Evaluation of the clinical effectiveness in routine practice of fluocinolone acetonide 190 µg intravitreal implant in people with diabetic macular oedema

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Abstract

Objective

The aim of the ILUVIEN Clinical Evidence study in the United Kingdom (ICE-UK) was to assess the real-world effectiveness of fluocinolone acetonide (FAc) 190 µg intravitreal implant for the treatment of clinically significant chronic diabetic macular oedema (DMO) in routine clinical practice.

Methods

This retrospective study collected data from patient medical records in 13 ophthalmology centres for people with DMO prescribed FAc intravitreal implant between 1 April 2013 and 15 April 2016. Visual acuity (VA) and intraocular pressure (IOP) measurements were collected for 12 months prior to and after implant.

Results

208 people contributing 233 eyes treated with FAc implant were included. Mean age was 68.1 years and 62% were male. In the 12 months prior to FAc implant, VA declined. Median (interquartile range, IQR) VA was 0.66 (0.50–1.00) LogMAR units (equivalent to 52.0 ETDRS letters) at implant, improving to 0.60 (0.40–0.86) LogMAR units (55.0 letters) at 12 months post implant ($p<0.001$). 44%, 30% and 18% of people achieved an improvement in ETDRS score of ≥5, ≥10 and ≥15 letters, respectively, over the same period. A small but significant ($p<0.001$) increase in median IOP was observed (median 15.0, IQR 13.0–18.0 mmHg at implant to 18.0, 15.0–21.0 mmHg at 12 months). In the 12 months following implant, additional IOP-lowering therapy was prescribed in 15% of subjects previously not requiring such therapy.

Conclusion

Following FAc implant, an overall significant improvement in VA was observed over a period of 12 months, accompanied by a significant but small increase in IOP.

Introduction

The fluocinolone acetonide (FAc) 190 µg intravitreal implant has been licensed in 17 European countries for the management of chronic diabetic macular oedema (DMO) when other treatments have proven to be insufficiently effective. The approval of the FAc implant was based on data from the Fluocinolone Acetonide in Diabetic Macular Edema (FAME) study programme.[1] This programme comprised two separate randomised controlled trials, FAME A and FAME B, and studied the clinical effectiveness of the FAc intravitreal implant in DMO.[2,3] Analysis of the combined data demonstrated that, versus the patients randomised to sham injection, the FAc 0.2µg/day intravitreal implant provided significant visual benefits over the three year period of follow-up.[2,3]

However, the treatment paradigm for centre-involving clinically significant DMO has changed since the FAME studies were conducted. At that time, laser photocoagulation was considered to be the cornerstone in the management of DMO, supported by evidence from the Early Treatment Diabetic Retinopathy Study (ETDRS).[4] However, several landmark trials have since demonstrated that anti-VEGF therapy can lead to an improvement in vision in people with DMO[5–8] and therefore anti-VEGF therapy is now considered to be the gold-standard, first-line treatment for the condition. People recruited for the FAME studies were previously treated with retinal laser therapy with no prior history of exposure to anti-VEGF therapies.[2,3] As the FAc intravitreal implant is currently only indicated when available therapies have proved to be insufficiently effective, there is a need to determine the effectiveness of FAc in those individuals previously exposed to anti-VEGF therapy.

The role of real-world clinical evidence in supplementing clinical trial data has been acknowledged by regulatory authorities,[9] with eye disorders previously investigated using either prospective (HELIOS)[10] or retrospective designs (TWIN).[11] Studies investigating the effectiveness of the FAc intravitreal implant using real-world data are limited, with most of the studies being short-term follow-up studies with small participant numbers and/or limited data collection.[12–16] However, in a recently published, larger prospective study by El-Ghrably and colleagues involving DMO

subjects previously treated with anti-VEGF (n=57), an improvement in best-corrected visual acuity and central macular thickness was observed at 3 months post FAc implant, with a sustained effect observed for the remainder of the 12 month follow-up period.[17]

Since FAME, no randomised clinical trials have been conducted to assess the impact of FAc intravitreal implant on visual acuity and other clinical outcomes after treatment with anti-VEGF. Therefore, the aim of the ILUVIEN Clinical Evidence study in the United Kingdom (ICE-UK) was to assess the real-world effectiveness of FAc intravitreal implant in routine clinical practice. Additionally, the project was conducted to assess the long-term effect of FAc intravitreal implant on intraocular pressure (IOP) and its management in clinical practice. The real-world evidence generated by the clinical use of FAc intravitreal implant since 2013 represents a retrospective method of collecting the evidence on treatment outcomes. The study design enabled data to be collected for at least 12 months prior to and at least 12 months post implant. The collection of data prior to implant is of considerable advantage to this study and is rarely available from randomised controlled trials.

Methods

Data Source

A retrospective cohort study was conducted. In this multi-centre, hospital-based study, data were taken from the medical records. Data collection was secondary, as the data used for this study were initially collected for purposes other than research. Data were collected from a representative cohort of people treated at 13 participating hospitals in the UK and combined into a single dataset for the purpose of analysis. These data were pseudonymised and entered into an online data entry tool (Real World Treatment Evaluator), where centre and subject identifiers were added. Data generated from retrospective case reviews were entered by the consultant themselves or by other members of the healthcare professional's team.

Data included demographics, medical history, implant data, and data from multi-disciplinary and medication reviews at several time points within a designated period (see Supplementary Figure 1). Quantitative data were generated from medical records, administrative records and clinical measurements and were collected only for those parameters that were necessary to answer the research question. Summaries by site were not performed other than for analysis relevant to evaluation of their healthcare service. No data linkage took place in the course of this project. At no point did Alimera Sciences, the manufacturer of ILUVIEN, have access to the data.

Ethical approval

The lead clinician and Caldicott Guardian at each centre gave written approval for extraction of anonymised data. The study protocol was approved by the head of research governance at the lead clinical centre. This study was conducted in accordance with the Declaration of Helsinki and the UK Data Protection Act.

Subjects

A cohort of people prescribed FAc 190 µg intravitreal implant was constructed based on past exposure to FAc intravitreal implant. People with type 1 and type 2 diabetes treated with FAc intravitreal implant for DMO in at least one eye were included in the cohort if they had received an implant at a participating site as part of their routine care between 1 April 2013 and 15 April 2015 and had a minimum of 12 months' history prior to implant. Subjects were excluded from the study if they had been involved in other, prior interventional studies for DMO. People who had insufficient follow-up because they had left the clinic, had no visits or had missed their last appointment post-index were also excluded from the study.

The index date was defined as the date of first recorded FAc intravitreal implant into the study eye. All subjects were followed from implant for one year. As the end of the observation period was 15 April 2016, all selected subjects had a follow-up of at least one year post implant. Individuals that received FAc intravitreal implant in both eyes were allowed to contribute both eyes to the study.

Outcomes

For these analyses, the following clinical outcomes were investigated at 3, 6 and 12 months post index date: change in visual acuity on the LogMAR (Logarithm of the Minimum Angle of Resolution) scale; proportion of eyes that demonstrated an improvement in ETDRS score of ≥5 letters, ≥10 letters and ≥15 letters; and change in IOP from implant.

Visual acuity was measured using one of: ETDRS scores, Snellen fractions or LogMAR scores. Snellen fractions were converted to approximate ETDRS scores for the purpose of analysis using the following formula derived by Gregori and colleagues: approximate ETDRS = 85 + 50 x log (Snellen fraction).[18] All approximate ETDRS scores were rounded to the nearest integer. Snellen fractions were converted to LogMAR scores using the following formula: -1 x log (Snellen fraction).[18] These formulae were rearranged to convert between LogMAR and ETDRS. Where a person could only

detect light, detect movement or count fingers, a LogMAR score of 2.3, equivalent to counting figures, was applied.[18]

Subgroups

Results are presented for four subgroups based on higher and lower visual acuity at implant (<0.7 and ≥0.7 on LogMAR scale, equivalent to an approximate ETDRS letter score of <50 and ≥50[18]) and number of treatments for DMO prior to implant (categorised as six or fewer treatments and more than six treatments). Treatments for DMO were defined as laser therapy, steroid treatment (triamcinolone and dexamethasone) and anti-vascular endothelial growth factor (anti-VEGF) injection (ranibizumab, aflibercept and bevacizumab). People with no baseline visual acuity score and no history of receiving any anti-VEGF, macular laser or steroid therapy prior to index date were excluded from the subgroup analyses.

Statistical analysis

Changes in visual acuity (LogMAR scale) and IOP were compared between implant and the 3, 6 and 12 month time points using the non-parametric Wilcoxon signed ranks test because the variables were not normally distributed. The proportions of people achieving an improvement in visual acuity between implant and the 3, 6 and 12 month time points were compared between subgroups using Fisher's exact test. Mean and median visual acuity (LogMAR scale) were calculated on a daily basis for the 12 months prior to and post FAc implant. In order to smooth the data, missing values for each day of this 24 month period were imputed using linear interpolation.[19] As linear interpolation could not be used before the first recorded value or after the last recorded value, nearest observation carried forward and backwards were used to impute the remaining missing values. Last observation carried forward was implemented to impute missing values in all other analyses where change in study outcomes were evaluated at 3, 6 and 12 month follow-up time points.[19] Missing values were imputed in two stages: ≤index date and >index date. Statistical analyses were carried out using IBM SPSS statistics version 20.

Results

Data were collected on 311 people, of which 208 people contributing 233 eyes treated with FAc intravitreal implant were eligible for inclusion in the study cohort (Figure 1). 205 people (99%) had bilateral DMO at implant. Of the 233 eyes treated, 208 were first eyes treated with the implant and 25 were a second eye in the same person.

Patient characteristics

Of the 208 people treated in any eye, 128 (62%) were male. Mean age was 68.1 years. 176 (85%) had type 2 diabetes (Table 1). Median (IQR) duration of diabetes was 18 (11–28) years.

216 treated eyes had a baseline visual acuity score and a history of receiving at least one treatment for DMO (steroid, macular laser or anti-VEGF therapies). Of these, 89 eyes (41%) had previously received six or fewer prior treatments. Visual acuity was <0.7 LogMAR units in 45 eyes (21%) and ≥0.7 LogMAR units in 44 eyes (20%). 127 eyes (59%) had received more than six prior anti-VEGF, macular laser or steroid therapies prior to implant. Here, visual acuity was <0.7 LogMAR units in 63 (29%) eyes and ≥0.7 LogMAR units in 64 eyes (30%).

207 treated eyes (89%) had a pseudophakic lens at the time of implant. Median (IQR) visual acuity at implant was 0.66 (0.48–1.00) LogMAR units. Mean (SD) central foveal thickness at implant was 482 μm (186 μm), and median (IQR) IOP was 15.0 (13.0–18.0) mmHg. Median (IQR) number of macular laser treatments, steroid treatments and anti-VEGF injections prior to index date was 1.0 (0.0–3.0), 0.0 (0.0–1.0) and 5.0 (2.0–7.0), respectively. Baseline characteristics by visual acuity and treatment subgroups are described in Table 1 and Supplementary Table 1.

Intraocular therapies

At FAc implant, 191 eyes (82%) had received at least one prior anti-VEGF treatment (Table 2). 13 (6%), 21 (9%) and 41 (18%) treated eyes received additional anti-VEGF treatment between 0 and 3 months, 3 and 6 months and 6 and 12 months post FAc implant. 3 (1%), 3 (1%) and 11(5%) treated eyes received additional steroid therapy between 0 to 3 months post index date, 3 to 6 months post index date and 6 to 12 months post index date, respectively. The corresponding figures for laser therapy were 4 (2%), 6 (3%) and 11 (5%) procedures, respectively. Over the 12 month follow-up period, additional treatments for DMO were used in 69 (30%) of treated eyes. Cataract operations were conducted in 19 eyes between 0 to 3 months. However, 14 of these operations were conducted on the same date as the eye was implanted. A cataract operation was conducted on one treated eye between 3 and 12 months post implant.

Visual acuity

In the 12 month period prior to FAc implant, a decrease in visual acuity was observed (median 0.6 to 0.66 LogMAR units [55.0 to 52.0 ETDRS letters], mean 0.72 to 0.76 LogMAR units [50 to 47.5 ETDRS letters] from 12 months prior to index date, Figure 2). Following implant, visual acuity improved (median 0.55 and 0.60 LogMAR units [57.5 and 55.0 ETDRS letters] and mean 0.65 and 0.67 LogMAR units [52.9 and 51.8 ETDRS letters] on months 4 and 12 post implant).

Median (IQR) visual acuity in treated eyes changed from 0.64 (0.48–1.00) to 0.54 (0.40–0.90) LogMAR units between implant and 3 months ($p<0.001$), from 0.66 (0.50–1.0) to 0.54 (0.32–0.82) LogMAR units between implant and 6 months ($p<0.001$) and from 0.66 (0.50–1.00) to 0.60 (0.40–0.86) LogMAR units between implant and 12 months ($p<0.001$, Table 3). Following conversion to ETDRS letter score, median (IQR) visual acuity changed from 53.0 (35.0–61.0) to 58.0 (40.0–65.0) letters between implant and 3 months, from 52.0 (35.0–61.0) to 58.0 (41.5–69.0) letters between implant and 6 months and from 52.0 (35.0–61.0) to 55.0 (40.0–66.0) letters between implant and 12 months.

Change in visual acuity score by subgroup is detailed in Figure 4 and Supplementary Figure 3. A significant improvement in visual acuity was observed at all time points in those eyes with a visual acuity score of ≥0.7 LogMAR units at implant, regardless of treatment subgroup (six or fewer and more than six anti-VEGF, steroid and macular laser therapies prior to index date; Table 3). At 12 months post FAc implant, a non-significant improvement in visual acuity was observed in those with a visual acuity score of <0.7 LogMAR units at baseline (median [IQR] 0.48 [0.3–0.54] LogMAR units or 65 [55–75 ETDRS] letters at implant and 0.4 [0.2–0.6] LogMAR units or 64.5 [55–74.5] letters at 12 months post implant, p=0.390). Similarly, a non-significant improvement in visual acuity was observed in the same eyes when analysed by treatment subgroup.

When analysed using ETDRS score, visual acuity improved by at least five letters in 91 (45%), 107 (49%) and 99 (44%) of the treated eyes at 3 months, 6 months and 12 months post implant, respectively (Figure 3). The corresponding visual acuity scores for an improvement of ≥10 letters were 56 (28%), 73 (33%) and 68 (30%), respectively. 30 (15%), 38 (17%) and 41 (18%) eyes had an improvement in ETDRS score of at least 15 letters at 3 months, 6 months and 12 months post index, respectively. The corresponding figures by visual acuity and treatment subgroup are detailed in Figure 3 and Supplementary Figure 2. No significant association between the number of prior treatments (six or fewer and more than six) and the achievement of an improvement of ≥5 letters, ≥10 letters and ≥15 letters in ETDRS score from implant to the three time points was observed within each visual acuity subgroup (<0.7 and ≥0.7 LogMAR units). In those eyes with a pseudophakic lens at implant, 36 (17%) had an improvement in ETDRS letter score of ≥15 letters at 12 months. Visual acuity worsened by ≥5 letters in 53 (24%) eyes, ≥10 letters in 31 (14%) eyes and ≥15 letters in 20 (9%) eyes between FAc implant and 12 months follow-up.

Intraocular pressure

Median (IQR) IOP increased from implant to each time point: 15.0 (13.0–18.0) mmHg at implant to 17.0 (14.0–20.0) mmHg at 3 months ($p<0.001$), 15.0 (13.0–18.0) mmHg at implant to 17.0 (15.0–20.0) mmHg at 6 months ($p<0.001$) and 15.0 (13.0–18.0) mmHg at implant to 18.0 (15.0–21.0) mmHg at 12 months ($p<0.001$; Table 4).

5 (3%), 15 (8%) and 29 (15%) people with no history of receiving IOP-lowering therapies prior to FAc intravitreal implant were prescribed IOP-lowering therapy between 0 to 3 months, 0 to 6 months and 0 to 12 months post implant (Table 5).

IOP was <21 mmHg in 141 (90%) treated eyes at FAc implant and 127 (81%) treated eyes at 3 months ($p=0.029$). 159 (91%) and 137 (78%) treated eyes had an IOP of <21 mmHg at FAc implant and 6 months, respectively ($p=0.002$). The corresponding values at implant and 12 months were 165 (91%) and 135 (75%), respectively ($p<0.001$).

Discussion

In the 12 months prior to the FAc implant, a decline in visual acuity was observed. Following FAc intravitreal implant, there was an overall improvement in visual acuity at 3, 6 and 12 months. Visual acuity improved by at least 15 letters in nearly one fifth of treated eyes at 12 months post implant. After insertion of FAc intravitreal implant, there was a small but statistically significant increase in median IOP recorded at 3, 6 and 12 months, but this remained below a median value of 21 mmHg at each time point. 15% of subjects were newly treated with IOP-lowering medication in the first 12 month period following FAc implant. Additional concomitant treatments for DMO were used in 30% of treated eyes during the 12 month study follow-up period. This needs to be taken into account when interpreting these results.

In the UK, NICE recommends the use of FAc only in DMO-affected eyes that have an artificial lens and are insufficiently responsive to other treatments.[20] 90% of treated eyes in the ICE-UK study cohort were pseudophakic, with a further 6% receiving a cataract operation on the same day as the FAc implant. 97% of eyes had previously been treated with at least one anti-VEGF, steroid or laser therapy prior to index.

In the FAME trial—randomised with a sham injection—it was found that 29% of eyes treated with 0.2 µg/day FAc intravitreal implant achieved a 15-letter improvement in visual acuity at 24 months following implant insertion versus 16% (p=0.002) in the sham treated group.[3] Of those patients randomised to 0.2 µg/day FAc implant, 23% demonstrated ≥15 letter improvement in visual acuity over baseline at 12 months.[3] At 12 months post implant, we similarly found that 18% of treated eyes achieved an improvement in visual acuity of ≥15 letters. The FAMOUS (Fluocinolone Acetonide in Human Aqueous) trial randomly allocated individuals with DMO previously treated with a least one laser therapy to receive high or low dose FAc intravitreal implant and reported that 15% of people receiving the 0.2 µg/day implant achieved a 15 letter improvement in visual acuity at 12 months post implant.[21]

Compared with FAME, there was a higher percentage of people with type 1 diabetes in the ICE study cohort.[3] In addition, the people included in the ICE study were generally older, with a higher proportion of treated eyes with a pseudophakic lens.[3]

Visual acuity at implant was lower in this study (median LogMAR 0.66 units, converting to an ETDRS score of 47 letters compared with a mean of 53.4 letters in the FAME study).[3] Cunha-Vaz and colleagues reported that the percentage of people in the FAME trial that gained a 15 letter improvement in visual acuity following implant was significantly higher in those with chronic DMO versus those with non-chronic DMO.[22] Unfortunately, chronicity of DMO was not recorded in the ICE-UK study. However, the highest percentage of people achieving a ≥15 letter improvement in ETDRS score at 12 months was observed in those with poorer vision at implant (≥0.7 LogMAR units) and a history of receiving a greater number of anti-VEGF, steroid or laser treatments (more than six). In a retrospective study by Elaraoud and colleagues, an improvement in visual acuity and central retinal thickness was observed in 15 out of 22 pseudophakic eyes treated with FAc intravitreal implant, the majority of which had been previously treated with multiple anti-VEGF and laser therapies.[14] In a recent retrospective study by El-Ghrably and colleagues, 5 out of 22 eyes (22.7%) achieved an increase in ETDRS letter score of ≥15 letters at 12 months.[17] As with this study, a small decrease in visual acuity was reported between 6 and 12 months post FAc implant.[17]

In the FAME study, the most commonly reported adverse event was cataract surgery, which was listed as an adverse event in 75% of the low-dose group, 85% of the high-dose group, and 23% of the sham group after 24 months of follow-up in those with no history of cataract surgery at implant.[3] At 36 months, cataracts were reported in 82%, 89%, and 50% of the people with no prior history of cataract surgery in each of the groups, respectively.[2] In this study, 19 cataract operations were observed between 0 and 3 months post-implant, where 14 of these operations were carried out on the day of implant. However, cataract development is likely to have pre-dated FAc implant in these cases and it is probable that these operations were carried out on pre-existing conditions. No cataract surgeries were recorded between 3 and 12 months post-implant. However, the high proportion of treated eyes with a pseudophakic lens at implant needs to be considered when interpreting this observation (90% versus 35% in the FAME study).[3]

Steroids are known to be associated with raised intraocular pressure and the FAc 190 µg intravitreal implant is contraindicated in people with glaucoma. Although the number of patients with glaucoma at the time of implant was not known, 19% of study eyes had been treated with IOP-lowering therapy prior to insertion of the FAc implant in the current study.[3] Following FAc implant, a small but statistically significant increase in IOP was found at 3, 6 and 12 months. However, the median IOP remained below 21 mmHg. 15% of eyes with no history of receiving IOP-lowering therapy prior to FAc intravitreal implant were prescribed IOP-lowering therapy between 0 and 12 months post implant. IOP-lowering surgery was required in only one eye between 3 and 6 months post implant and in one eye at 6 to 12 months post index. The first eye (treated between 3 and 6 months post implant) had a history of IOP-lowering therapy prior to implant. The second eye had no history of glaucoma prior to implant. In the FAME trials, people with glaucoma were excluded. A higher proportion of treated eyes required glaucoma surgery in the FAME study, where laser trabeculoplasty and incisional IOP-lowering surgery were carried out in 1.3% and 4.8% of eyes treated with the 0.2 µg/day FAc implant and 0% and 0.5% of those treated with sham, respectively.[2] However, IOP increases were manageable and did not affect vision outcomes.[23] In the FAME trials, FAc was not associated with significant glaucomatous changes in the optic nerve head in those with or without raised IOP.[24]

Strengths and limitations

Several measures were taken to maintain consistency in data entry. All data-entry personnel received one-to-one training and continued support. Eligibility criteria were checked both prior to data entry and after any new record had been entered. The online database included partial validation upon data entry, and the user interface and data entry processes were designed to minimise errors and achieve consistency between centres. New data entered were checked daily for irregularities and data entry progress was monitored and logged.

As this is an observational study, several limitations may occur. Retrospective studies are subject to bias and confounding and can only be used to infer association and not causation. Medical records may be incomplete for patients who switch ophthalmology centres. Recording of procedures occurring near the end of the study observation period (15 April 2016) may also be incomplete. Misclassification of outcomes, effectiveness and safety may have occurred, although data were taken from patient notes and electronic medical records. As data were collected from routine secondary care, outcomes were not measured at set times post index. Individual information on exposures and outcome was not consistently available across all participating centres for all the time points planned in the analysis. Last observation carried forward minimised the elimination of individuals from the analysis but can produce a biased estimate of treatment effect and smaller standard errors. However, as visual acuity continued to improve over the follow-up period, we believe that the use of last observation carried forward will provide a conservative estimate of the effectiveness of FAc. However, for IOP, which continued to worsen over the period of follow-up, the results may be optimistic. Recall of participants for review may have led to differential misclassification and missing values. Duration of diagnosed DMO was not recorded. Unfortunately, information recorded for lens status and cataract status was inconsistent in some people, potentially leading to misclassification. Data on lens status and cataract operations for each eye were scrutinised in order to classify phakic and pseudophakic lens status at implant and the presence of cataract operations post implant. However, some eyes were classified as having a pseudophakic lens at index date but had no history of receiving a cataract operation. Visual acuity scores recorded on the same date as the first administration of FAc intravitreal implant were assumed to have been measured prior to implant. Analysis was restricted to 12 months follow-up post implant because available follow-up after this date varied from person to person.

First and second treated eyes from the same individual were analysed as independent observations. However, FAc implant in a second eye may be more likely if the first eye responded positively to FAc implant. In addition, bilateral treatment with FAc implant may be more likely to occur at certain treatment centres.

The date on which age and duration of diabetes was recorded was not documented. Therefore, it was not possible to determine the subject's exact age or their duration of diabetes at implant. The dataset included other parameters where a specific event date was not recorded (lens status, visual acuity score, central foveal thickness and IOP). In these cases, the date of the event was defined as the review date. Due to the retrospective nature of the ICE-UK study, it was not possible to ensure that visual acuity was recorded using the same standardised method. Visual acuity was recorded as one of: Snellen fractions, ETDRS letter score or LogMAR units. Conversion was required for data analysis, and the method adopted by Gregori and colleagues was used.[18] However, the use of a standardised method for measuring visual acuity using ETDRS letter score is likely to have provided more accurate visual acuity measurements. People who could only count fingers or detect movement or light at implant were attributed a LogMAR score of 2.3, the LogMAR score applied to people who can count fingers. Therefore, visual acuity on the LogMAR scale was overestimated in those people that could only detect movement or light.

Conclusion

In the 12 months prior to FAc implantation, a decline in visual acuity was observed. Following FAc implantation, an overall improvement in visual acuity was observed over a period of 12 months. A small but significant increase in IOP was observed following FAc implant, which required emergent IOP-lowering therapy in 15% of FAc-treated eyes.

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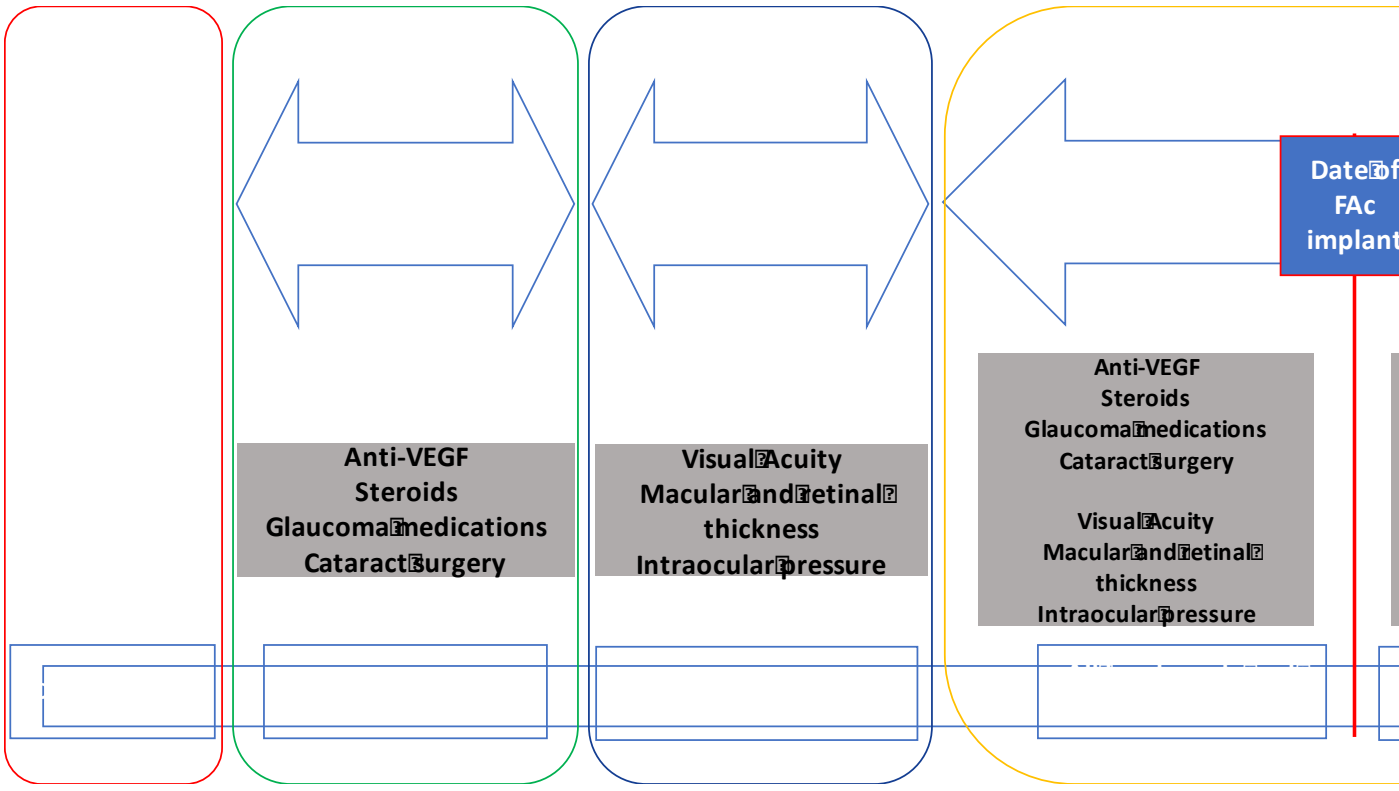
These results have been presented at The Association for Research in Vision and Ophthalmology (ARVO) 2017 meeting and the Royal Colloge of Ophthalmology (RCOphth) Congress 2017.

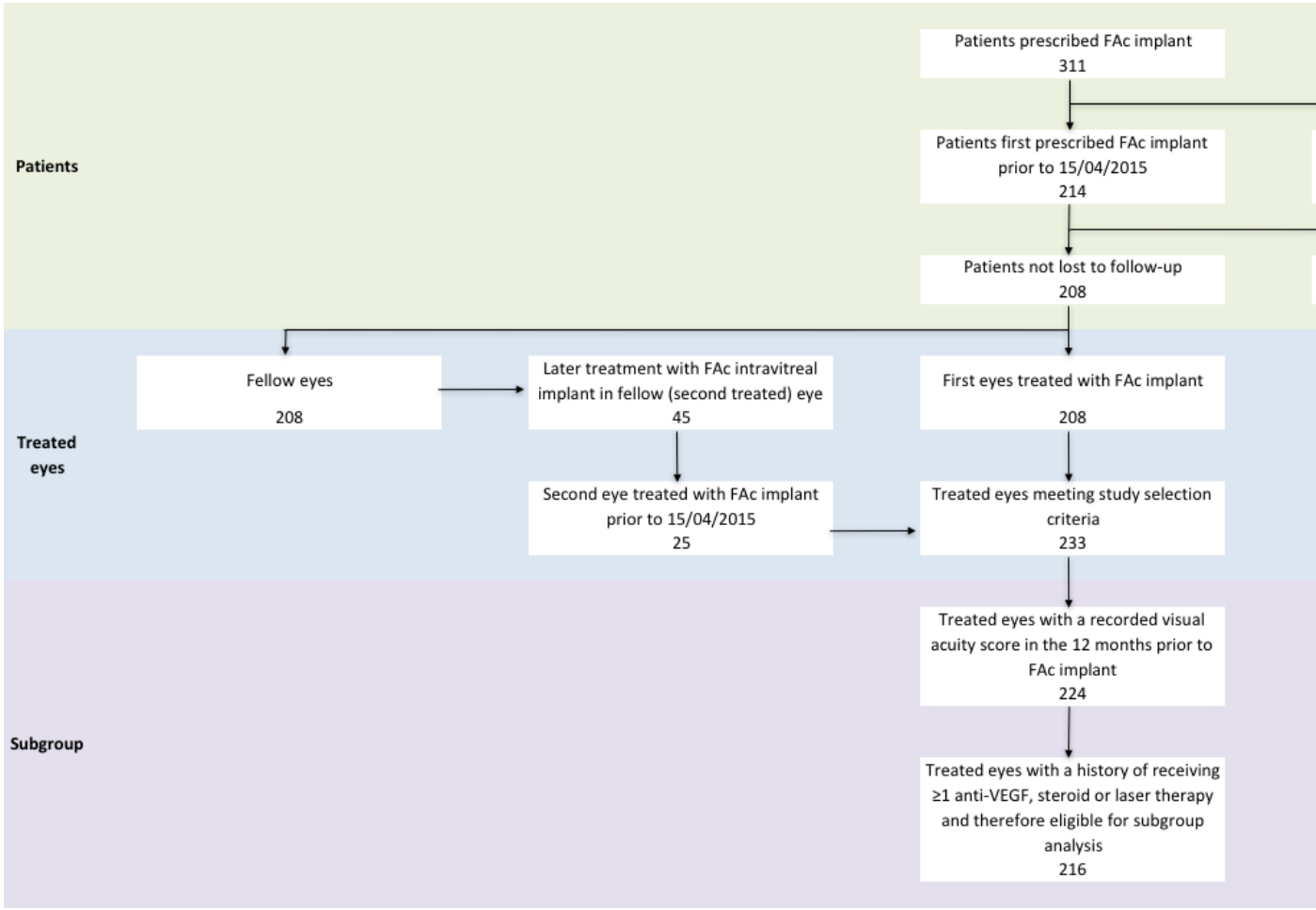
Tables and figures

Supplementary Figure 1 | Flow diagram illustrating patient data capture for first treated ILUVIEN included in ICE-UK



Anti-VEGF = anti-vascular endothelial growth factor, FAc = fluocinolone acetonide.

Figure 1 | Attrition



FAc = fluocinolone acetonide, VEGF = vascular endothelial growth factor

Table 1 | Baseline characteristics overall and by visual acuity and treatment subgroup

Parameter	All study eyes		VA <0.7 LogMAR units at FAc implant				
			≤6 prior treatments for DMO		>6 prior treatments for DMO		≤6
Subjects, n	208						
First eyes treated, n (%)[a]	208	(89%)	43	(96%)	51	(81%)	41
Second eyes treated, n (%)[b]	25	(11%)	2	(4%)	12	(19%)	3
All treated eyes, n (%)	233		45	(19%)	63	(27%)	44
			0.21		0.29		0
Patient characteristics							
Age last clinic visit, mean (SD), years[c]	68.1	(10.7)	69	(11.5)	67.6	(10.9)	69
Males, n (%)	128	(62%)	30	(68%)	39	(71%)	23
Type 2 diabetes, n (%)	176	(85%)	36	(82%)	43	(78%)	39
Oral antihyperglycaemic agents	76	(43%)	17	(47%)	17	(40%)	19
Insulin	43	(24%)	11	(31%)	10	(23%)	9
Insulin plus oral antihyperglycaemic agents	57	(32%)	8	(22%)	16	(37%)	11
Type 1 diabetes, n (%)	32	(15%)	8	(18%)	12	(22%)	4
Oral antihyperglycaemic agents	0	(0%)	0	(0%)	0	(0%)	0
Insulin	28	(88%)	6	(75%)	11	(92%)	3
Insulin plus oral antihyperglycaemic agents	4	(13%)	2	(25%)	1	(8%)	1
Duration of diabetes, median (IQR), years[c]	18	(11–27)	14.5	(10–25)	20	(14.5–30.5)	15
Treated eye characteristics							
Duration of treated DMO, median (IQR), years	2.7	(1.1–4.8)	1.0	(0.7–2.7)	4.1	(2.3–6)	2
Pseudophakic lens status, n (%)[d]	207	(89%)	38	(84%)	56	(89%)	40
Visual acuity, LogMAR units							
n (%)	224	(96%)	45	(100%)	63	(100%)	44
Median (IQR)	0.66	(0.48–1)	0.42	(0.3–0.5)	0.5	(0.34–0.54)	1
Central subfield thickness, µm							
n (%)	198	(85%)	41	(91%)	54	(86%)	38
Median (IQR)	447	(352–587)	433	(330–523)	424	(324–492)	500
Central foveal thickness, µm							

n (%)	191	(82%)	42	(93%)	52	(83%)	37
mean (SD)	482	(186)	449.9	(171.4)	422	(154.8)	530
IOP, mmHg							
n (%)	185	(79%)	40	(89%)	53	(84%)	35
Median (IQR), mmHg	15	(13–18)	15	(13–17)	15	(12–18)	14
Prior macular laser treatments							
n (%)	146	(63%)	17	(38%)	48	(76%)	31
Median (IQR)	1	(0–3)	0	(0–1)	2	(1–5)	1
Time since first laser, median (IQR), years	3.8	(2.1–6.1)	3.3	(1.1–5.5)	4.2	(3.1–6.8)	3
Time since last laser, median (IQR), years	2.2	(1.2–3.9)	1.9	(1–3.6)	2.7	(2–4.2)	1
Prior anti–VEGF injections							
n (%)	191	(82%)	37	(82%)	62	(98%)	27
Median (IQR)	5	(2–7)	3	(1–4)	7	(5–10)	1
Time since first injection, median (IQR), years	1.2	(0.8–2.5)	0.7	(0.6–1)	1.3	(1–2.7)	0
Time since last injection, median (IQR), years	0.4	(0.2–0.7)	0.3	(0.2–0.6)	0.4	(0.2–0.7)	0
Prior ranibizumab injections							
n (%)	162	(70%)	31	(69%)	56	(89%)	22
Median (IQR)	3	(0–6)	2	(0–4)	6	(3–8)	0
Prior aflibercept injections							
n (%)	1	(0%)	0	(0%)	0	(0%)	0
Median (IQR)	0	(0–0)	0	(0–0)	0	(0–0)	0
Prior bevacizumab injections							
n (%)	74	(32%)	6	(13%)	23	(37%)	6
Median (IQR)	0	(0–2)	0	(0–0)	0	(0–3)	0
Prior steroid injections,							
n (%)	101	(43%)	9		30		16
Median (IQR)	0	(0–1)	0	(0–0)	0	(0–1)	0
Time since first injection, median (IQR), years	2.2	(1.1–2.9)	2.1	(1.1–2.7)	2.0	(0.9–2.7)	1
Time since last injection, median (IQR), years	1.8	(0.7–2.7)	2.1	(1.1–2.7)	1.2	(0.5–2.5)	1
Prior dexamethasone injections							
n (%)	17	(7%)	0	(0%)	6	(10%)	3
Median (IQR)	0	(0–0)	0	(0–0)	0	(0–0)	0
Prior triamcinolone injections							

n (%)	88	(38%)	9	(20%)	25	(40%)	13
Median (IQR)	0	(0–1)	0	(0–0)	0	(0–1)	0
IOP-lowering medication, n (%)	44	(19%)	8	(18%)	6	(10%)	9
Prostaglandin analogues, n (%)	26	(11%)	5	(11%)	4	(6%)	6
Beta blockers, n (%)	17	(7%)	1	(2%)	2	(3%)	5
Alpha agonists, n (%)	5	(2%)	1	(2%)	1	(2%)	0
Carbonic anhydrase inhibitors, n (%)	11	(5%)	2	(4%)	0	(0%)	1
Other, n (%)	8	(3%)	3	(7%)	1	(2%)	2

FAc = fluocinolone acetonide, VA = visual acuity, DMO = diabetic macular oedema, SD = standard deviation, IQR = interquartile ra
vascular endothelial growth factor, IQR = interquartile range, LogMAR = logarithm of the minimum angle of resolution, ETDRS = E
[a] These are approximate estimates as it was not possible to determine the exact date on which these parameters were recorded i
Although some of the characteristics relate to the individual and not the eye, each eye was analysed as an independent observati

Supplementary Table 1 | Baseline characteristics by visual acuity or treatment subgroup

Parameter	VA <0.7 LogMAR units at FAc implant		VA ≥0.7 LogMAR units at FAc implant		≤6 prior treatments f DMO	
Subjects, n						
First eyes treated, n (%)[a]	94	(87%)	99	(92%)	84	(94%)
Second eyes treated, n (%)[b]	14	(13%)	9	(8%)	5	(6%)
All treated eyes, n (%)	108	(46%)	108	(46%)	89	(38%)
Patient characteristics						
Age last clinic visit, mean (SD), years[c]	68.2	(11.2)	68.3	(10)	69.1	(10.8)
Males, n (%)	68	(69%)	58	(57%)	51	(60%)
Type 2 diabetes, n (%)	79	(81%)	93	(91%)	73	(86%)
Oral antihyperglycaemic agents	34	(43%)	42	(45%)	34	(47%)
Insulin	21	(27%)	20	(22%)	20	(27%)
Insulin plus oral antihyperglycaemic agents	24	(30%)	31	(33%)	19	(26%)
Type 1 diabetes, n (%)	19	(19%)	9	(9%)	12	(14%)
Oral hypoglycaemic agents	0	(0%)	0	(0%)	0	(0%)
Insulin	16	(84%)	8	(89%)	9	(75%)
Insulin plus oral antihyperglycaemic agents	3	(16%)	1	(11%)	3	(25%)
Duration of diabetes, median (IQR), years[c]	18	(11–27.5)	19	(11.5–26.5)	15	(10–25)
Treated eye characteristics						
Duration of treated DMO, median (IQR), years	2.7	(1–4.8)	2.8	(1.8–5.1)	1.4	(0.8–3.3)
Pseudokaphic lens status, n (%)[d]	94	(87%)	97	(90%)	78	(88%)
Visual acuity, LogMAR units						
n (%)	108	(100%)	108	(100%)	89	(100%)
Median (IQR)	0.48	(0.3–0.52)	1	(0.8–1.3)	0.66	(0.42–1)
Central subfield thickness, µm						
n (%)	95	(88%)	97	(90%)	79	(89%)
Median (IQR)	429	(327–514)	510	(374–634)	450	(361–600
Central foveal thickness, µm						

n (%)	94	(87%)	91	(84%)	79	(89%)
mean (SD)	434.4	(162.1)	538.5	(197)	487.4	(191.6)
IOP, mmHg						
n (%)	93	(86%)	83	(77%)	75	(84%)
Median (IQR), mmHg	15	(13–17)	15	(13–18)	15	(13–17)
Prior macular laser treatments						
n (%)	65	(60%)	78	(72%)	48	(54%)
Median (IQR)	1	(0–2.5)	1	(0–3)	1	(0–2)
Time since first laser, median (IQR), years	4.1	(2.6–6.2)	3.1	(2–6.1)	3.0	(1.6–5.5)
Time since last laser, median (IQR), years date	2.6	(1.6–4.2)	2.0	(1–3.2)	1.9	(0.8–3.1)
Prior anti–VEGF injections						
n (%)	99	(92%)	85	(79%)	64	(72%)
Median (IQR)	5	(3–7)	5	(1–8)	2	(0–4)
Time since first injection, median (IQR), years	1.1	(0.7–1.8)	1.3	(0.8–2.6)	0.7	(0.5–1)
Time since last injection, median (IQR), years	0.4	(0.2–0.6)	0.4	(0.3–0.6)	0.3	(0.2–0.6)
Prior ranibizumab injections						
n (%)	87	(81%)	74	(69%)	53	(60%)
Median (IQR)	4	(1.5–6)	3	(0–6)	1	(0–3)
Prior aflibercept injections						
n (%)	0	(0%)	1	(1%)	0	(0%)
Median (IQR)	0	(0–0)	0	(0–0)	0	(0–0)
Prior bevacizumab injections						
n (%)	29	(27%)	39	(36%)	12	(13%)
Median (IQR)	0	(0–1)	0	(0–3)	0	(0–0)
Prior steroid injections,						
n (%)	39		59		25	
Median (IQR)	0	(0–1)	1	(0–1)	0	(0–1)
Time since first injection, median (IQR), years	2.1	(0.9–2.7)	2.3	(1.3–3.3)	1.8	(0.7–2.7)
Time since last injection, median (IQR), years	1.4	(0.5–2.7)	2.2	(0.9–3.2)	1.3	(0.5–2.4)
Prior dexamethasone injections						
n (%)	6	(6%)	11	(10%)	3	(3%)
Median (IQR)	0	(0–0)	0	(0–0)	0	(0–0)
Prior triamcinolone injections						

n (%)	34	(31%)	51	(47%)	22	(25%)
Median (IQR)	0	(0–1)	0	(0–1)	0	(0–0)
IOP–lowering medication, n (%)	14	(13%)	23	(21%)	17	(19%)
Prostaglandin analogues, n(%)	9	(8%)	15	(14%)	11	(12%)
Beta blockers, n (%)	3	(3%)	11	(10%)	6	(7%)
Alpha agonists, n (%)	2	(2%)	3	(3%)	1	(1%)
Carbonic anhydrase inhibitors, n (%)	2	(2%)	6	(6%)	3	(3%)
Other, n (%)	4	(4%)	3	(3%)	5	(6%)

FAc = fluocinolone acetonide, VA = visual acuity, DMO = diabetic macular oedema, SD = standard deviation, IQR = interquartile ra
vascular endothelial growth factor, IQR = interquartile range, LogMAR = logarithm of the minimum angle of resolution, ETDRS = E
[a] These are approximate estimates as it was not possible to determine the exact date on which these parameters were recorded i
Although some of the characteristics relate to the individual and not the eye, each eye was analysed as an independent observati

Table 2 | Number of eyes prescribed other interventions before and after treatment with fluocinc

	Prior to implant		0 to 3 months		3 to 6 months	
Anti-VEGF injections						
Overall	191	(82%)	13	(6%)	21	(9%)
Visual acuity subgroup						
<0.7 LogMAR units	99	(92%)	8	(7%)	12	(11%)
≥0.7 LogMAR units	85	(79%)	2	(2%)	7	(6%)
Treatment subgroup						
≤6 treatments	64	(72%)	2	(2%)	7	(8%)
>6 treatments	120	(94%)	8	(6%)	12	(9%)
Visual acuity and treatment subgroups combined						
<0.7 LogMAR units and ≤6 treatments	37	(82%)	1	(2%)	6	(13%)
<0.7 LogMAR units and >6 treatments	62	(98%)	7	(11%)	6	(10%)
≥0.7 LogMAR units and ≤6 treatments	27	(61%)	1	(2%)	1	(2%)
≥0.7 LogMAR units and >6 treatments	58	(91%)	1	(2%)	6	(9%)
Steroid injections (excluding FAc implant)						
Overall	101	(43%)	3	(1%)	3	(1%)
Visual acuity subgroup						
<0.7 LogMAR units	39	(36%)	1	(1%)	1	(1%)
≥0.7 LogMAR units	59	(55%)	2	(2%)	2	(2%)
Treatment subgroup						
≤6 treatments	25	(28%)	0	(0%)	1	(1%)
>6 treatments	73	(57%)	3	(2%)	2	(2%)
Visual acuity and treatment subgroups combined						
<0.7 LogMAR units and ≤6 treatments	9	(20%)	0	(0%)	0	(0%)
<0.7 LogMAR units and >6 treatments	30	(48%)	1	(2%)	1	(2%)
≥0.7 LogMAR units and ≤6 treatments	16	(36%)	0	(0%)	1	(2%)
≥0.7 LogMAR units and >6 treatments	43	(67%)	2	(3%)	1	(2%)
Macular laser						
Overall	146	(63%)	4	(2%)	6	(3%)

Visual acuity subgroup						
<0.7 LogMAR units	65	(60%)	1	(1%)	2	(2%)
≥0.7 LogMAR units	78	(72%)	3	(3%)	3	(3%)
Treatment subgroup						
≤6 treatments	48	(54%)	3	(3%)	1	(1%)
>6 treatments	95	(75%)	1	(1%)	4	(3%)
Visual acuity and treatment subgroups combined						
<0.7 LogMAR units and ≤6 treatments	17	(38%)	0	(0%)	1	(2%)
<0.7 LogMAR units and >6 treatments	48	(76%)	1	(2%)	1	(2%)
≥0.7 LogMAR units and ≤6 treatments	31	(70%)	3	(7%)	0	(0%)
≥0.7 LogMAR units and >6 treatments	47	(73%)	0	(0%)	3	(5%)
Glaucoma surgery						
Overall	0	(0%)	0	(0%)	1	(0%)
Visual acuity subgroup						
<0.7 LogMAR units	0	(0%)	0	(0%)	0	(0%)
≥0.7 LogMAR units	0	(0%)	0	(0%)	1	(1%)
Treatment subgroup						
≤6 treatments	0	(0%)	0	(0%)	0	(0%)
>6 treatments	0	(0%)	0	(0%)	1	(1%)
Visual acuity and treatment subgroups combined						
<0.7 LogMAR units and ≤6 treatments	0	(0%)	0	(0%)	0	(0%)
<0.7 LogMAR units and >6 treatments	0	(0%)	0	(0%)	0	(0%)
≥0.7 LogMAR units and ≤6 treatments	0	(0%)	0	(0%)	0	(0%)
≥0.7 LogMAR units and >6 treatments	0	(0%)	0	(0%)	1	(2%)
Vitrectomy						
Overall	50	(21%)	1	(0%)	1	(0%)
Visual acuity subgroup						
<0.7 LogMAR units	29	(27%)	1	(1%)	0	(0%)
≥0.7 LogMAR units	17	(16%)	0	(0%)	1	(1%)
Treatment subgroup						
≤6 treatments	19	(21%)	0	(0%)	1	(1%)

>6 treatments	27	(21%)	1	(1%)	0	(0%)
Visual acuity and treatment subgroups combined						
<0.7 LogMAR units and ≤6 treatments	11	(24%)	0	(0%)	0	(0%)
<0.7 LogMAR units and >6 treatments	18	(29%)	1	(2%)	0	(0%)
≥0.7 LogMAR units and ≤6 treatments	8	(18%)	0	(0%)	1	(2%)
≥0.7 LogMAR units and >6 treatments	9	(14%)	0	(0%)	0	(0%)
Incident cataract operations[a]						
Overall	207	(89%)	19[b]	(73%)	1	(14%)
Visual acuity subgroup						
<0.7 LogMAR units	94	(87%)	10	(71%)	0	(0%)
≥0.7 LogMAR units	97	(90%)	9	(82%)	1	(50%)
Treatment subgroup						
≤6 treatments	78	(88%)	6	(55%)	0	(0%)
>6 treatments	113	(89%)	13	(93%)	1	(100%
Visual acuity and treatment subgroups combined						
<0.7 LogMAR units and ≤6 treatments	38	(84%)	3	(43%)	0	(0%)
<0.7 LogMAR units and >6 treatments	56	(89%)	7	(100%)	0	(0%)
≥0.7 LogMAR units and ≤6 treatments	40	(91%)	3	(75%)	0	(0%)
≥0.7 LogMAR units and >6 treatments	57	(89%)	6	(86%)	1	(100%

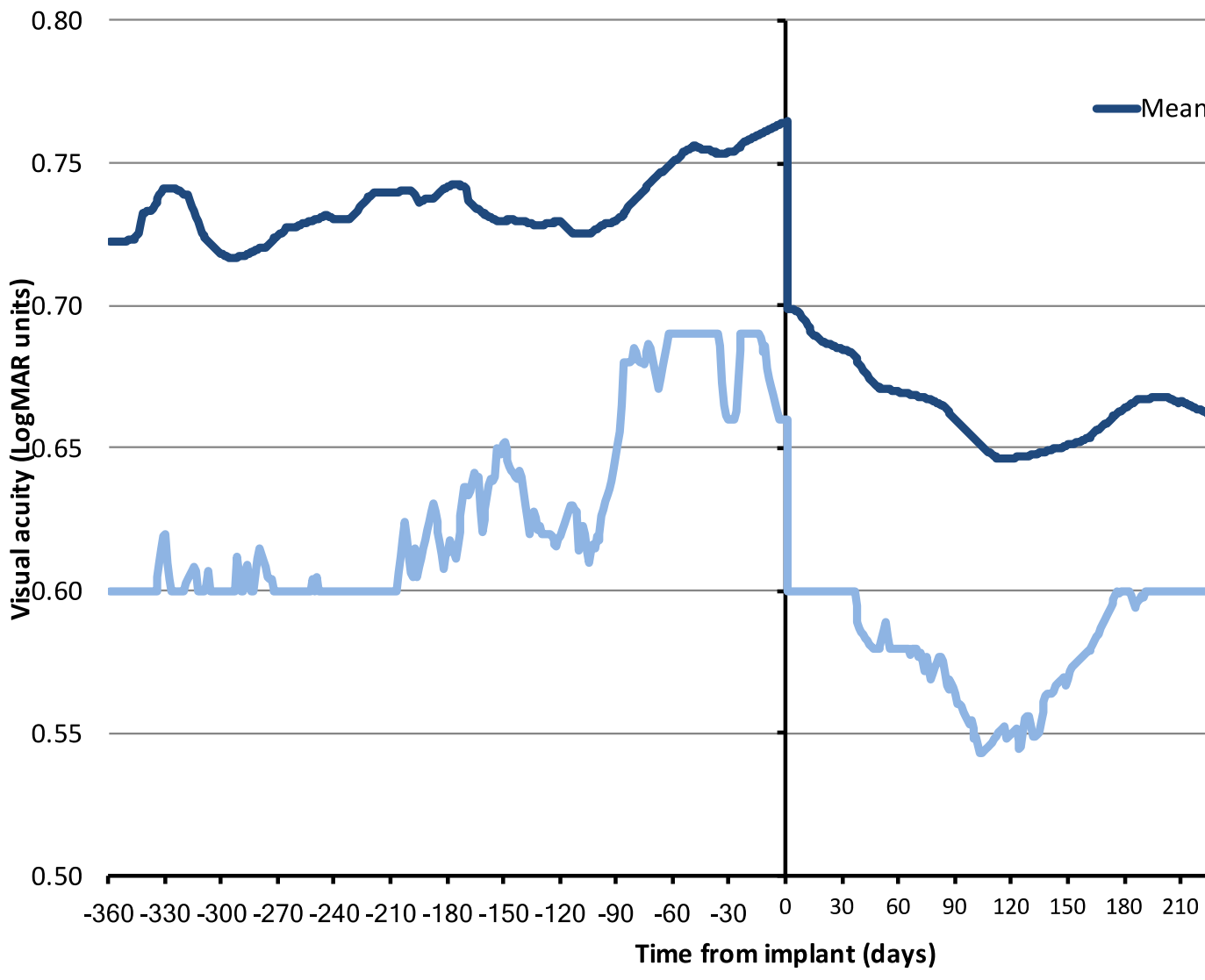
FAc = fluocinolone acetonide

[a] Percentage is calculated as number of operations in eyes with a phakic lens

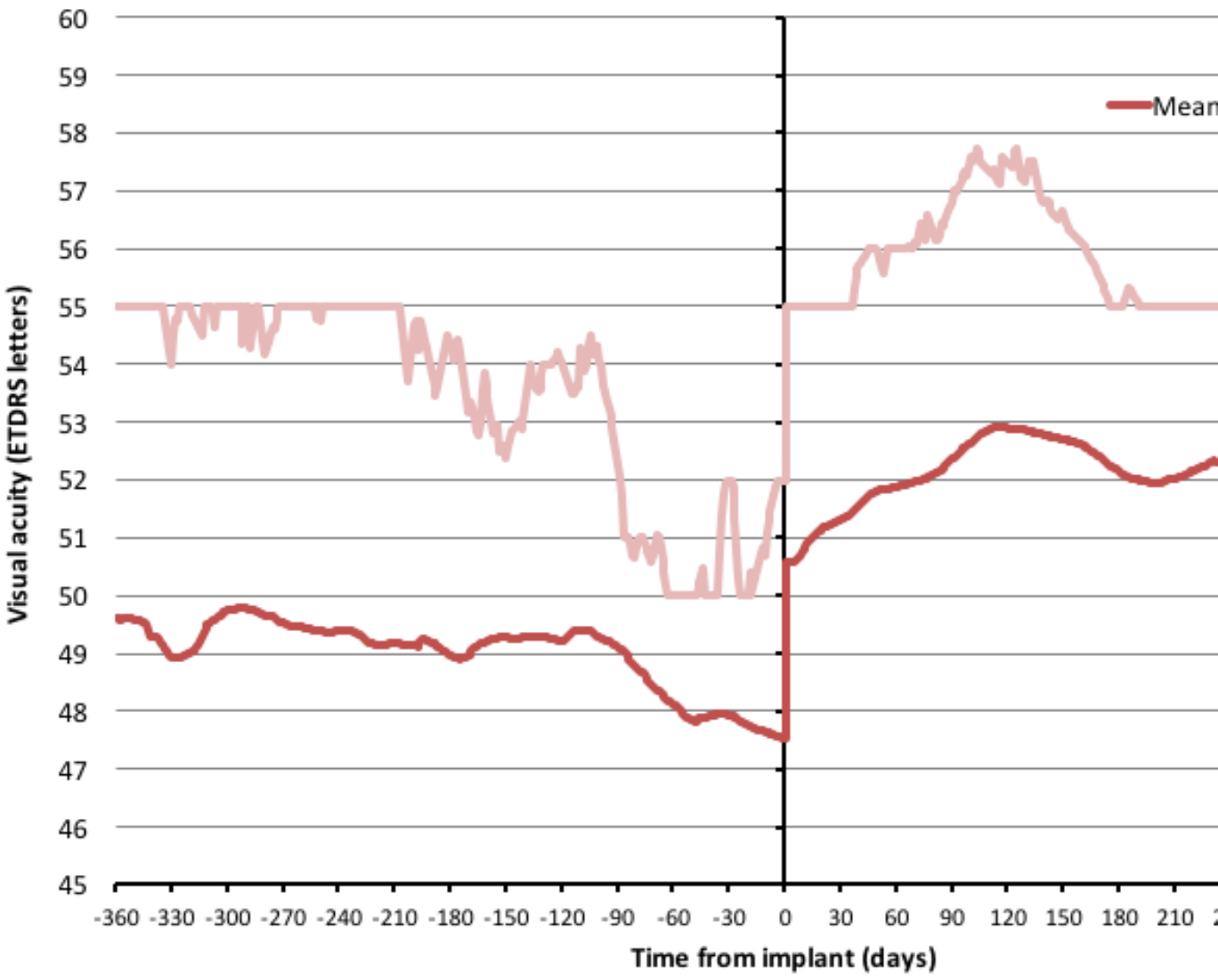
[b] 14 cataract operations carried out on day of FAc implant

Figure 2 | Change in visual acuity in the 12 months before and after fluocinolone intravitreal impl

a) LogMAR scale



b) ETDRS letters



Visual acuity measurements recorded in the 12 months before and after FAc implant were included. Linear interpolation was use
acuity scores. Nearest observation carried forward and backwards was used to impute missing values prior to the first and after t
Imputation was carried out in two parts, day -365 to day 0 and day 1 to 365.

Table 3 | Change in visual acuity (implant value varies according to availability of pairs of visual a

during follow-up)

	N	At implant, median (IQR)		Post
At 3 months post FAc implant				
Overall	202	0.64	(0.48–1)	
Visual acuity subgroup				
<0.7 LogMAR units	97	0.48	(0.3–0.5)	
≥0.7 LogMAR units	97	1.00	(0.8–1.3)	
Treatment subgroup				
≤6 treatments	78	0.65	(0.42–1.04)	
>6 treatments	116	0.68	(0.5–1)	
Visual acuity and treatment subgroups combined				
<0.7 LogMAR units and ≤6 treatments	39	0.42	(0.3–0.5)	
<0.7 LogMAR units and >6 treatments	58	0.50	(0.34–0.5)	
≥0.7 LogMAR units and ≤6 treatments	39	1.04	(0.9–1.56)	
≥0.7 LogMAR units and >6 treatments	58	1.00	(0.8–1.1)	
At 6 months post FAc implant				
Overall	220	0.66	(0.48–1)	
Visual acuity subgroup				
<0.7 LogMAR units	106	0.48	(0.3–0.5)	
≥0.7 LogMAR units	106	1.00	(0.8–1.3)	
Treatment subgroup				
≤6 treatments	87	0.66	(0.42–1)	
>6 treatments	125	0.70	(0.5–1)	
Visual acuity and treatment subgroups combined				
<0.7 LogMAR units and ≤6 treatments	44	0.42	(0.3–0.5)	
<0.7 LogMAR units and >6 treatments	62	0.50	(0.34–0.54)	
≥0.7 LogMAR units and ≤6 treatments	43	1.00	(0.9–1.56)	
≥0.7 LogMAR units and >6 treatments	63	1.00	(0.8–1.1)	
At 12 months post FAc implant				
Overall	223	0.66	(0.48–1.00)	

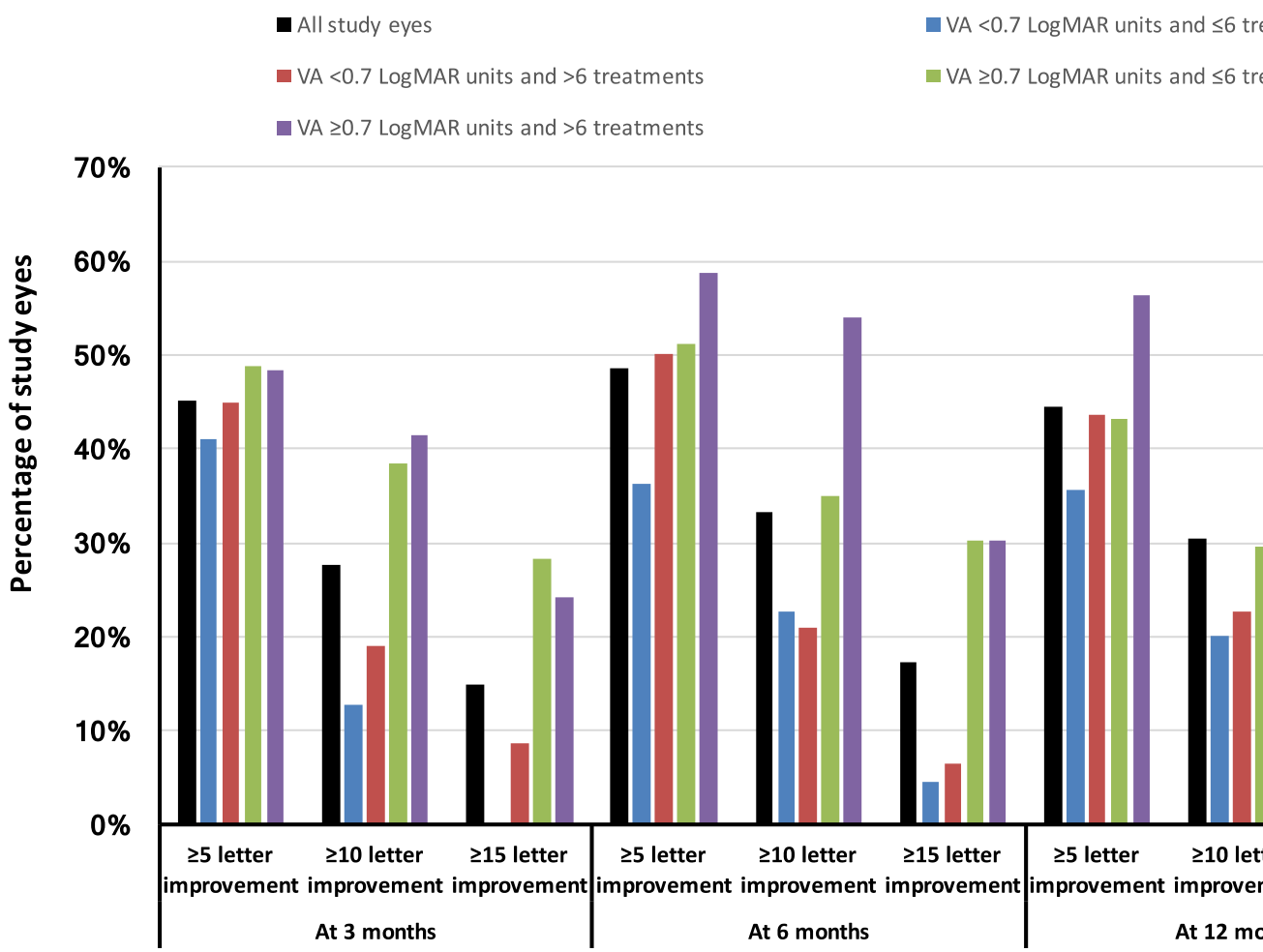
Visual acuity subgroup			
<0.7 LogMAR units	107	0.48	(0.3–0.54)
≥0.7 LogMAR units	108	1.00	(0.8–1.3)
Treatment subgroup			
≤6 treatments	89	0.66	(0.42–1)
>6 treatments	126	0.70	(0.5–1)
Visual acuity and treatment subgroups combined			
<0.7 LogMAR units and ≤6 treatments	45	0.42	(0.3–0.5)
<0.7 LogMAR units and >6 treatments	62	0.50	(0.34–0.54)
≥0.7 LogMAR units and ≤6 treatments	44	1.00	(0.89–1.53)
≥0.7 LogMAR units and >6 treatments	64	1.00	(0.8–1.1)

FAc = fluocinolone acetonide, IQR = interquartile range.

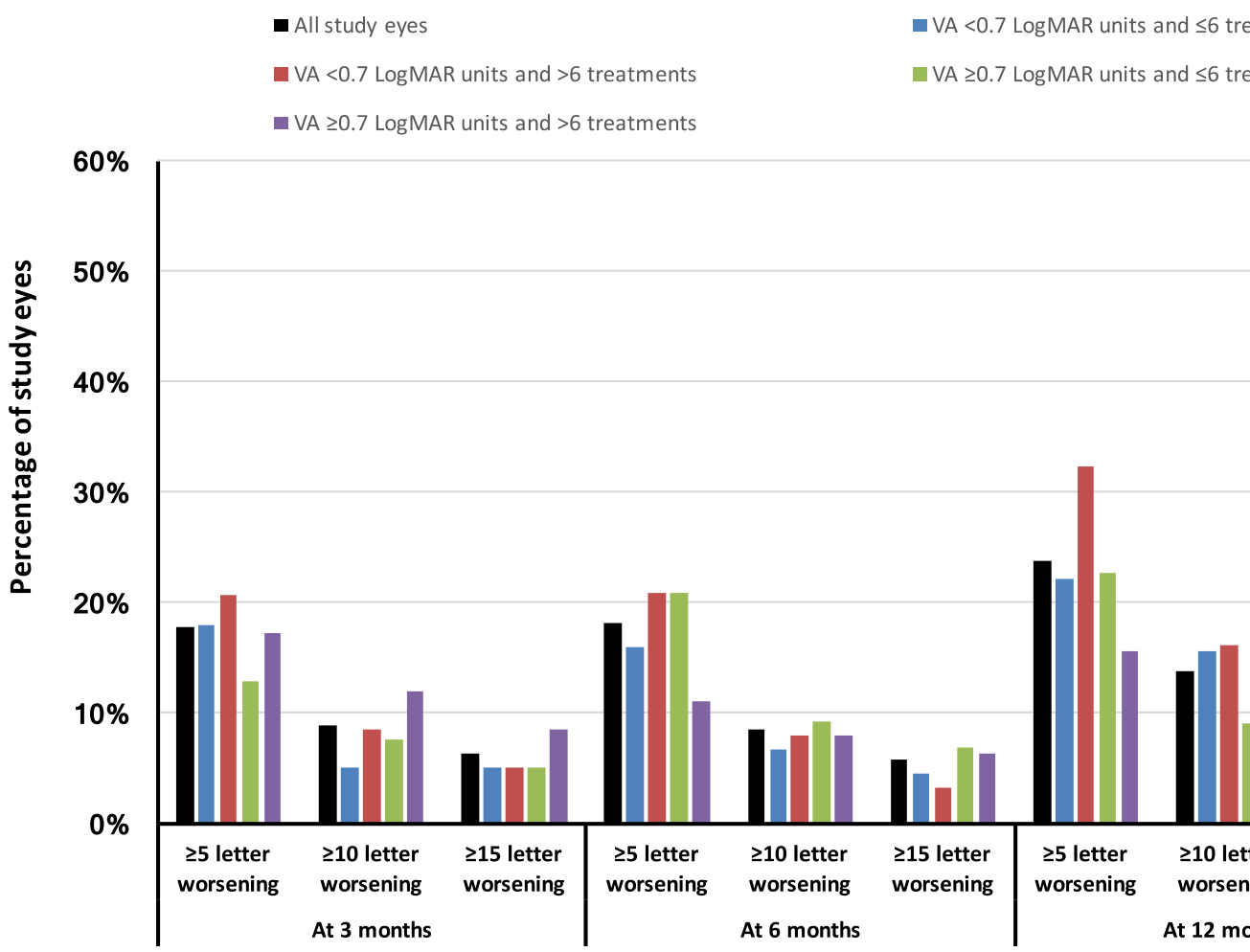
Figure 3 | Percentage of fluocinolone acetonide treated eyes achieving a) ≥5, ≥10 and ≥15 letter i

b) ≥5, ≥10 and ≥15 letter worsening in ETDRS score overall and by visual acuity and treatment sub

a)



b)

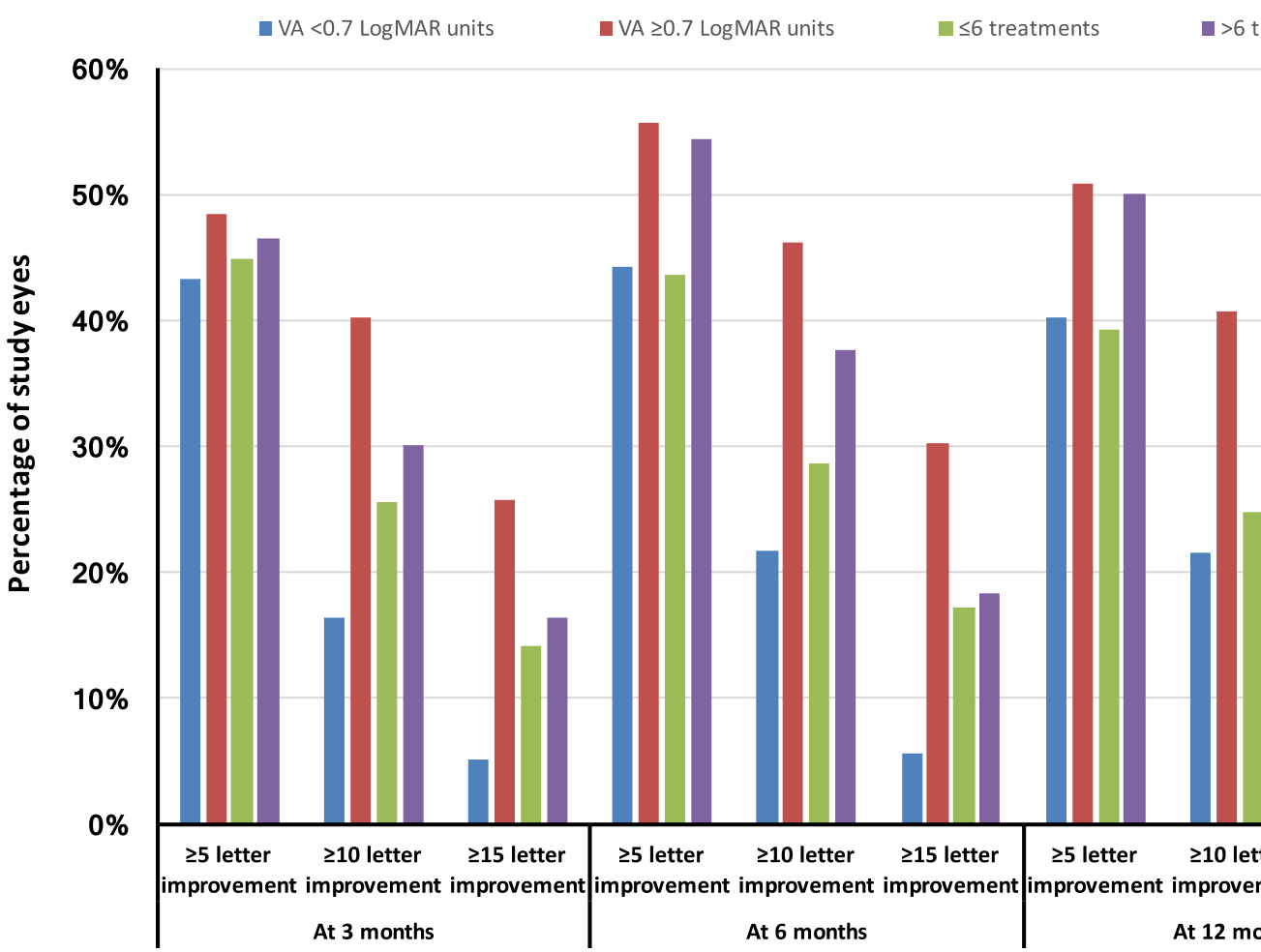


VA = visual acuity.

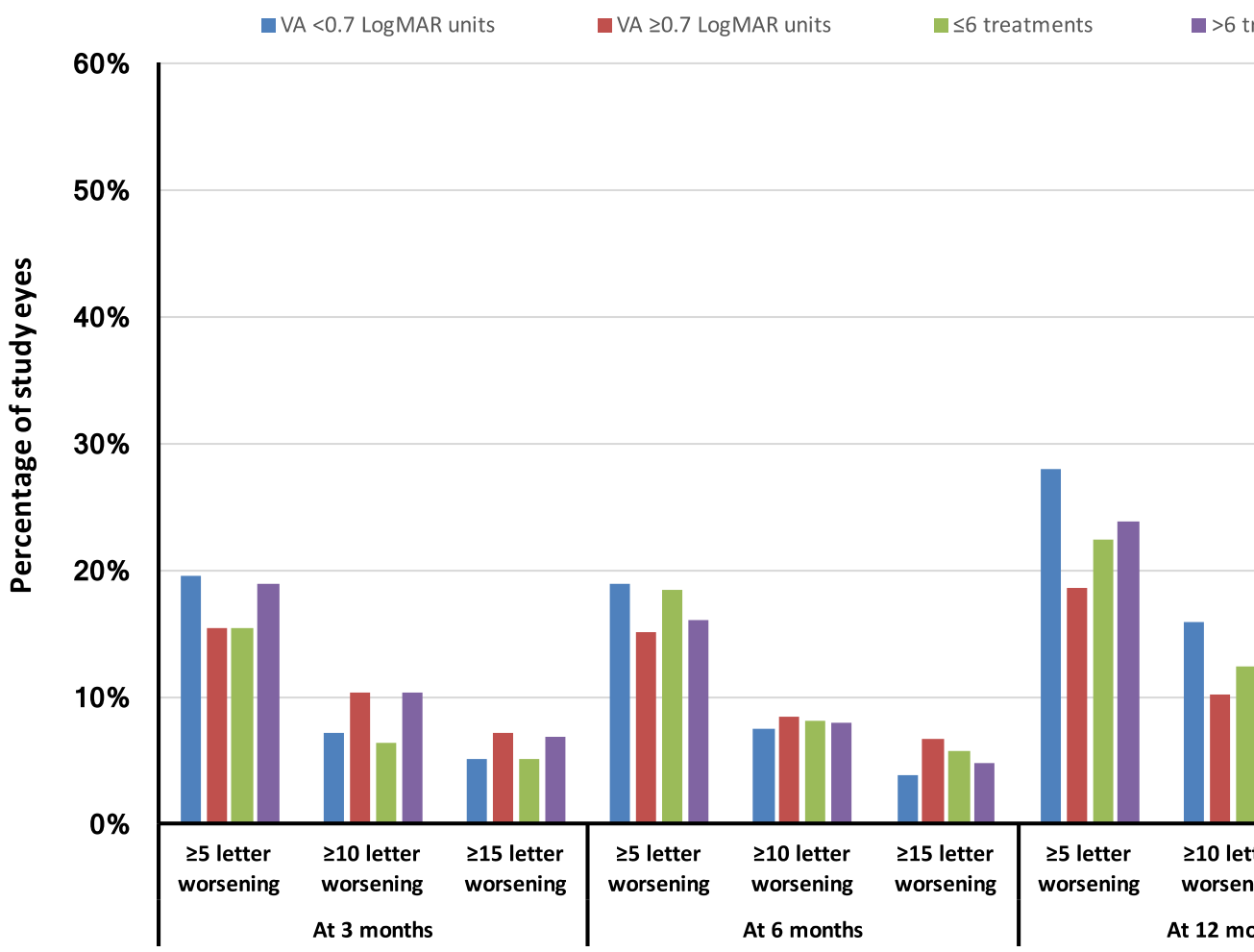
Supplementary Figure 2 | Percentage of fluocinolone acetonide treated eyes achieving a) ≥5, ≥10

ETDRS score and b) ≥5, ≥10 and ≥15 letter worsening in ETDRS score by visual acuity or treatment

a)



b)



VA = visual acuity.

Table 4 | Change in intraocular pressure for paired values where these were available (baseline v

availability of IOP at baseline and the respective time-point)

	N	Implant IOP, median (IQR), mmHg	Implant IOP,
At 3 months post FAc implant			
Overall	157	15 (13–18)	
Visual acuity subgroup			
<0.7 LogMAR units	77	15 (13–18)	
≥0.7 LogMAR units	71	16 (13–18)	
Treatment subgroup			
≤6 treatments	59	15 (13–18)	
>6 treatments	89	16 (13.2–18)	
Visual acuity and treatment subgroups combined			
<0.7 LogMAR units and ≤6 treatments	29	15.4 (14–17)	
<0.7 LogMAR units and >6 treatments	48	15 (12–18)	17
≥0.7 LogMAR units and ≤6 treatments	30	15 (13–18)	
≥0.7 LogMAR units and >6 treatments	41	17 (14–18.4)	
At 6 months post FAc implant			
Overall	175	15 (13–18)	
Visual acuity subgroup			
<0.7 LogMAR units	88	15 (12.5–18)	
≥0.7 LogMAR units	78	16 (13–18)	17.
Treatment subgroup			
≤6 treatments	70	15 (13–17)	
>6 treatments	96	16 (13.6–18)	
Visual acuity and treatment subgroups combined			
<0.7 LogMAR units and ≤6 treatments	37	15 (13–17)	
<0.7 LogMAR units and >6 treatments	51	15 (12–18)	
≥0.7 LogMAR units and ≤6 treatments	33	15 (13–18)	
≥0.7 LogMAR units and >6 treatments	45	17 (14–18)	

At 12 months post FAc implant				
Overall	181	15	(13–18)	
Visual acuity subgroup				
<0.7 LogMAR units	91	15	(12–18)	
≥0.7 LogMAR units	81	15	(13–18)	
Treatment subgroup	81	18		
≤6 treatments	73	15	(13–17)	
>6 treatments	99	16	(13–18)	
Visual acuity and treatment subgroups combined	99	19		
<0.7 LogMAR units and ≤6 treatments	39	15	(13–17)	
<0.7 LogMAR units and >6 treatments	52	15	(12–18)	
≥0.7 LogMAR units and ≤6 treatments	34	14.5	(13–18)	17
≥0.7 LogMAR units and >6 treatments	47	17	(14–18)	

FAc = fluocinolone acetonide, IQR = interquartile range.

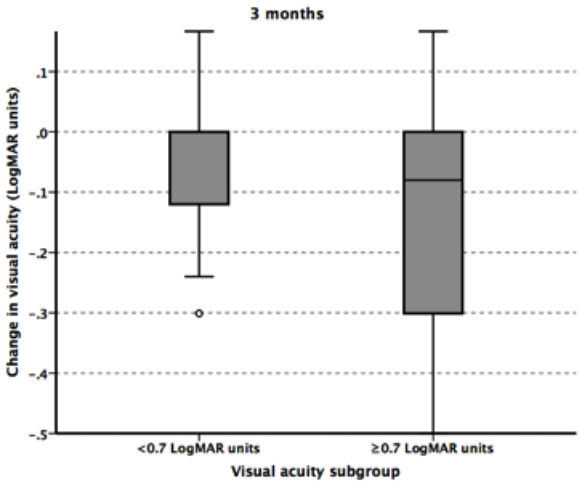
Table 5 | Intraocular pressure-lowering therapy before and after implant

	All eyes treated with IOP-lowering therapy prior to implant, n (%)	Eyes not treated with IOP-lowering therapy prior to implant, n (%)	Eyes newly prescrib
			0 to 3 months
Overall	44 (19%)	189 (81%)	5 (3%)
Visual acuity subgroup			
<0.7 LogMAR units	14 (13%)	94 (87%)	2 (2%)
≥0.7 LogMAR units	23 (21%)	85 (79%)	3 (4%)
Treatment subgroup			
≤6 treatments	17 (19%)	72 (81%)	2 (3%)
>6 treatments	20 (16%)	107 (84%)	3 (3%)
Visual acuity and treatment subgroups combined			
<0.7 LogMAR units and ≤6 treatments	8 (18%)	37 (82%)	0 (0%)
<0.7 LogMAR units and >6 treatments	6 (10%)	57 (90%)	2 (4%)
≥0.7 LogMAR units and ≤6 treatments	9 (20%)	35 (80%)	2 (6%)
≥0.7 LogMAR units and >6 treatments	14 (22%)	50 (78%)	1 (2%)

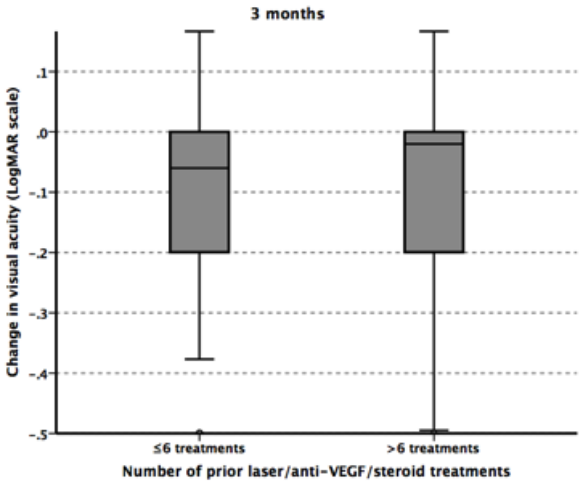
IOP = intraocular pressure.

Figure 4 | Change in visual acuity (LogMAR scale) post index by subgroup

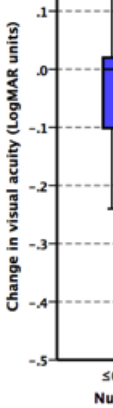
a) At 3 months by visual acuity subgroup



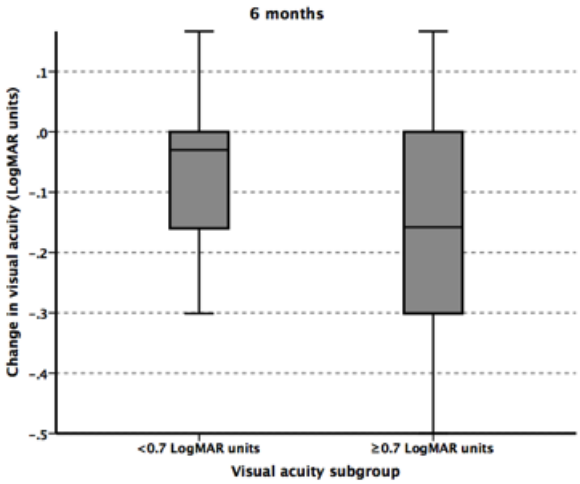
b) At 3 months by treatment subgroup



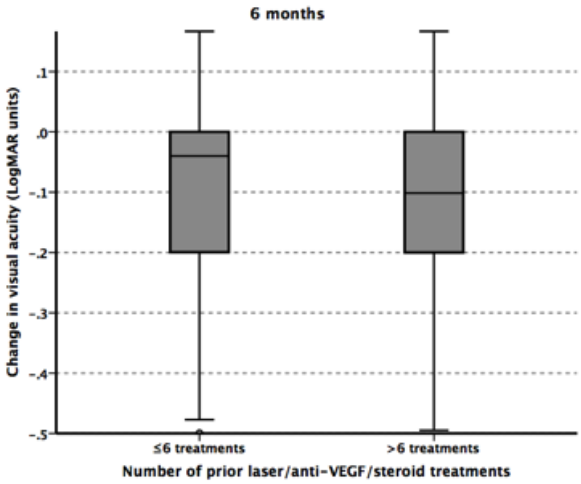
c) At 3 mo
subgroup



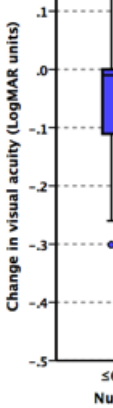
d) At 6 months by visual acuity subgroup



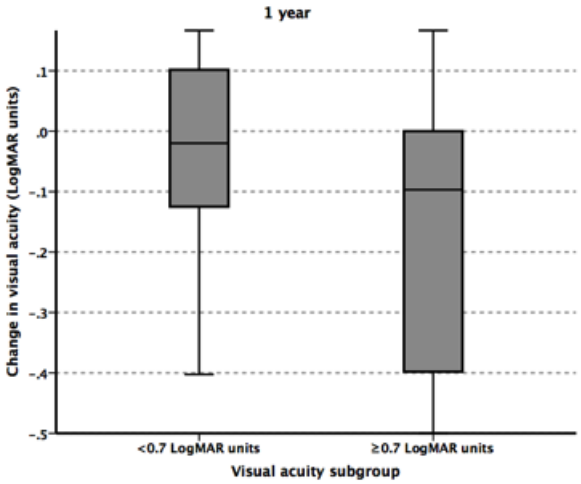
e) At 6 months by treatment subgroup



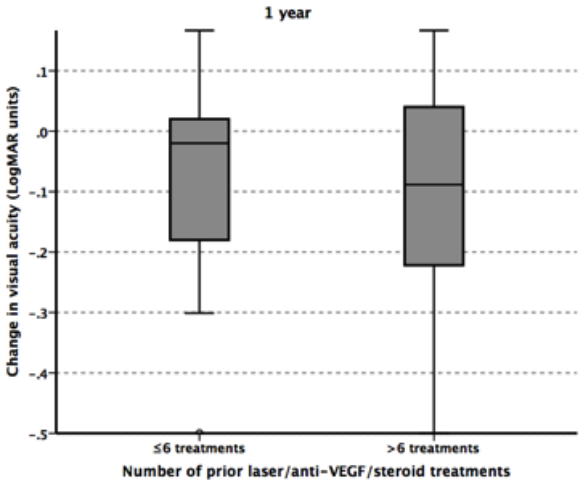
f) At 6 mo
subgroup



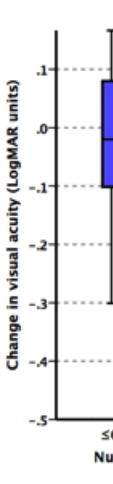
g) At 12 months by visual acuity subgroup



h) At 12 months by treatment subgroup

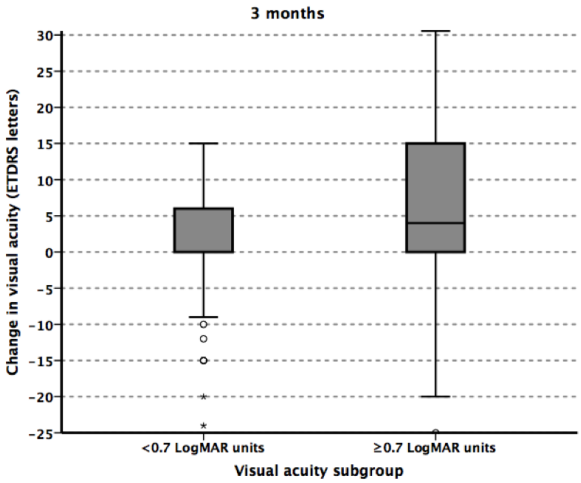


i) At 12 mo
subgroup

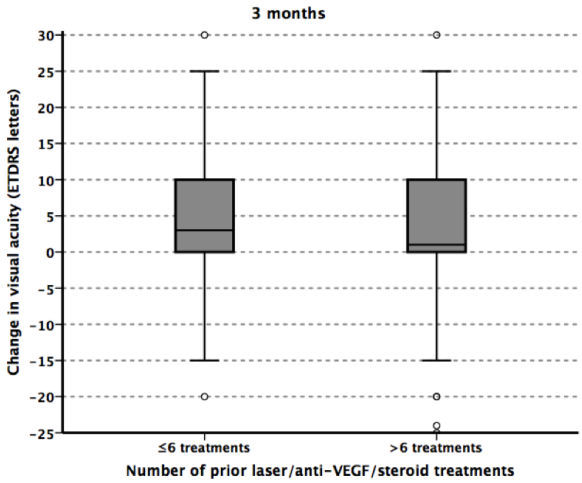


Supplementary Figure 3 | Change in visual acuity (by ETDRS letter score) post-index by subgroup

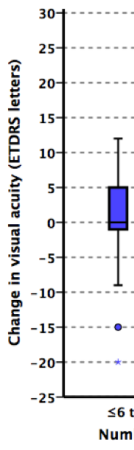
a) At 3 months by visual acuity subgroup



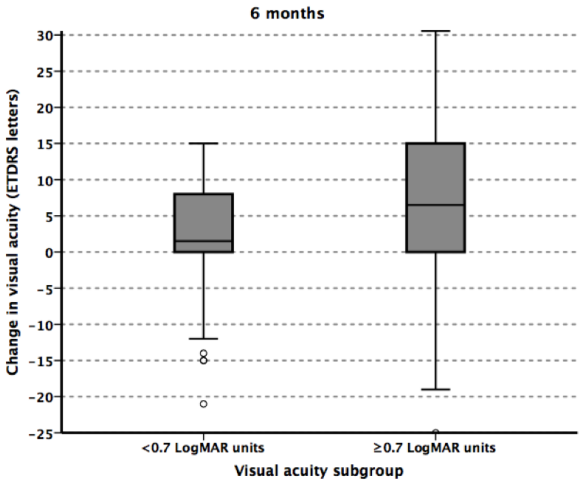
b) At 3 months by treatment subgroup



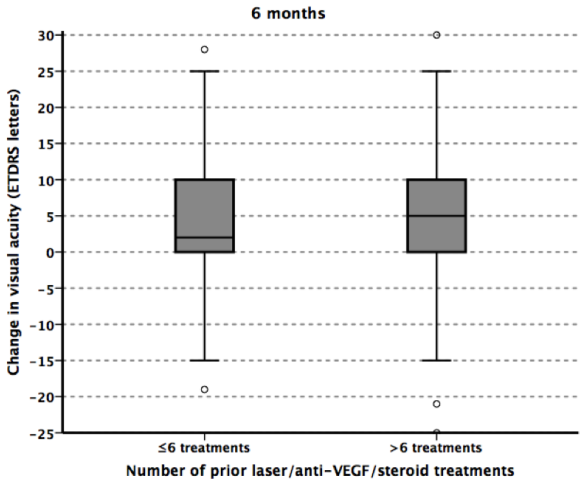
c) At 3 mont
subgroup



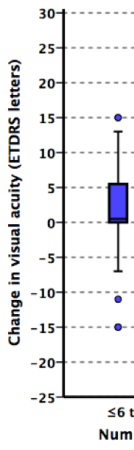
d) At 6 months by visual acuity subgroup



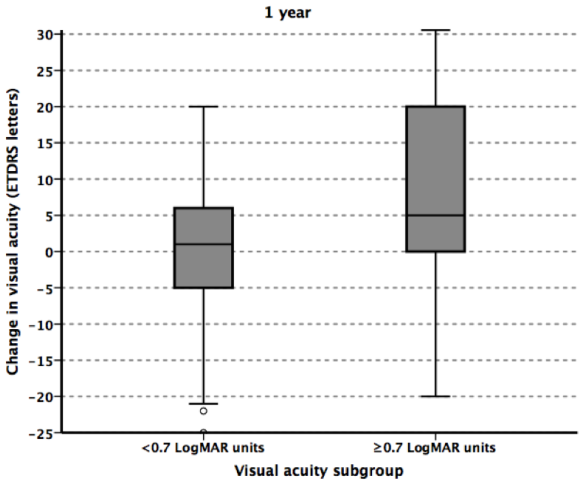
e) At 6 months by treatment subgroup



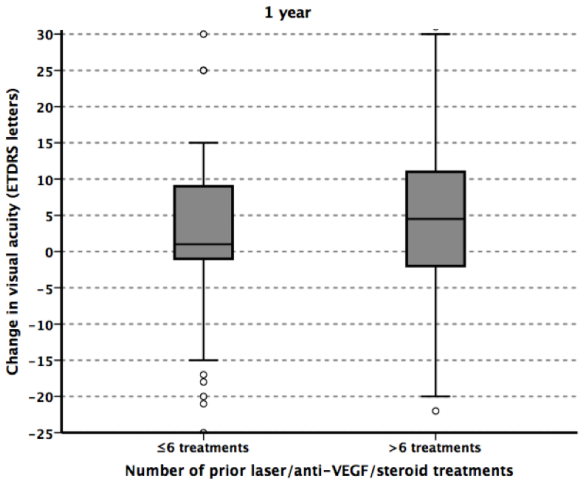
f) At 6 mont
subgroup



g) At 12 months by visual acuity subgroup



h) At 12 months by treatment subgroup



i) At 12 mon
subgroup