\right)$$

where, n is the total number of events that occurred during the risk period, T the total patient-time-at-risk for systemic events and treated eye-time-at-risk for ocular events, and t_i, the patient's exposure time in years, was defined as time elapsed, for any ranibizumab injection, from the injection to a maximum of 30 plus 1 subsequent days.

The time at risk for systemic events was defined for a 15-day and 30-day period, and the time-at-risk for ocular events was defined for a 30-day period. The 15-day risk period was defined as the sum of the 15 days following each ranibizumab injection; if a patient received consecutive injections, his/her risk period was defined as: the sum of all the days between one

injection and the subsequent (if it happens after 15+ 7 days) plus 15 days. The sum of all of the risk periods for all of the injections the patient received during the 1 year follow up period have been considered in the analyses. Similar analysis was performed for the 30-day risk period for systemic and ocular events, considering a time window of 30 days; and for systemic and ocular serious and non-serious AEs. The incidence rate of ocular/systemic events of interest/drug-related AEs were also evaluated by means of a self-controlled case series approach, in which any window of time different from the risk periods (i.e. 30 days following each ranibizumab injection for ocular and systemic events and 15 days for systemic events) constituted the control periods. The ocular/systemic annual incidence rate of events of special interest/drug-related AEs during the control period was defined as the number of events occurring during the treated eye's/patient's control period divided by the duration of the control period. The incidence rate ratio with the corresponding 95% CI was computed in order to compare the results between risk and control periods.

Two sub-populations, systemic safety and ocular safety sub-populations, were introduced in order to evaluate patient safety by means of a sensitivity analysis of the primary objective. Systemic safety sub-population was defined as patients valid for the safety population without certain pre-specified protocol deviations (EC007, EC008, EC009, CMED3, CMED4, CMED5, CMED6 [**Online Supplementary Table 1**]) and without concomitant use of ranibizumab in the non-study eye. Ocular safety sub-population consisted of all patients, valid for the safety population, without certain pre-specified protocol deviations (EC001, EC002, EC003, EC005, CMED1, CMED2, CMED3, CMED6 [**Online Supplementary Table 1**]).