Supplementary File S4: Treat-and-extend (T&E) regimen and study design description

1) Ranibizumab treatment–all three groups. For all three treatment groups, there was an initial period of monthly treatment until the vision was stabilised, and after which the intertreatment intervals could be extended to 2 months or greater. Patients went back to monthly injections upon experiencing any visual acuity (VA) loss. As the study was a first time assessment of the treat-and-extend (T&E) concept in DME, patients in all three treatment groups were required to attend monitoring visits.

(i) All treatment groups–monthly treatment until reaching stability

Patients received monthly injections of ranibizumab 0.5 mg for 3 consecutive months until VA was stable, i.e. neither improvement nor deterioration for three consecutive monthly visits observed while on treatment. At the visit at which BCVA stabilisation was confirmed, the patient did not receive any treatment (no ranibizumab or laser) and followed the next stage in the T&E design.

(ii) After stability had been confirmed

a) Ranibizumab T&E with or without laser. For these two groups, there were two types of visits: (i) T&E visits which were scheduled for mandatory treatment and included a decision point for potential reinitiating of monthly injections and (ii) Intermediary visits for patients to remain masked to their treatment assignment and to collect efficacy and safety data as routine in clinical practice. At these visits, no treatment was administered or no decisions for study treatment were made.

The first T&E visit followed 1 month after the visit at which stabilisation was confirmed, i.e. for a patient who had stable VA (for an ideal case, at the end of the third month in the study, i.e. end of Month 2) the first T&E visit with mandatory injection was 2 months after the end of monthly injection phase (for an ideal case, Month 4). If there was no loss of BCVA that was attributable at this visit, the next T&E visit was scheduled 3 months later (for an ideal case, Month 7). Hence, the treatment-free interval was increased by an additional 1 month and the following two visits were intermediary visits. This schedule for T&E visits persisted as long as stabilisation was confirmed at the subsequent T&E visits. The study design did not permit treatment intervals of >3 months.

The retreatment criterion was based on VA stability criteria. Though not defined by the study protocol, Optical Coherence Tomography (OCT) may well have been used to guide/aid the retreatment decisions by certain centres, thereby providing an opportunity for a proactive approach at detecting the early signs of disease activity before the actual vision loss.

b) Ranibizumab 0.5 mg PRN. Patients in this treatment group continued on the ranibizumab pro re nata (PRN) treatment regimen as per the European Summary of Product Characteristics (EU SmPC) 2011. Thus, each monitoring visit for PRN entailed assessment of BCVA stability and a decision about potential reinitiation of monthly injections if VA was not stable over the last 3 consecutive monthly visits.

Laser treatment in the T&E+laser group

In the T&E+laser group, patients received laser treatment on Day 1, following which treatment could be readministered based on the early treatment diabetic retinopathy study (ETDRS) guidelines. Treatment was at the discretion of the investigator, and the minimum recommended interval between laser treatments was 3 months. If the investigator deemed the patient required both ranibizumab and laser treatments on the same day, then laser was administered ≥30 minutes prior to the ranibizumab injection.

Retreatment criteria

The retreatment criterion was as defined in the EU SmPC 2011, i.e. treatment is resumed if a patient's vision worsens due to their disease. Accordingly, as soon as at a T&E visit BCVA loss due to recurrent DME disease activity was observed, in comparison to the last T&E visit or to the last visit of monthly injections, whichever occurred later, the patient re-entered the monthly injection phase. The treatment given at this visit was considered the first treatment of the newly entered monthly injection phase. The patient subsequently received monthly treatment until BCVA was stable again. If two consecutive attempts to extend the treatment-free interval in T&E were unsuccessful i.e. there was a loss of BCVA at the end of each extension and the patient re-entered monthly injection phase twice, the future maximum treatment-free period was shortened by 1 month. Thus, patients could fall back to mandatory monthly treatment by this mechanism. Further, the respective intervals between treatments could have been too long to maintain stable BCVA in a given patient. In the PRN regimen, each visit following VA

stabilisation was a potential treatment visit, with the treatment being administered based upon assessment of the patient's vision at that visit.

Individual patients may have received retreatment based on anatomical findings (OCT imaging) in the absence of VA loss, as would have been the standard procedure in routine clinical practice. This practise may help to treat the disease at an earlier stage.