Comment on ‘Fluocinolone Acetonide Intravitreal Implant for Treating Recurrent Non-infectious Uveitis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal’

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Dear Editor,

With interest and concern we read “Fluocinolone Acetonide Intravitreal Implant for Treating Recurrent Non-infectious Uveitis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal” by Pouwels et al. [1], published in the November 2019 issue of *PharmacoEconomics*. While we appreciate the role of the Evidence Review Group (ERG) in scrutinising the company submission and providing a different view on the evidence presented by the company, we believe there are several misunderstandings and methodological errors in the publication by Pouwels et al. [1]. Due to the necessary brevity of this letter, only the most substantial of these are addressed here.

1 Place of the Fluocinolone Acetonide (FAC) Implant in the Treatment Pathway

The ERG stated that the position of the fluocinolone acetonide (FAC) implant in the treatment pathway is unclear; an impression that could result from the precise indication for the FAC implant still being in discussions with the Medicines and Healthcare products Regulatory Agency (MHRA) at the time (November 2018) when the initial company submission to the National Institute for Health and Care Excellence (NICE) was made. Consequently, several possible positions of the FAC implant within the treatment pathway

were initially proposed; however, these were subsequently refined in line with the marketing authorisation, which was finalised by the MHRA following the first NICE Appraisal Committee meeting (March 2019). The FAC implant is indicated for prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye (NIU-PS) [2] and is thus placed between first-line and second-line treatment. However, as highlighted by the company, clinicians, and TA460 [3], there is no nationally agreed pathway for the treatment of NIU-PS; as it is a heterogeneous disease, treatment may vary between patients.

2 Comparators

Regarding the ERG criticism of the comparator used within the economic model, the company had argued throughout the appraisal process that various factors speak against a comparison with the treatments initially listed in the scope, especially dexamethasone. The use of (limited) current practice [(L)CP] as a comparator is in line with the strategy of TA460. Furthermore, (L)CP, comprising local and systemic treatments for any uveitis recurrence, included several of the comparators listed in the initial NICE scope.

As far as the comparison with dexamethasone is concerned, the dexamethasone implant is licensed for the treatment of active NIU-PS and no evidence exists with regards to its efficacy in recurrence prevention. Indeed, the authors state that the “company decided not to perform an indirect comparison”, which infers that this was a matter of choice, rather than of the suitability of such a comparison and availability of evidence. There are key differences between the study design of the pivotal trial for dexamethasone (HURON) [4] and the pivotal trial for the FAC implant (PSV-FAI-001) [5]. These include, but are not limited to, incompatible primary and secondary outcomes, differences in the studied populations, and incompatible definitions of

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both supplemental therapies and (L)CP (the comparator). Hence, there is no scientific basis for a comparison (naïve or adjusted) between dexamethasone and the FAc implant. It was further advised by clinicians that dexamethasone may be regarded as a treatment option prior to treatment with the FAc implant in UK clinical practice. Thus, the FAc and dexamethasone implants represent different stages in the treatment pathway and are not directly comparable, as was initially thought during the scoping process. This is similar for adalimumab, whose use in uveitis is relatively restricted by TA460 [3]. At the explicit request from NICE, an informal analysis versus dexamethasone was provided by the company. It was stressed that the results should be interpreted with extreme caution, due to the large number of assumptions necessary in the absence of source data.

We also disagree that (L)CP, as used in the PSV-FAI-001 trial, cannot be considered representative of UK clinical practice. Patients involved in PSV-FAI-001 had relatively quiescent disease at enrolment and, for both arms, they were tapered off systemic therapies over the initial 3 months. In case a patient experienced recurrence after this time, the investigators were encouraged to treat patients first with local therapies, that is, periocular or intravitreal steroids and, if this proved insufficient, with systemic treatments, such as systemic steroids or immunosuppressants. Clinical experts confirmed that reduction of the adverse events (AEs) associated with systemic therapies is an important clinical goal, and that using local treatments before systemic ones is consistent with UK clinical practice. However, NIU-PS is a heterogenous disease that may be accompanied by other conditions, and there is no strictly established treatment pathway. To accommodate this heterogeneity, the progression from local to systemic therapy for uveitis recurrences was a guidance rather than a strict requirement in the pragmatic PSV-FAI-001 trial, allowing the investigators to exercise their clinical judgment.

3 Clinical Evidence Submitted by the Company

The ERG also seems to have misinterpreted the design of the PSV-FAI-001 trial, considering the trial results to be difficult to interpret and uncertain. As a foreword, it is worth clarifying that, the FAc implant is the longest-acting treatment for NIU-PS available in the EU, with a single implant delivering daily micro-doses of FAc directly into the eye over a 3-year period. The PSV-FAI-001 trial investigated whether the FAc implant used as 'background' therapy reduces the number of uveitis recurrences compared with standard management of recurrence alone. While guidance was given to the investigators on the preferred management of recurrences, this was a pragmatic trial permitting variations in recurrence

treatment on a local and patient level, as described above. The ERG stated that patients in the (L)CP arm would not have received any active treatment for NIU-PS after approximately 3 months until recurrence. This is correct for patients without uveitis recurrence but should be viewed in light of the patients recruited into the PSV-FAI-001 trial having relatively quiescent disease at enrolment and the trial protocol permitting investigators to treat patients to achieve the inclusion criteria. Any patients who at baseline were still receiving systemic medications with a potential effect on NIU-PS were tapered off these medications within 3 months from study entry; however, this taper was not enforced if disease recurred and patients could have the tapering stopped (or dose increased) at clinical signs of recurrence. Importantly, the trial did permit treatment of NIU-PS at any point during the study (also after the initial 3-month taper) in both arms of the study. In fact, it is highly unlikely that a trial depriving patients of treatment for active NIU-PS over a 3-year period would be considered ethical and allowed by the regulatory authorities to proceed.

The ERG also noted that most of the events for the primary outcome were imputed in PSV-FAI-001. While this is correct, the PSV-FAI-001 trial protocol stated a recurrence should be imputed not only in the case of missing data, but also where medications with a potential effect on NIU-PS in the study eye were used. At 36 months, only four out of 52 patients with imputed recurrences had missing eye examination data, while the remaining patients had a recurrence imputed due to the use of local or systemic steroids/immunosuppressants. The PSV-FAI-001 trial allowed clinicians to treat patients if there was any sign of uveitis recurrence that required treatment (even if the protocol-defined criteria for recurrence have not been met) and any such treatment administered was classified as an 'imputed recurrence'. This represented a pragmatic, real-world, practice-like approach to study design, since clinicians could treat patients for uveitis at their discretion and these patients remained on study, while the use of imputed recurrence allowed appropriate quantification of the protocol-specified trial endpoints. The company agree that this conservative approach could result in recurrence rate to be somewhat overestimated. However, this affected both trial arms equally without favouring the FAc implant, as the same non-study treatments were permitted in both arms. Additionally, the FAc implant showed a statistically significant reduction in recurrence in the intention-to-treat population as well as in the per-protocol population where only observed (and not imputed) recurrences were considered. Therefore, the benefits of the FAc implant observed in the trial were independent of, and unbiased by, the conservative imputation approach.

4 Cost-Effectiveness Evidence

Regarding cost-effectiveness evidence presented by the company, the ERG raised several issues: visual acuity not being captured in the model, a single implant and single eye being modelled, the use of a Remission state and no transition from ‘on treatment’ to ‘permanent blindness’. The first three critique points can be readily addressed, and are all related to limitations of available data from PSV-FAI-001, the trial informing efficacy estimates in the model. Visual acuity was a descriptively analysed exploratory endpoint in PSV-FAI-001, and therefore not the preferred endpoint to be modelled. The trial also did not investigate retreatment with the FAc implant or bilateral use of the implant. In addition, concurrent treatment of both eyes with the FAc implant is not recommended until the patient’s ocular and systematic response to the first implant is known [2].

With regards to the inclusion of a transition from ‘on treatment’ to ‘permanent blindness’, while a patient may experience an AE resulting in blindness, no patients experienced blindness as a result of treatment with the FAc implant in PSV-FAI-001. Nonetheless, this possibility was indirectly captured in the model, as NIU-PS recurrence in PSV-FAI-001 was characterised, among other clinical signs, by decreasing visual acuity. Therefore, if a patient experienced an AE that caused substantial decrease in visual acuity, this would be recorded as a recurrence and reflected in the model as a move to ‘subsequent therapy’ prior to the move to ‘permanent blindness’. It is also probable that patients with worsening vision or inflammation due to an AE would use a prohibited treatment, resulting in an imputed recurrence reflected in the modelled efficacy estimates. The ERG acknowledged that the company approach was consistent with observations in PSV-FAI-001, but inconsistent with TA460 and used the same assumption that was applied and considered arbitrary in TA460 [3]—the transition from ‘on treatment’ to ‘blindness’ was assumed to be half that from ‘subsequent treatment’ to ‘blindness’. It is critical to highlight here that the company approach was heavily based on available evidence, and only the data available can be modelled without making substantial assumptions that will increase uncertainty and impede decision making; the goal of an HTA.

Regarding the comparison of the FAc implant with dexamethasone, the company has highlighted throughout the appraisal process that no evidence is available to conduct this. The two implants differ in a number of aspects, so that neither the company nor the ERG comparisons can be considered informative. Nonetheless, when specifically requested to perform a comparison with dexamethasone, the company provided a ‘scaled’ efficacy curve,

assuming the time to recurrence profile of dexamethasone over 6 months is the same as that of the FAc implant over 3 years. This was confirmed by clinicians to be reflective of patient experience and clinical expectation for dexamethasone.

Finally, the company considers various scenarios and assumptions used in the ERG analysis as not appropriate or helpful to decision making. It is unsurprising that these scenarios resulted in dominating results; for example, the use of arbitrary hazard ratios to make dexamethasone more effective than the FAc implant, or applying large utility decrements to all AEs regardless of their grade, such that there was no benefit in receiving treatment.

5 The ‘Bigger Picture’

The communication from the ERG highlights an important issue that reaches broader than the NICE appraisal of the FAc implant in NIU-PS. The generalisability of clinical trial results to real-world populations has been criticised [6, 7], mainly due to trial populations being highly selected and trial protocols imposing strict guidance on treatment. The PSV-FAI-001 trial can be considered pragmatic for several reasons, such as permitting patients to be treated to reach the inclusion criteria and allowing investigators to exercise their clinical judgment in patients’ best interest while maintaining these patients on-trial. This approach should be considered as providing a better approximation of UK clinical practice compared with stricter trial protocols; instead it was unduly criticised and misunderstood by the ERG, despite repeated and active communications with the ERG, which may disfavour similar pragmatic trials providing evidence for HTAs in the future.

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Compliance with Ethical Standards

Conflict of interest JJ, KB, KB, VG and PMcE are employees of Health Economics and Outcomes Research Ltd. SM is an employee of Alimera Sciences. AB was an employee of Alimera Sciences at the time of the conception and drafting.

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