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RESPONSE TO LETTER

Comment on "Effectiveness of 190 µg Fluocinolone Acetonide versus 700 µg Dexamethasone Intravitreal Implants in Diabetic Macular Edema Using the Area-Under-the-Curve Method: The CONSTANT Analysis" [Response to Letter]

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Dear editor

With interest, we read the letter to the Editor regarding the Effectiveness of 190 µg fluocinolone acetonide versus 700 µg dexamethasone intravitreal implants in diabetic macular edema using the area-under-the-curve method: The CONSTANT analysis by Stewart and Taylor published in Clinical Ophthalmology. The key concerns raised by the authors relate to the design deficiencies of the MEAD studies[1] and highlight two specific issues – the six month dosing of the dexamethasone implant and the potentially delayed removal of cataracts.

We acknowledge that both concerns raised will have impacted the visual outcomes reported in the MEAD trial and may have therefore affected the area-under-the-curve (AUC) analysis for the dexamethasone implant in the analysis which aimed to compare the long-term effectiveness of the 190 µg fluocinolone acetonide and 700 µg dexamethasone intravitreal implants based on their supporting pivotal studies.[1,2] However, we would like to highlight that the retreatment for the dexamethasone implant is based on the six month time point and that this is in-line with the approved usage for the dexamethasone in Europe[3] (although the USA label is not as restrictive) and is based on the inclusion criteria in the MEAD studies – ie, "patients who met eligibility criteria could be retreated no more often than every 6 months; maximum of 7 treatments over 3 years."[1] As Stewart and Taylor comment in their letter and as we stated in our original manuscript, we definitely agree that this retreatment criteria may have impacted the visual acuity outcomes observed in the MEAD trial. However, these methodologic deficiencies unfortunately cannot be controlled further, as these are indeed the trial results. The purpose of our study was to compare the visual outcomes of both trials with an AUC analysis approach, and we believe that our conclusions are in-line with this comparison and driven by the trial designs.

The second point concerned the delayed removal of the cataracts. Yang et al[4] analysed the long-term outcomes of phakic patients with diabetic macular edema in the FAME studies and reported that the median time to development of cataract was 12 months and that the median time to extraction was 18 months,[4] with most

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cataract extractions being completed by year two.[5] The MEAD studies also observed an increase in the incidence of cataract surgery from year one with surgeries being conducted between months 18 and 30 (ie, a further 6 months to that reported in the FAME studies). With this data in mind, the delayed time to cataract surgery may support the need for a timelier intervention to provide better, long-term visual outcomes for the patient.

In summary, we do acknowledge that the AUC analysis does have limitations and that these have been acknowledged in the manuscript and are based on the retrospective nature of the analysis as well as the comparison of different study protocols and patients.[6] However, the 190 µg fluocinolone acetonide implant's constant and near zero-order drug release kinetics[7] means it is less affected by the timing of appointments and delayed injections, and is a key design feature that has long-term benefits for patients with diabetic macular edema.

Disclosure

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