Patterns of retinal thickness prior to and following treatment with fluocinolone acetonide 190 µg intravitreal implant for diabetic macular oedema

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Abstract

Objectives

To compare retinal thickness before and after treatment with the fluocinolone acetonide (FAc) 190 μg intravitreal implant in people with diabetic macular oedema (DMO) using data from the ILUVIEN Clinical Evidence study in the United Kingdom (ICE-UK).

Methods

For this retrospective cohort study, data on people attending any one of 13 participating ophthalmology departments and treated with FAc intravitreal implant between 1 April 2013 and 15 April 2015 were collected for 12 months prior to and at least 12 months after implantation. Cross sectional and longitudinal patterns of central foveal thickness (CFT) were compared before and after FAc implant.

Results

There were 208 people contributed data from 233 individual eyes treated with the FAc implant. Mean age was 68.1 years and 62% were male. Median (interquartile range) CFT decreased from 462 μm (354–603 μm) at time of implant to 309 μm (222–433 μm) at 12 months post implant ($p<0.001$). Over the same period, a reduction of ≥10%, ≥25% and ≥50% in CFT was observed in 113 (65%), 87 (50%) and 37 (21%) treated eyes, respectively. Eyes with a CFT of ≥400 μm at the time of implant were significantly more likely to achieve a reduction in CFT of ≥10%, ≥25% and ≥50% at 12 months (all $p<0.001$) compared with eyes with a CFT of <400 μm at implant. Both retinal thickness and changes in retinal thickness were loosely correlated with visual acuity.

Conclusion

A marked reduction in retinal thickness was observed in people following FAc intravitreal implant for DMO. The response was related to the degree of retinal thickness prior to treatment.

Introduction

The typical thickness of the retina in people with healthy eyes is around 200 μm, which can vary slightly according to the part of the retina measured and type of ocular coherence tomography (OCT) used, with separate studies having reported either no change or a small decrease in thickness with increasing age.[1,2] Damage to the eye caused by conditions such as macular oedema or trauma can lead to abnormal fluid accumulation resulting in thickening of the retina. Along with other microvascular changes, thickening of the retina follows sustained periods of hyperglycaemia in people with diabetes. Although macular oedema does not always result in a deterioration in vision, disruption of the fovea can cause severe visual impairment.[1]

The fluocinolone acetonide (FAc) 190 μg intravitreal implant was evaluated in the Fluocinolone Acetonide in Diabetic Macular Edema (FAME) study programme.[3,4] Continuous daily release of low levels of FAc from the implant has been found to result in a reduction in foveal thickness and oedema for up to three years.[4]

Historically, laser photocoagulation was considered to be the treatment of choice for DMO due to favourable results from the Early Treatment Diabetic Retinopathy Study (ETDRS).[5] The FAME study therefore evaluated FAc intravitreal implant in people with an inadequate response to retinal laser therapy. However, since the FAME study was conducted, several landmark trials have demonstrated that anti-vascular endothelial growth factor (anti-VEGF) therapy can lead to a significant improvement in vision in people with DMO,[6–9] and anti-VEGF therapy is now generally considered to be the first-line therapy for this condition. Therefore, in Europe, FAc intravitreal implant is presently indicated for the management of chronic DMO only where an insufficient response has been achieved with first-line anti-VEGF therapy. The aim of the ILUVIEN Clinical Evidence Study in the UK (ICE-UK) was to assess the effectiveness of FAc intravitreal implant for DMO in real world clinical practice. The purpose of this study was specifically to evaluate retinal thickness 12 months before and after treatment with the FAc 190 μg intravitreal implant.

Methods

Data Source

The dataset and study methodology have been described in detail elsewhere.[10] Briefly, for this retrospective, multi-centre, hospital-based study, data were extracted from medical records for a representative cohort of people treated at 13 participating hospitals in the UK and combined into a single dataset for the purpose of analysis. Data were generated from retrospective case reviews, pseudonymised and entered into an online data entry tool. The following data were collected at several time points within a pre-specified period: patient demographics, medical history, implant data, and data from multi-disciplinary and medication reviews.

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

Subjects were people with type 1 or type 2 diabetes treated with FAc 190 µg intravitreal implant for DMO in at least one eye at a participating site as part of their routine care between 1 April 2013 and 15 April 2015. A requirement was a minimum of 12 months' history prior to implant. Those with a history of taking part in any other interventional study for DMO or who were lost to follow-up were excluded. The index date was defined as the date of first recorded FAc intravitreal implant into the study eye. The follow-up period was defined as 12 months post implant and subjects who received FAc intravitreal implant in both eyes were allowed to contribute both eyes to the study.

Outcomes

The following clinical outcomes were investigated at 3, 6 and 12 months post index date: changes in central foveal thickness (CFT) and central subfield thickness (CST) and the proportion of treated eyes that demonstrated a 10%, 25% and 50% improvement in CFT or CST. The distribution of CFT and CST from 12 months prior to and 12 months post implant was also investigated. Due to the observational nature of this study, there was no restriction on the OCT machine type used to measure retinal thickness.

Subgroups

Results are presented overall and for two subgroups based on higher and lower CFT at implant (≥400 μm and <400 μm, respectively). Eyes with no recorded CFT measurement at baseline were excluded from the subgroup analyses.

Statistical analysis

Changes in retinal thickness were compared between implant and the 3, 6 and 12 month time points using the non-parametric Wilcoxon signed ranks test. The proportion of people achieving a reduction in retinal thickness between implant at these time points was compared between subgroups using Fisher's exact test. The proportion of people achieving a target retinal thickness was compared between implant and the 3, 6 and 12 month time points using McNemar's test. Last observation carried forward was implemented to impute missing values in two stages: on or before index date and after index date.[11]

Mean and median CFT and CST were calculated on a daily basis for the 12 months before and after FAc implant. In order to smooth the data, missing values for each day of this 24 month period were imputed using linear interpolation.[11] As linear interpolation could not be used before the first recorded value or after the last recorded value, nearest observation carried forward and backwards was used to impute the remaining missing values. In order to investigate whether CFTs <200 μm

have a detrimental effect on vision, visual acuity (ETDRS letter score) in the 12 months prior to and post FAc implant was investigated for study eyes with a CFT of <200 µm at baseline using the same methodology.

The strength and direction of the association between pairs of visual acuity and CFT measurements recorded at FAc implant, 12 months post FAc implant and at any time in the 12 months prior to and post FAc implantation were measured using the Pearson's correlation coefficient. Statistical analyses were carried out using IBM SPSS Statistics version 20.

Results

Data were collected on 311 people, of whom 208 people contributing data from 233 eyes treated with FAc intravitreal implant (study eyes) were eligible for inclusion in the study cohort. An attrition flow diagram has been previously presented.[10] Of the 233 study eyes, 208 were first eyes treated with the implant and 25 were a second treatment in the subject's other eye.

Patient demographics

Of the 208 people treated with FAc intravitreal implant in any eye, 128 (62%) were male. The mean age was 68.1 years. 176 (85%) had type 2 diabetes (Table 1). Median (interquartile range, IQR) duration of diabetes was 18 (11–27) years. 63 eyes (27%) had a CFT of <400 μm at the time of implant and 128 (55%) eyes had a CFT of ≥400 μm at the time of implant. 42 study eyes had no recorded CFT measurement within the 12 month period prior to implant and were therefore excluded from the subgroup analysis.

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 (equivalent to median 52, IQR 35–61, ETDRS letters). CFT at implant was a mean (SD) of 482 μm (186 μm). Median (IQR) CST at the time of implant was 447 (352–587) μm. Median (IQR) numbers of macular laser treatments, steroid treatments and anti-VEGF injections prior to index date were 1.0 (0.0–3.0), 0.0 (0.0–1.0) and 5.0 (2.0–7.0), respectively.

Central foveal thickness

Not all subjects had relevant observations at all time points. Following multiple imputation of missing values and reporting only paired observations, the median (IQR) CFT decreased following implant at each time point: 472 μm (365–616 μm) at implant to 355 μm (254–474 μm) at 3 months ($p<0.001$), 464 μm (362–605 μm) at

implant to 331 µm (239–462 µm) at 6 months (p<0.001) and 462 µm (354–603 µm) at implant to 309 µm (222–433 µm) at 12 months (p<0.001; Table 2).

A reduction of ≥10% in CFT from implant was observed in 76 (51%), 96 (57%) and 113 (65%) treated eyes at 3 months, 6 months and 12 months post implant, respectively. A reduction of ≥25% and ≥50% in CFT from implant was observed in 61 (41%) and 21 (14%) treated eyes at 3 months, 75 (44%) and 30 (18%) at 6 months and 87 (50%) and 37 (21%) at 12 months, respectively. When compared with eyes with a CFT of <400 µm at the time of implant, eyes with a CFT of ≥400 µm at implant were significantly more likely to achieve a reduction in CFT of ≥25% and ≥50% at 3 months (p<0.001, p<0.001 and p=0.004, respectively), 6 months (all p<0.001) and 12 months (all p<0.001).

Mean CFT was higher in the 12 months prior to implant compared with the 12 months after implant and tended to increase in the 3 months immediately prior to implant (Figure 1a). CFT continued to gradually decrease throughout the 12 months following implant.

When compared with baseline, a steeper cumulative frequency curve was observed at 12 months follow-up, with more study eyes achieving lower CFTs at 12 months following FAc implant (Figure 2). However, the proportion of study eyes with a CFT of ≤150 µm was the same prior to and 12 months post FAc implant (2%). The distribution of study eyes by CFT category of <200 µm, ≥200 and <300 µm, ≥300 and <400 µm and ≥400 µm at FAc implant and 12 months post FAc implant is described in Figure 3a and b. Most study eyes had a CFT of ≥400 µm at the time of FAc implantation (66%). At 12 months post FAc implant, 51% of study eyes moved to a lower CFT category, 7% moved to a higher CFT category and 42% remained in the same category. CFT was <300 µm in 16% of eyes at implant and 47% of eyes at 12 months post implant (p<0.001, Figure 2). For eyes with a CFT <400 µm at the time of implant, CFT was <300 µm in 47% of eyes at the time of FAc implant and 66% of eyes at 12 months (p=0.382). In those eyes with a CFT of ≥400 µm at the time of FAc implant, 38% achieved a CFT of <300 µm at 12 months post implant. 6% of eyes had a CFT of <200 µm at the time of FAc implant and 19% of eyes had a CFT of <200 µm at 12 months following FAc implant (p<0.001). Change in visual acuity in the 12

months prior to and post FAc implant are detailed in Figure 4 for these study eyes. For study eyes with a CFT of <200 µm at FAc implant, visual acuity was slightly higher in the 12 months post FAc implant than in the 12 months prior to FAc implant. Comparing the 12 months prior to and post FAc implant, a larger improvement in visual acuity was observed in study eyes with a CFT of >200 µm at FAc implant and a CFT of <200 µm at 12 months post FAc implant.

At FAc implantation, Heidelberg SPECTRALIS OCT machine was used to measure retinal thickness in 61% of eyes with a recorded CFT; Topcon 3D OCT-2000 was used in 38% of eyes; and Topcon 3D OCT-1000 was used in 1% of eyes. The corresponding values were 56%, 41% and 3%, respectively, at 3 months; 58%, 38% and 3%, respectively, at 6 months; and 59%, 38% and 3%, respectively, at 12 months. Retinal thickness was measured using different OCT machine types at baseline and at 3, 6 and 12 months post FAc implant in 5%, 7% and 7% of eyes, respectively. In study eyes, whose CFT was measured using a Heidelberg SPECTRALIS machine both prior to FAc implant and 12 months following implant, median CFT decreased from 492 µm (IQR 388–647 µm) to 302 µm (210–421 µm, n=99). In study eyes where a Topcon 3D OCT-2000 was used both at baseline and 12 months follow-up, median CFT decreased from 413 µm (IQR 323-514 µm) to 317 µm (293–436 µm, n=62).

Correlation between central foveal thickness and visual acuity

There was a statistically significant negative correlation between visual acuity (ETDRS letter score) and CFT at FAc implantation (Pearson's correlation coefficient r=-0.311, p<0.001) and at 12 months post FAc implant (r=-0.250, p<0.001, Figure 5a and b). A statistically significant negative correlation between visual acuity and CFT was also observed when all pairs of CFT measurements and visual acuity measurements recorded between 12 months prior to FAc implant and 12 months post FAc implant were analysed (r=-0.259, p<0.001, Figure 5c). However, the variance in visual acuity accounted for by CFT was small (coefficient of determination R^2=0.097 at FAc implant, R^2=0.067 at 12 months post FAc implant and R^2=0.067 for all measurements in the 12 months prior to and post FAc implant). Change in CFT and change in visual

acuity between FAc implant and 12 months post FAc implant were also significantly related (r=-0.285, p<0.001, R^2=0.094, Figure 5d).

Central subfield thickness

Median (IQR) CST decreased from baseline at each time point: 448 µm (354–587) at baseline to 356 µm (276–453 µm) at 3 months (p<0.001), 448 µm (359–581 µm) at baseline to 337 µm (268–445 µm) at 6 months (p<0.001) and 446 µm (359–569 µm) at baseline to 318 µm (262–419 µm) at 12 months (p<0.001, Table 3).

A reduction of ≥10% in CST was observed in 83 (54%), 103 (58%) and 118 (65%) treated eyes at 3 months, 6 months and 12 months post implant. A reduction of ≥25% and ≥50% in CFT from implant was observed in 47 (30%) and 13 (8%) treated eyes at 3 months, 62 (35%) and 23 (13%) at 6 months, and 76 (42%) and 25 (14%) at 12 months, respectively.

Following linear interpolation of missing values (with nearest observation carried forward and backwards to impute missing values before the first recorded measurement and after the last recorded measurement), mean CST was higher in the 12 months prior to implant than in the 12 months post implant (Figure 1b). An increase in mean CST was observed in the four months prior to implant. CST continued to decrease gradually throughout the 12 month period following implant.

Discussion

In the 12 months prior to the insertion of the FAc intravitreal implant, central retinal thickness continued to increase. Following implant, there was a marked reduction in the central retinal thickness. The onset of the beneficial changes in the morphology of the retina appeared to be both rapid and sustained for the period of this study. Response was based on CFT prior to treatment with the FAc intravitreal implant, being greater in those with a higher CFT (≥400 µm) at baseline and less in those eyes with a lower CFT (<400 µm) at baseline.

Several types of OCT machine types were used to measure retinal thicknesses across the 13 participating ophthalmology centres. Retinal thickness measurements have been shown to vary depending on machine type, which is thought to be due to variation in the retinal segmentation algorithms.[12] The same OCT machine in each unit was used to measure retinal thickness at baseline and the three follow-up time points in most study eyes.

Whilst bearing in mind that retinal thinning due to cell loss can also be harmful,[13] in the longer term, it has been reported that eyes that improve most in visual acuity, have the greatest decrease in retinal thickness.[14] Nevertheless, the association between visual acuity and retinal thickness is still poorly understood.[15,16] In this study, a significant negative association between visual acuity (ETDRS letter score) and CFT was observed. However, the variation in visual acuity explained by CFT was low. The Diabetic Retinopathy Clinical Research Network has previously investigated the relationship between retinal thickness and visual acuity before and after laser treatment in patients with DMO, and a moderate correlation between visual acuity and centre point thickness was observed (correlation coefficient of 0.52 at baseline and 0.49, 0.36 and 0.38 at 3.5, 8 and 12 months post laser photocoagulation). Furthermore, a correlation between change in visual acuity and change in centre point thickness was also reported (correlation coefficient of 0.44, 0.30 and 0.43 at 3.5, 8 and 12 months post laser photocoagulation).[17] However, the researchers also observed considerable variation in visual acuity for a particular level of retinal oedema.[17]

What is not a matter of conjecture is that any increase in retinal thickness from the norm represents physiological morbidity. Cataract surgery increases retinal thickness,[18] and recovery in retinal thickness varies by the region of the retina.[19] However, central point thickness has been shown to recover relatively quickly following cataract surgery in people pre-treated with the FAc intravitreal implant.[20] PRP is reported to increase local inflammation resulting in effects such as localised cytokine release.[21] In the later stages of diabetic eye diseases, multiple treatments are typically used together in complex patterns of treatment to salvage sight. Retinal thickness is thought to be an important, and objective measure of clinical outcome.[14]

Anti-VEGF therapy is now considered to be the first-line treatment for DMO, and this class of drugs has been shown to be effective in reducing retinal thickness.[6,22–27] The two licensed anti-VEGF products for DMO available in the UK—ranibizumab and aflibercept—have been recommended by NICE for the treatment of DMO in eyes with a central retinal thickness ≥400 µm, since both products have been determined to be cost-effective only in those eyes with this central retinal thickness.[28,29] However, the NICE recommendation for FAc intravitreal implant does not include any restrictions based on central retinal thickness.[30] Laser therapy or intravitreal steroids (in eyes with a pseudophakic lens) are the only recommended treatment options in eyes with a central macular thickness of <400 µm. In this study, we examined changes in CST and CFT in subgroups based on baseline CFT of <400 µm and ≥400 µm. The change in CFT between implant and the end of the 12 month observation period was statistically significantly greater in those with a CFT of ≥400 µm at the time of implant but not in those eyes with a CFT of <400 µm. Eyes with a smaller CFT at the time of FAc implant have less potential to improve. Sample size was relatively small in the CFT subgroups.

A reduction in retinal thickness post FAc implant has also been observed in other studies. In the FAME study, baseline mean foveal thickness was 451 µm and 461 µm in the sham and low dose (0.2 µg/day) groups, respectively.[4] At six months, the mean foveal thickness was 396 µm in the sham group and 318 µm in the 0.2 µg/day group.[4] At 36 months, mean foveal thickness was 309 µm and 280 µm respectively.[4] Similar results were observed in this study, where median CFT in study eyes had

decreased from 464 µm at implant to 331 µm at 6 months. By 12 months, median CFT was 309 µm. In the largest published observational study to date, El-Ghrably and colleagues reported a mean reduction in central macular thickness of 126 µm at 12 months following FAc implant.[31] In line with the findings from this study, central macular thickness decreased rapidly after implant and this was sustained for the 12 month follow-up period.[31] Several other smaller observational studies have investigated the change in central retinal thickness following FAc intravitreal implant for DMO. In a retrospective study conducted by Elaraoud and colleagues, central retinal thickness was found to have decreased by a mean of 149 µm at three months post FAc implant.[32] In this study, 7% of study eyes moved into a higher CFT category between baseline and 12 months post FAc implant. Elaraoud and colleagues also reported a worsening in CFT in 4 out of the 22 eyes included in their retrospective study at 3 months post implant.[32] In a prospective, non-randomised, phase 4, pilot study, Figueira and colleagues observed a statistically significant decrease in CST 12 months after FAc implant, and a rapid decrease in CST in the first week after implant.[33] Rapid and sustained reductions in CST following FAc implant were also observed in a prospective study conducted by Massin and colleagues.[34]

Strengths and limitations

The strengths and limitations of the study have been described previously.[10] As this is an observational study, several limitations are likely to apply including the misclassification of outcomes, effectiveness and safety. Outcomes were not measured at set times post index and were not consistently available across all participating centres for all the time points. Recall of participants to attend measurement may have led to differential misclassification and missing values. There were inconsistencies in the information recorded on cataract operations and lens status. Duration of DMO was not recorded. 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 person were analysed as independent observations. However, second eyes may be more likely to be treated with FAc intravitreal implant if the patient had a positive response to treatment in the first eye. In addition, treatment of the second eye may be more likely to occur at certain treatment centres. Whilst minimising the elimination of individuals from the analysis, methods used to impute missing values have inherent limitations. Last observation carried forward can produce a biased estimate of treatment effect. However, as retinal thickness continued to improve over the duration of the period of follow-up, we believe that last observation carried forward will provide a conservative estimate for the effect of FAc on retinal thickness.

Conclusions

In our cohort of people with DMO, where 96% had a prior history of receiving anti-VEGF injections, laser therapy and/or other intravitreal steroids, central retinal thickness increased in the 12 months prior to the insertion of the FAc intravitreal implant. Following treatment with the FAc intravitreal implant, a marked and sustained reduction in Central foveal thickness was observed in the 12 months following implant. A statistically significant negative correlation between central foveal thickness and visual acuity (ETDRS letters score) was also observed. However, the variance in visual acuity accounted for by central foveal thickness was low.

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Tables and figures

Table 1 | Baseline characteristics overall and by baseline central foveal thickness

Parameter	Overall		By CF	
			<400 µm	
Subjects, n	208		53	(25%)
First eyes treated, n (%)	208	(89%)	53	(25%)
Second eyes treated, n (%)	25	(11%)	10	(40%)
All treated eyes, n (%)	233		63	(27%)
Patient characteristics				
Age last clinic visit, mean (SD)[a]	68.1	(10.7)	68.2	(11.7)
Males, n (%)	128	(62%)	36	(59%)
Type 2 diabetes, n (%)	176	(85%)	50	(82%)
Tablets	76	(43%)	18	(36%)
Insulin	43	(24%)	14	(28%)
Insulin plus tablets	57	(32%)	18	(36%)
Type 1 diabetes, n (%)	32	(15%)	11	(18%)
Tablets	0	(0%)	0	(0%)
Insulin	28	(88%)	10	(91%)
Insulin plus tablets	4	(13%)	1	(9%)
Number of years with diabetes, median (IQR)[a]	18	(11–27)	18	(12–27)
Eye characteristics				
Pseudophakic lens status, n (%)[b]	207	(89%)	53	(84%)
Visual acuity, LogMAR units				
n (%)	224	(96%)	63	(100%)
Median (IQR)	0.66	(0.48–1)	0.6	(0.3–0.8)
Visual acuity, ETDRS letters				
n (%)	224	(96%)	63	(100%)

Median (IQR)	52	(35–61)	55	(45–70)
CST, µm				
n (%)	198	(85%)	58	
Median (IQR)	447	(352–587)	324	(281–371)
CFT, µm				
n (%)	191	(82%)	63	(100%)
mean (SD)	482	(186)	285	(77)
IOP, mmHg				
n (%)	185	(79%)	51	(81%)
Median (IQR), mmHg	15	(13–18)	16	(13–18)
Prior macular laser treatments				
n (%)	146	(63%)	41	(65%)
Median (IQR)	1	(0–3)	1	(0–0)
Prior anti–VEGF injections				
n (%)	191	(82%)	50	(79%)
Median (IQR)	5	(2–7)	4	(2–7)
Prior ranibizumab injections				
n (%)	162	(70%)	44	(70%)
Median (IQR)	3	(0–6)	3	(0–6)
Prior aflibercept injections				
n (%)	1	(0%)	1	(2%)
Median (IQR)	0	(0–0)	0	(0–0)
Prior bevacizumab injections				
n (%)	74	(32%)	17	(27%)
Median (IQR)	0	(0–2)	0	(0–1)
Prior steroid injections,				
n (%)	101	(43%)	27	(43%)
Median (IQR)	0	(0–1)	0	(0–1)
Prior dexamethasone injections				
n (%)	17	(7%)	2	(3%)
Median (IQR)	0	(0–0)	0	(0–0)
Prior triamcinolone injections				
n (%)	88	(38%)	25	(40%)

Median (IQR)	0	(0–1)	0	(0–1)
IOP-lowering medication, n (%)	44	(19%)	12	(19%)
Prostaglandin analogues, n (%)	26	(11%)	6	(10%)
Beta blockers, n (%)	17	(7%)	4	(6%)
Alpha agonists, n (%)	5	(2%)	2	(3%)
Carbonic anhydrase inhibitors, n (%)	11	(5%)	0	(0%)
Other, n (%)	8	(3%)	3	(5%)

CFT = central foveal thickness, SD = standard deviation, IQR = interquartile range, LogMAR = logarithm of the minimum angle of r
Diabetic Retinopathy Study, CST = central subfield thickness, CFT = central foveal thickness, IOP = intraocular pressure, VEGF = va
[a] These are approximate estimates as it was not possible to determine the exact date on which these parameters were recorded i
[b] Include operations carried out on day of implant (n=18).
Although some of the characteristics relate to the individual and not the eye, each eye was analysed as an independent observati

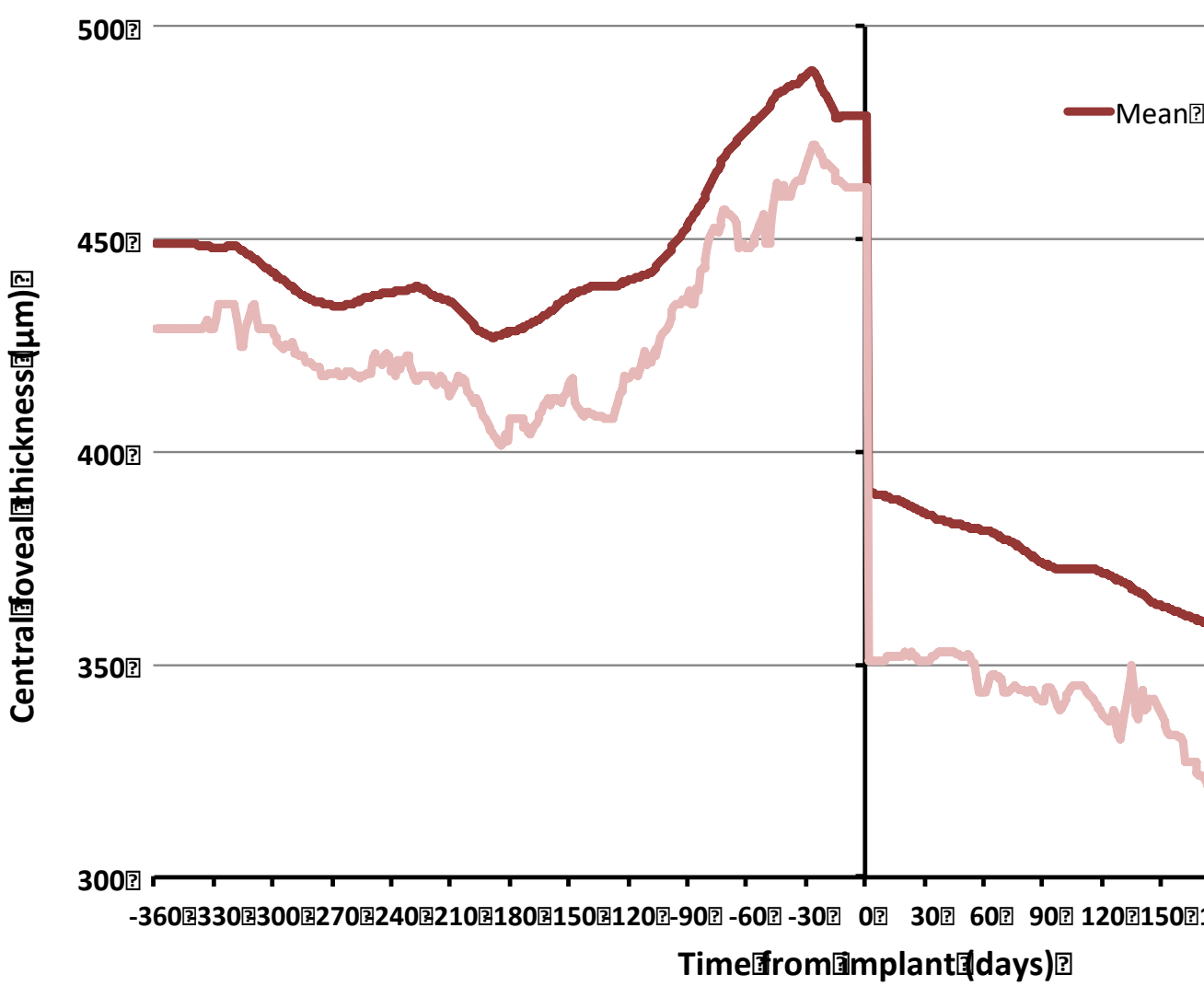
Table 2 | Change in central foveal thickness

	N	Baseline CFT(µm) Median (IQR)		Post-index CFT (µm) Median (IQR)		p-value	≥10% reduction in CFT		≥25% red CF
3 months									
Overall	148	472	(365–616)	355	(254–474)	<0.001	76	(51%)	61
CFT subgroup									
<400 µm	47	302	(244–362)	282	(211–343)	0.453	14	(30%)	9
≥400 µm	101	530	(462–662)	398	(273–515)	<0.001	62	(61%)	52
6 months									
Overall	169	464	(362–605)	331	(239–462)	<0.001	96	(57%)	75
CFT subgroup									
<400 µm	56	302	(233–358)	279	(210–357.5)	0.718	18	(32%)	11
≥400 µm	113	531	(464–674)	388	(259–501)	<0.001	78	(69%)	64
12 months									
Overall	173	462	(354–603)	309	(222–433)	<0.001	113	(65%)	87
CFT subgroup									
<400 µm	58	302	(222–354)	245	(202–357)	0.353	23	(40%)	14
≥400 µm	115	531	(462–674)	349	(245–467)	<0.001	90	(78%)	73

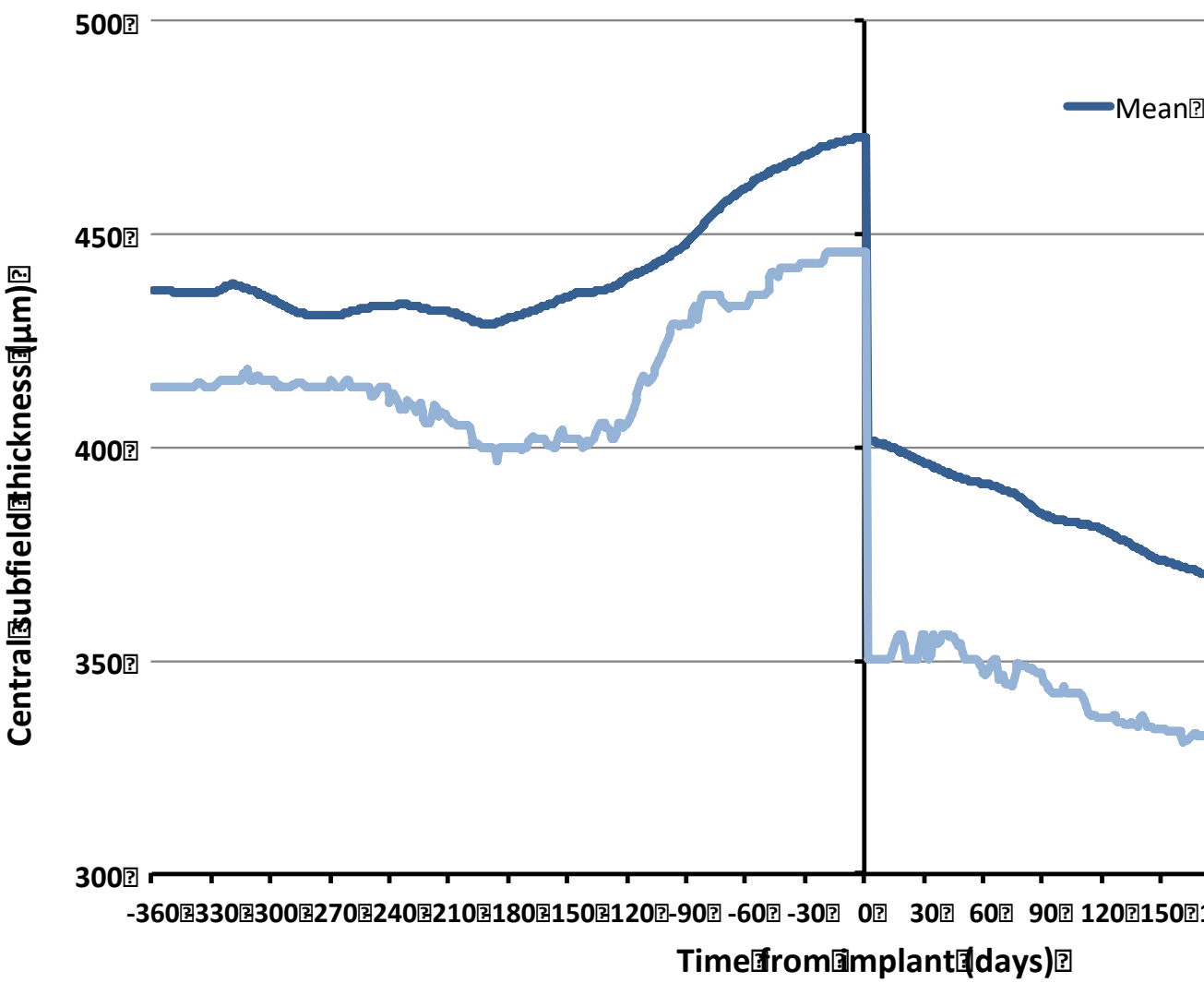
CFT = central foveal thickness, IQR = interquartile range.

Figure 1 | Change in a) central foveal thickness and b) central subfield thickness 12 months before intravitreal implant

a)



b)



Linear interpolation was used to impute missing values between CFT and CST scores. Nearest observation carried forward and ba
values prior to the first and after the last recorded measurement. Imputation was carried out in two parts, day -365 to day 0 and
measurement prior to and post implant were excluded (n=60 for a) and n=52 for b).

Figure 2 | Cumulative frequency for central foveal thickness recorded at baseline and 12 months

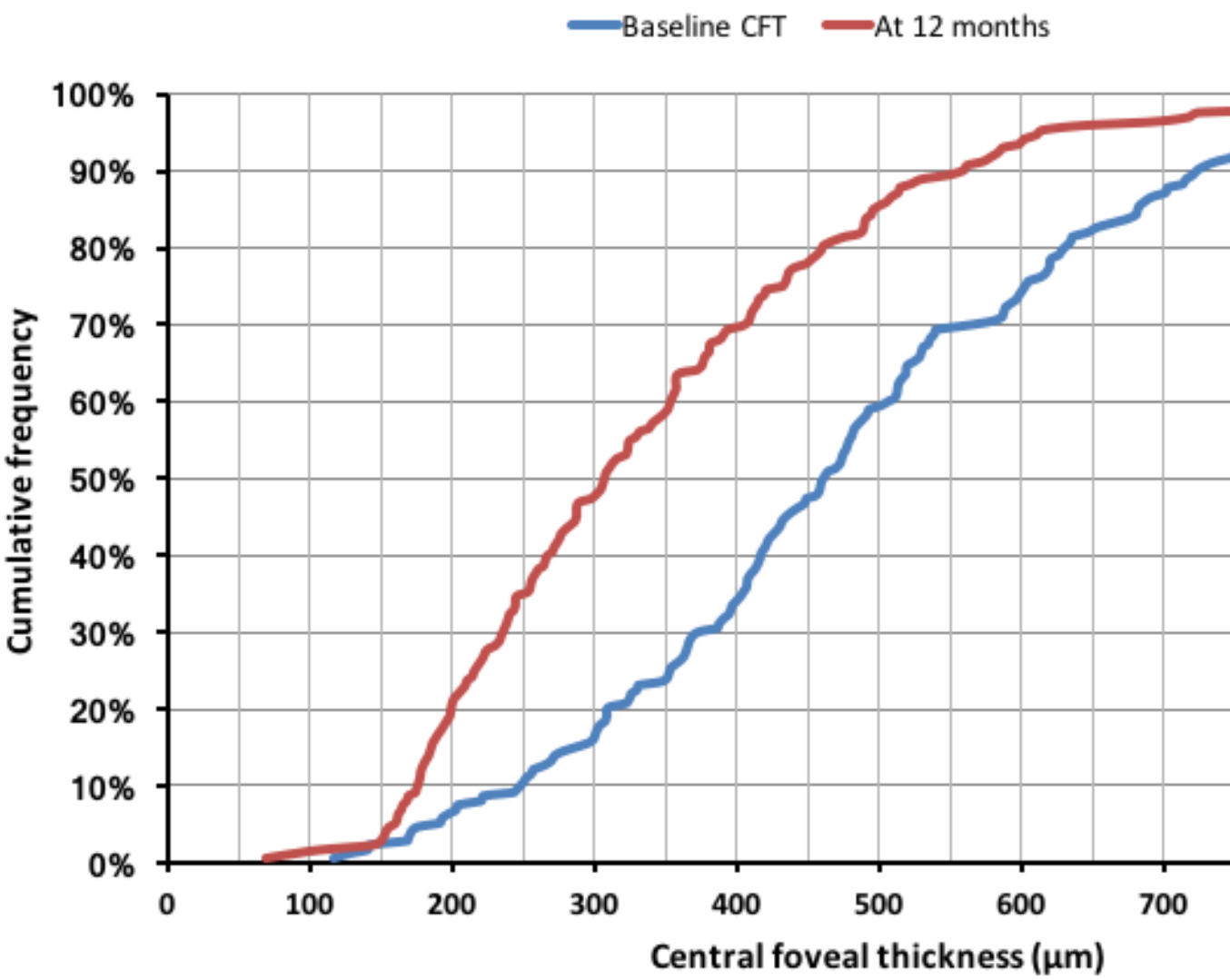
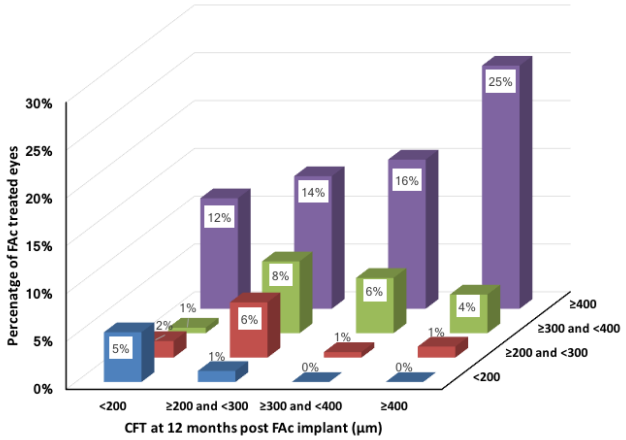
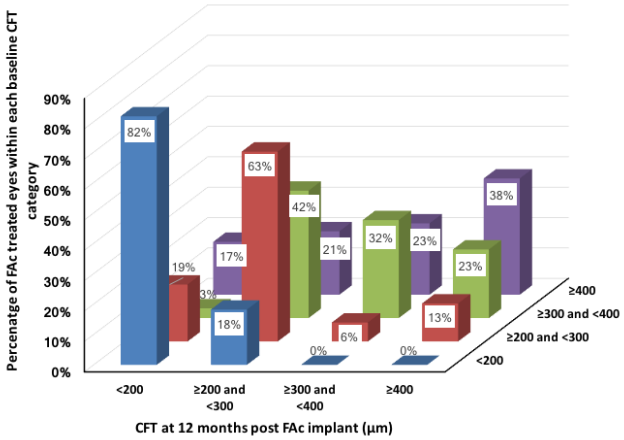


Figure 3 | Central foveal thickness (CFT) at baseline and 12 months post implant

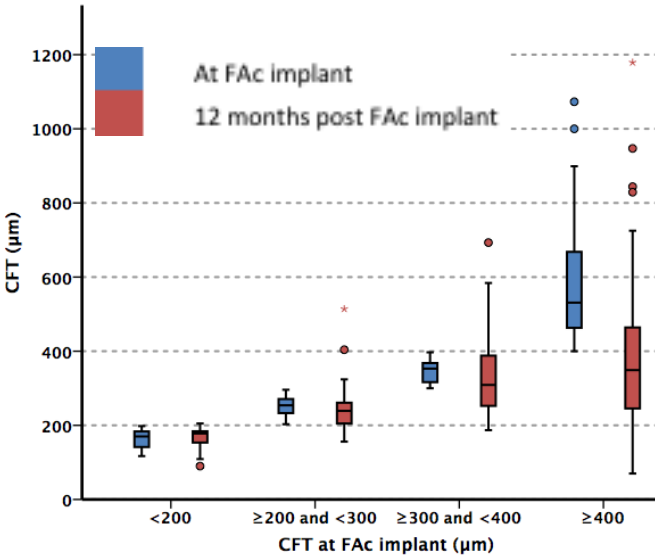
a) Distribution of FAc treated eyes by CFT category at FAc implant and after 12 months follow-up



b) Distribution of FAc treated eyes achieving a CFT of ≤200 µm, >200 and ≤300 µm, >300 µm and ≤400 µm and >400 µm at 12 months post implant by CFT at time of FAc implant



c) CFT at FAc implant and after 12 months follow-up by CFT category at implant



d) Change in CFT between FAc implant and 12 months follow-up by CFT category at implant

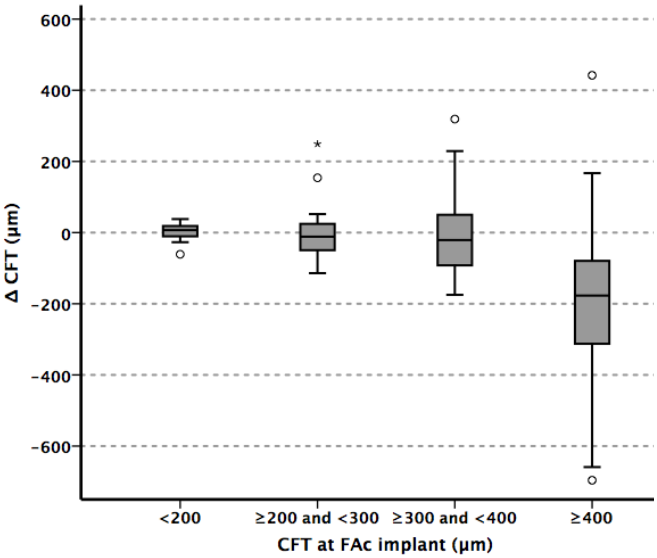
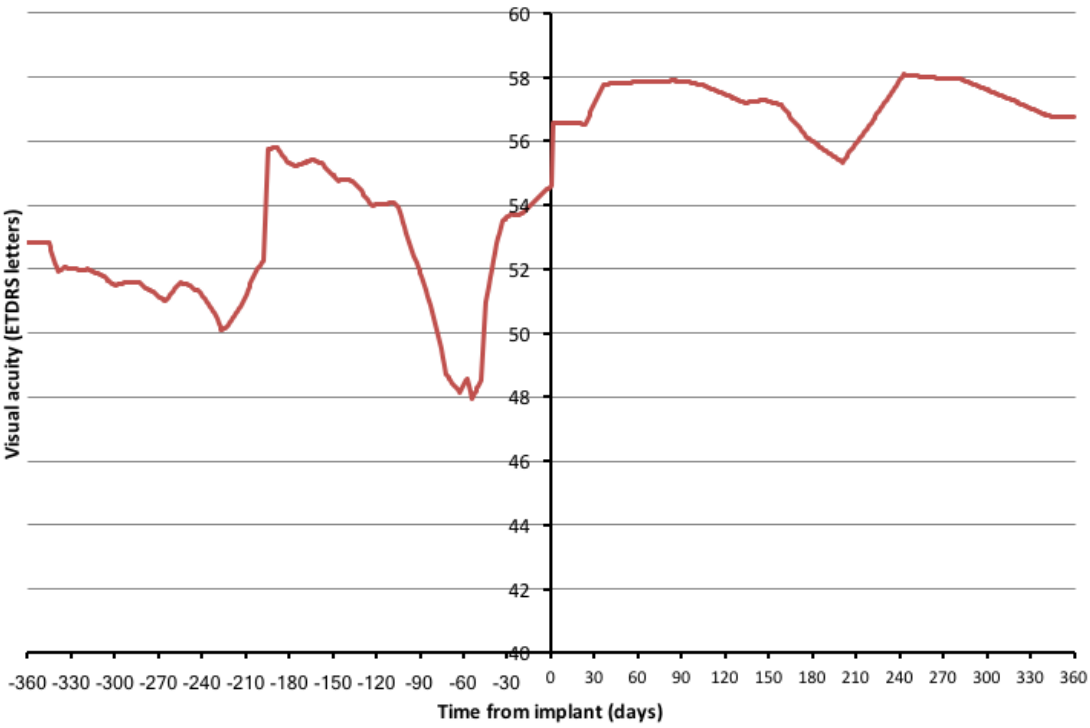


Figure 4 | Visual acuity 12 months prior to and post FAc implant in study eyes a) with a central foveal thickness (CFT) <200 µm at FAc implant (N=12) and b) CFT ≥200 µm at FAc implant and <200 µm at 12 months post FAc implant (N=24)

a)



b)

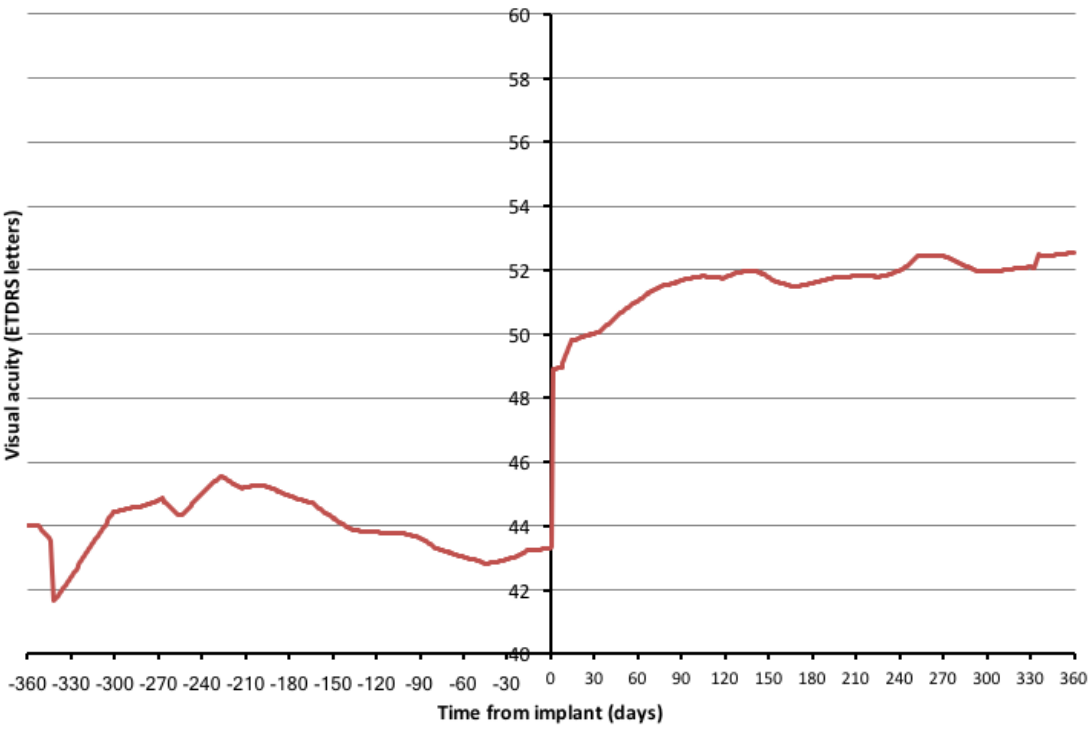
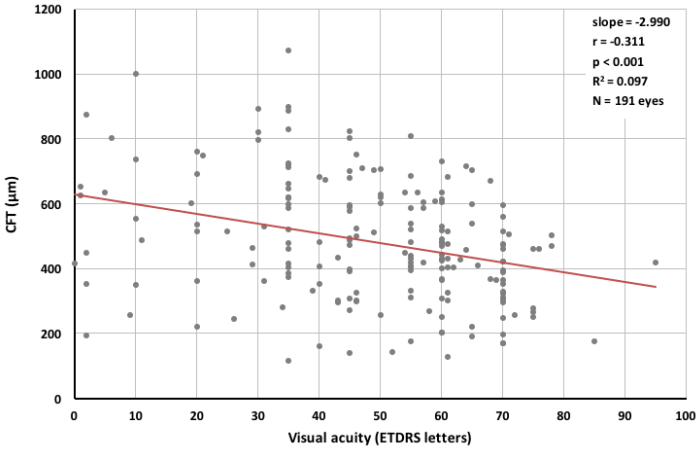
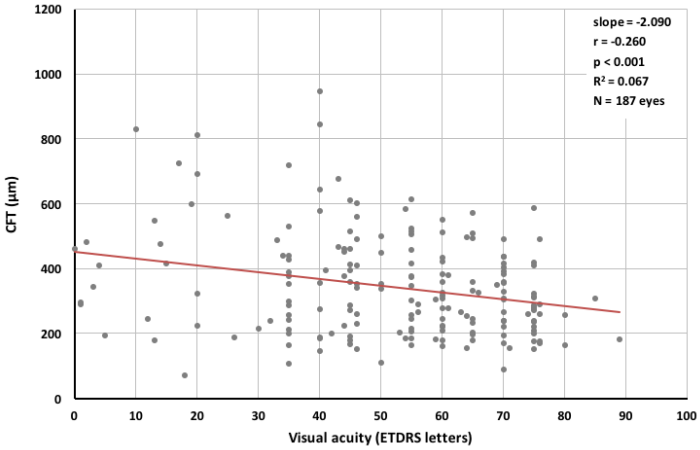


Figure 5 | Correlates between central foveal thickness (CFT) and visual acuity

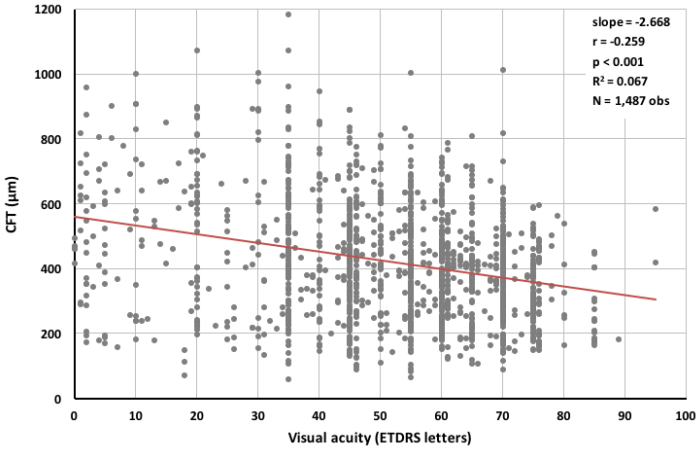
a) Visual acuity and CFT at FAc implantation



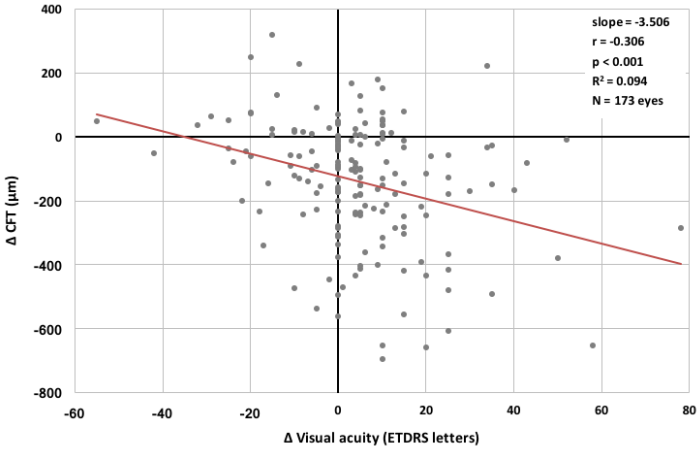
b) Visual acuity and CFT at 12 months post FAc implant



c) All pairs of visual acuity and CFT measurements between 12 months prior to and 12 months post FAc implant



d) Change in visual acuity and change in CFT between FAc implant and 12 month follow-up



R = Pearson's correlation coefficient, R^2 = coefficient of determination.
Only visual acuity and CFT measurements recorded on the same date were included.

Table 3 | Change in central subfield thickness

	N	Baseline CST (µm)		Post-index CST (µm)		p-value	≥10% reduction in CST		≥25%
		Median (IQR)		Median (IQR)					
3 months									
Overall	155	448	(354–587)	356	(276–453)	<0.001	83	(54%)	47
CFT subgroup									
<400 µm	43	327	(269–377)	289	(257–343)	0.015	15	(35%)	5
≥400 µm	99	503	(429–617)	382	(294–472)	<0.001	61	(62%)	40
6 months									
Overall	177	448	(359–581)	337	(268–445)	<0.001	103	(58%)	62
CFT subgroup									
<400 µm	51	327	(273–371)	291	(239–344)	0.012	19	(37%)	6
≥400 µm	110	516	(436–622)	368	(274–460)	<0.001	76	(69%)	53
12 months									
Overall	181	446	(359–569)	318	(262–419)	<0.001	118	(65%)	76
CFT subgroup									
<400 µm	53	327	(281–371)	274	(251–333)	0.005	24	(45%)	10
≥400 µm	112	516	(436–620)	337	(270–445)	<0.001	86	(77%)	62

CFT = central foveal thickness, CST = central subfield thickness, IQR = interquartile range.