19 October 2012

UK Glaucoma Treatment Study Report to Pfizer

Title: The United Kingdom Glaucoma Treatment Study (UKGTS), a multicentre, randomized, double-masked, placebo-controlled trial of the effectiveness of a topical prostaglandin analogue in delaying visual field deterioration in patients with glaucoma

Abstract:

Background: Elevated intraocular pressure (IOP) is a major risk factor for the deterioration of open angle glaucoma (OAG); medical IOP reduction is the standard treatment, yet no randomized placebo-controlled study of medical IOP reduction has been undertaken previously. The typical observation period in therapeutic trials in OAG with conventional study designs is 5 years; patients would benefit if new therapies could be evaluated in a shorter period.

Purpose: The United Kingdom Glaucoma Treatment Study (UKGTS) tests the hypothesis that treatment with a topical prostaglandin analogue, compared to placebo, reduces the frequency of visual field (VF) deterioration events in OAG patients by 50% over a 2-year period. Its main goals are to evaluate study power with novel clinical trial outcomes: i) VF deterioration velocity and ii) VF and quantitative imaging measurements modelled as joint outcomes. Furthermore, the trial aims to identify risk factors for deterioration, establish whether initial observation, rather than immediate treatment, is feasible for selected patients and evaluate the association of VF loss with measures of quality of life.

Methods: The UKGTS is a randomized, double-masked, placebo-controlled, multi-centre treatment trial for OAG. The observation period was 2 years, with subjects monitored by VF testing, quantitative imaging, optic disc photography and tonometry at 11 visits. Data were acquired according to novel protocols optimized for the analysis of deterioration velocity. Eligible patients were assigned by concealed telephone allocation to treatment with a prostaglandin analogue (latanoprost 0.005%) or placebo. The primary outcome measure was time to VF deterioration within 24 months. Secondary outcomes included the deterioration velocity of VF and quantitative imaging measures, and the relationship between these velocities and risk factors for deterioration. The sample size was determined for a two-sided error $\alpha = 0.05$ to detect the difference between 24% and 11% in incident deterioration over a 24-month follow-up at 90% power and assuming a 25% attrition rate. 516 newly-diagnosed (previously untreated) patients with OAG were prospectively recruited at 10 UK centres between 2007 and 2010.

Results: In January 2011, the Data and Safety Monitoring Committee (DSMC) requested an interim analysis. This revealed a significant difference between treatment arms and the DSMC requested that the trial be terminated. Patients were scheduled for exit visits over the following 6 months. Survival analysis showed a statistically significant difference in the time from baseline to the event of confirmed VF progression between the two treatment groups (Group A and Group B) over 24 months following entry to the trial (p=0.0012). The adjusted Hazard Ratio by site was 0.498 (95% CI 0.332, 0.747). The IOP reduction from the pre-allocation visit to the first visit post-treatment allocation was found to be greater in the Group B (4.46mmHg) as compared to the Group A (0.64mmHg). 127 patients who did not reach an endpoint failed to complete 2 years' follow-up (24.6%).
Conclusions: The UKGTS is the first randomised, placebo-controlled trial to show the efficacy of medical treatment in reducing VF deterioration in OAG. The observation period was short (2 years) compared to most trials; the analysis of deterioration velocity and inclusion of quantitative imaging has the potential to reduce the number of patients and/or duration required for subsequent clinical trials and will be modelled in subsequent analyses.

Introduction:

Background: Evidence to date for the beneficial effect of IOP-lowering treatment in OAG with established VF loss comes from a number of sources, particularly the Collaborative Normal Tension Glaucoma Study, the Early Manifest Glaucoma Trial, the Collaborative Initial Glaucoma Treatment Study (CIGTS) and the Advanced Glaucoma Intervention Study (AGIS). The first two of these studies were unmasked and compared treatment with no treatment using an objective VF primary outcome measure; the CIGTS compared medical and surgical interventions, whilst the AGIS compared two surgical management strategies. The UKGTS is the first randomised, double-masked, placebo-controlled, multi-centre trial to evaluate the benefit of medical IOP lowering.

Objectives: The primary objective was to test the hypothesis that medical treatment with a topical prostaglandin analogue reduces the incidence VF deterioration events compared to placebo by 50% over a 2-year observation period. Secondary objectives were to i) evaluate velocity of deterioration as a trial outcome, ii) evaluate quantitative imaging measurements as additional trial outcomes, iii) identify risk factors for OAG deterioration, iv) establish whether initial observation, rather than immediate treatment, is feasible for selected patients, and v) evaluate the association of VF loss with measures of quality of life (QoL).

Methods:

Trial design: The UKGTS is a multi-centre, randomized, double masked, placebo controlled medical treatment trial for OAG. Eligible patients were randomized in a 1:1 ratio to receive

either latanoprost 0.005% or placebo once in the evening to both eyes for 24 months or until reaching an endpoint. After 24 months, subjects who had not reached an endpoint were invited to continue for a further 24 months either on Latanoprost (open-label) or without treatment (no drops) to provide greater power for risk factor analyses (the UK Glaucoma Risk Factor Study; UKGRiFS). UKGRiFS is scheduled to conclude in July 2013.

Participants: Eligibility criteria for participants were modelled on those for the EMGT. OAG was defined as glaucomatous VF defects in at least one eye with corresponding damage to the ONH (cup disc ratio ≥0.7 and/or focal narrowing of the neural rim), with an open angle on gonioscopy and the absence of retinal or neurological condition that could account for VF loss.

Inclusion criteria:

- Newly detected, previously untreated OAG (including primary OAG, normal tension glaucoma and pseudoexfoliation glaucoma) in either eye
- Age over 18 years
- Snellen visual acuity equal to or better than 20/40
- VF mean deviation (MD; location-weighted mean difference from average age-corrected VF sensitivity) of two post-screening VFs differing by no more than 3dB, for an MD better than -6.0dB, or by no more than 4dB, for an MD worse than -6.0dB.
- Ability to give informed consent and attend for the duration of the study

Exclusion criteria:

- Moderately advanced VF loss (MD worse than -10dB in the better eye or worse than -16 dB in the other eye) or a threat to fixation (a paracentral point with sensitivity < 10dB in both the upper and lower hemifields) in either eye
- IOP > 35mmHg on two consecutive occasions in either eye or mean (two visits) baseline IOP ≥ 30mmHg
- Inability to perform reliable VF testing
- Poor quality Heidelberg Retina Tomograph images (HRT; see 'structural imaging' below): mean pixel height standard deviation >40μm
- Cataractous lens gradings of more than N1, C2, or P1 according to LOCS III
- Previous intraocular surgery (other than uncomplicated cataract extraction more than 1 year previously)
- Diabetic retinopathy

Settings and locations where the data were collected: Consecutive potentially eligible patients were identified at the 'New Patient' clinics of participating centres (Table 1 below). Data collection was standardized and procedures for all investigations were set out the in the trial *Manual of Procedures* and the *Manual of Standard Operating Procedures*. Technicians and clinicians performing the investigations underwent training and certification before initiation of recruitment. Case report forms were collected at the Data Centre and primary data entry into the electronic database was performed by the Trial Manager; primary outcomes were double data entered by a data entry clerk. The Trial Manager monitored adherence to trial protocols, completeness and validity of data and contacted sites to recover missing data.

Participating Centres	**Local Principal Investigator**	**Screening start date**	**Screening end date**
Moorfields Eye Hospital	Professor DF Garway-Heath	December 2006	March 2010
Aberdeen Royal Infirmary	Professor A Azuara-Blanco	March 2007	March 2010
Addenbrookes Hospital	Professor K Martin	December 2008	March 2010
Birmingham Heartlands and Solihull	Mr I Cunliffe Mr A Negi	May 2007	March 2010
Bristol Eye Hospital	Mr J Diamond Dr P Spry	November 2007	March 2010
Cheltenham General Hospital	Professor A McNaught	December 2007	March 2010
Hinchingbrooke Hospital	Professor R Bourne	April 2007	March 2010
Huddersfield/Harrogate	Mr N Anand	February 2009	March 2010

Norfolk and Norwich University Hospital	Mr DC Broadway	February 2007	March 2010
Sunderland Eye Infirmary	Mr S Fraser	March 2007	March 2010
West of England Eye Unit, Exeter	Mr D Byles	January 2009	March 2010

Table 1. The UKGTS participating centres

The source of referrals across all sites is presented in Table 2.

Referral Source	Patients Participated n (%)
GP	15 (3%)
Hospital	43 (8%)
Optometrist	454 (88%)
Unknown	4 (1%)

Table 2. Source of referrals across all UKGTS sites

Interventions: Active: per mL latanoprost 50 micrograms, benzalkonium chloride 0.20mg, sodium chloride, sodium dihydrogen phosphate monohydrate, disodium phosphate anhydrous, water for Injection. Placebo: per mL benzalkonium chloride 0.20mg, sodium chloride, sodium dihydrogen phosphate monohydrate, disodium phosphate anhydrous, hydrochloric acid, sodium hydroxide, water for injection.

Outcomes: The primary outcome is time to confirmed VF deterioration. VF deterioration was based on the GPA pattern deviation maps and defined as, in either eye, at least three test points showing significant negative change compared with baseline (p-value <5%), at the same locations in two consecutive VFs (tentative deterioration) AND deterioration according to the same criterion present in the next two VFs (confirmed deterioration). The secondary outcomes are velocity of uniocular and binocular VF loss, rate of CSLO neural rim area loss and rate of RNFL loss (OCT and SLP), and change in IOP from baseline at 4 and 24 months (or time of deterioration). The outcomes for the sub-study investigations are i) the identification of risk factors for glaucomatous deterioration, including IOP level, IOP fluctuation, age, race, degree of glaucoma damage at baseline (MD in dB), and other ocular and systemic variables, and ii) the association of visual function with measures of QoL.

Sample size: The trial sample size was based on the outcome of the EMGT: deterioration rates at 24 months were 24% in the untreated group and 11% in the treated group, and IOP reduction was 25% in the treated group. Latanoprost typically achieves a 20 to 30% IOP reduction, depending on baseline IOP. Based on 90% power (1 - β) at a two-sided error α = 0.05 to detect the difference between 24% and 11% in incident deterioration over a 24-month follow-up, 193 patients were needed in each arm (386 total). Allowing for a 25% attrition over the study period, 516 patients needed to be recruited to the study.

Randomisation: A randomisation schedule was drawn up by the statisticians in the R & D Department at Moorfields Eye Hospital using randomised permuted blocks of varying centres with stratification by centre. The randomisation schedule was then sent to the Pharmaceutical Manufacturing Unit (PMU) for labelling of treatments. The unit of randomization was the patient, with both eyes allocated receiving treatment.

Allocation concealment mechanism: Pfizer provided latanoprost and placebo drops in identical containers with tear-off labels identifying the container contents; the tear-off labels were removed by Moorfields PMU and replaced with the Study ID number (according to the randomization schedule) prior to packaging. The randomization codes were held securely by Moorfields PMU and Moorfields R&D and were not available to study personnel. On exiting the study (at deterioration or at 24 months), patients were asked to guess whether they had been taking the active or placebo drops.

Implementation: Potentially eligible subjects attended a 'Training' visit where VF tests were repeated twice and ONH imaging performed; these were assessed for eligibility at the accredited Moorfields Eye Hospital Reading Centre. Once eligibility was confirmed and informed consent obtained, a study identification number was assigned by the Moorfields Clinical Trials Unit. Patients were enrolled between 1st December 2006 and 16th March 2010.

Blinding: This was a double-masked study. In an attempt to maintain masking, investigators were encouraged not to tell patients their IOP measurements.

Statistical methods: The sample size estimation, randomization and study design were based on the patient as the unit of observation; the event time to deterioration was defined by the first deterioration in either eye. For eye-based analyses, two approaches will be taken: 1) 'worse' eye analysis and 2) analysis of both eyes, using appropriate statistical techniques to account for correlations between eyes of the same patient. Except for patients for whom no data are available, analyses were carried out on all patients in the treatment group to which they were randomized, using all the available data up to the point that they withdrew, to retain the validity of the randomization process.

The primary trial analysis concerns the incidence of primary deterioration events in Latanoprost- versus placebo-treated eyes over 24 months following entry to the trial.

Survival analysis compares the differences in time from baseline to the event of confirmed deterioration between treatment groups. The survival analysis takes into account subjects who have only been observed for part of the trial period. A comparison of the proportion of subjects with deterioration events in the treatment groups is made using univariate tests. All statistical tests use a two-sided p-value of 0.05, unless otherwise specified. No interim analyses were planned and therefore no overall adjustment of p-values was deemed necessary; however, p-values are formally adjusted in order to account for multiple comparisons when necessary. Baseline characteristics will be summarised by randomized group to assess whether chance differences could impact on treatment effect.

In a clinical trial over a two-year time frame patients are inevitably lost to follow-up. Reasons for missingness will be investigated using logistic regression of covariates (including treatment group, IOP, age, gender, ethnicity and social class) on an indicator of missingness. Estimates from linear regression models will be summarised by regression coefficients and 95% confidence intervals. Summary measures for continuous normally distributed outcome measures will be differences in means and 95% confidence intervals for differences in means. Non-parametric equivalents will be used for non-Normally distributed outcome measures. For categorical variables, the Pearson's $\chi 2$ test or Fisher's exact test will be used.

Linear mixed models and generalized estimating equations will be used for analysis of the secondary outcomes. Treatment, study centre and time will be modelled along with the interaction between them. This interaction will be the parameter of central interest. It is interpreted as the difference in rate of the secondary outcome measurement for patients on latanoprost compared to those on placebo. Random intercepts and slopes will be fitted for each patient along with a random or fixed centre effect depending on intra-class correlation (ICC). If ICC is low, the random effect will be replaced by a fixed effect. Significance of random effects will be based on likelihood ratio tests, while fixed effects will be assessed using Wald tests.

For risk factors for glaucomatous deterioration analyses, multiple variable analyses using Cox proportional hazard models (with Breslow adjustment for ties in time to deterioration) will be employed to model the hazard (follow-up specific conditional probability of deterioration) of the treated group as a constant multiple of the hazard in the control group, while simultaneously adjusting for other study covariates. Model selection will be guided by the findings of the univariate analysis, simultaneous adjustment for important covariates, and identification of the most parsimonious, clinically interpretable, and statistically fitting model, using appropriate variable selection algorithms.

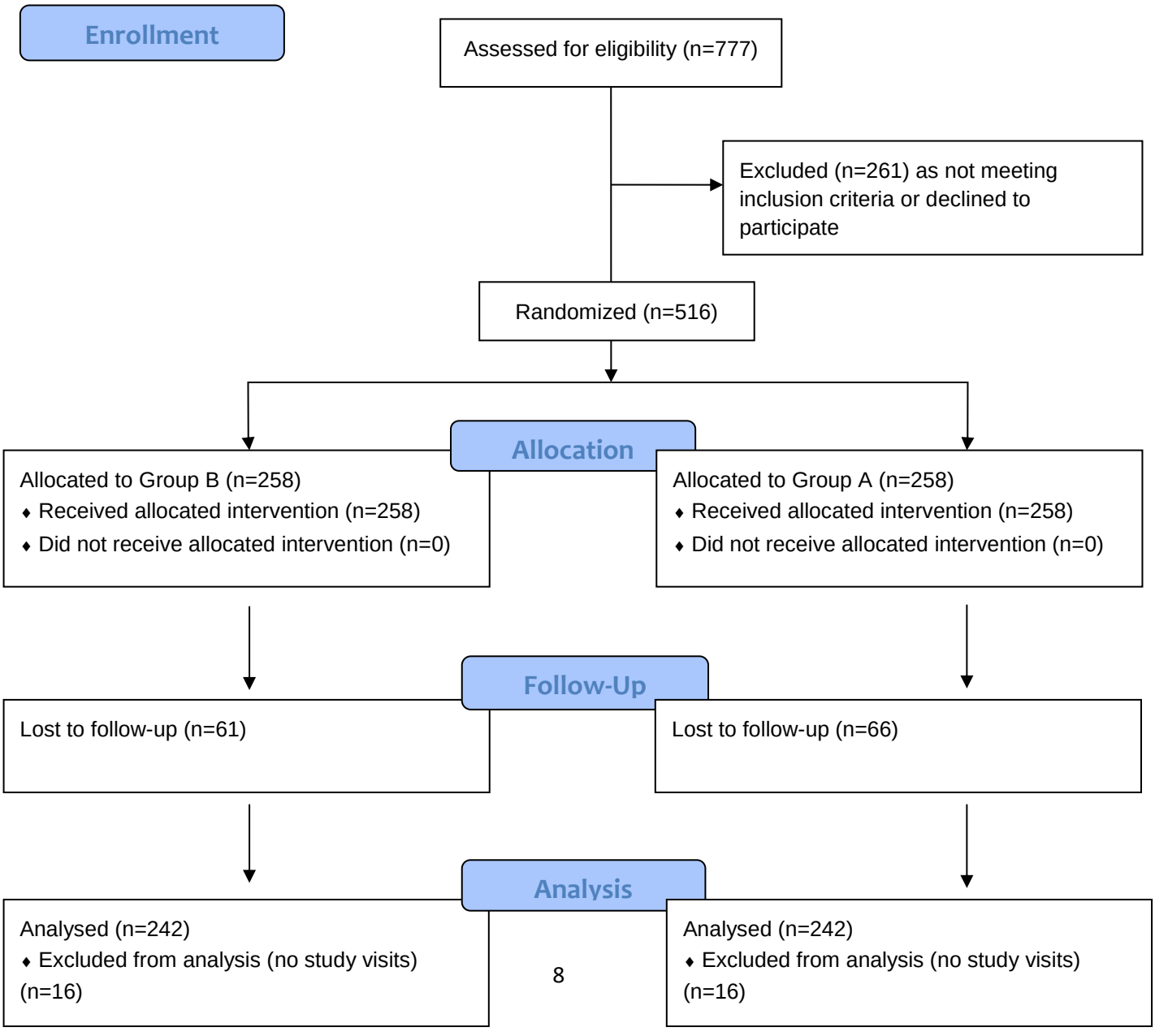
The main QoL analyses are concerned with 1) the association between driving and falls responses with visual function, 2) the association between health and physical activity responses and deterioration status, and 3) the association between health and physical activity responses and integrated visual field sensitivity and overall QoL. As with the other secondary analyses, QoL findings will be investigated using linear mixed models.

Other analyses: exploratory analyses will be performed, such as pointwise linear regression of VF data, Topographic Change Analysis and Statistic Image Mapping of HRT data, and similar approaches for GDx and OCT measurements. The strength of IOP as a risk factor for VF deterioration will be estimated for IOP measurements obtained by the various tonometers. Novel analyses to combine VF and imaging data will be explored in order to attempt to better estimate glaucomatous deterioration rates. In particular, the application of Bayesian linear regression of VF measurements with a prior for the slope derived from longitudinal imaging data will be examined.

Results:

Participant flow: A diagram describing participant flow can be found below.

UKGTS Flow Diagram



Recruitment start and end dates: These are shown for each UKGTS site in Table 1 above.

Baseline data: The baseline characteristics of all the randomised UKGTS participants (n=516) are shown below in Table 3.

	(n=516)	
	n (%)	Mean ±SD
*Centre:		
MEH	91 (17.6%)	
ARI	42 (8.1%)	
NNUH	83 (16.1%)	
BHS	74 (14.4%)	
CGH	24 (4.7%)	
BEH	26 (5%)	
SEI	32 (6.2%)	
HH	109 (21.1%)	
AH	21 (4.1%)	
WEEU	2 (0.4%)	
H&H	12 (2.3%)	
*Family history of glaucoma:		
None	348 (67.4%)	
1st–degree relative	164 (31.8%)	
Other family history	2 (0.4%)	
Unknown	2 (0.4%)	
*Age (years):		66 ± 11
20-29	2 (0.4%)	
30-39	4 (0.8%)	
40-49	40 (7.8%)	
50-59	97 (18.8%)	
60-69	181 (35%)	

70-79	162 (31.4%)	
≥80	30 (5.8%)	
*Gender:		
Female	243 (47.1%)	
Male	273 (52.9%)	
*Education achieved:		
Up to age 16	244 (47.3%)	
Up to age 18	33 (6.4%)	
Apprenticeship/certificate/diploma	137 (26.6%)	
Degree	96 (18.6%)	
Unknown	6 (1.1%)	
*Ethnicity:		
White	465 (90.1%)	
Black	27 (5.2%)	
Asian	16 (3.1%)	
Other	3 (0.6%)	
Unknown	5 (1%)	
*History of:		
Blood loss	35 (6.8%)	
Myocardial infarction	28 (5.4%)	
Obstructive pulmonary disease	31 (6%)	
Diabetes mellitus	54 (10.5%)	
Concomitant neurological disease (Parkinson's, Alzheimer's, multiple sclerosis, deafness)	65 (12.6%)	
*Medication use:		
Antihypertensives	207 (40.1%)	

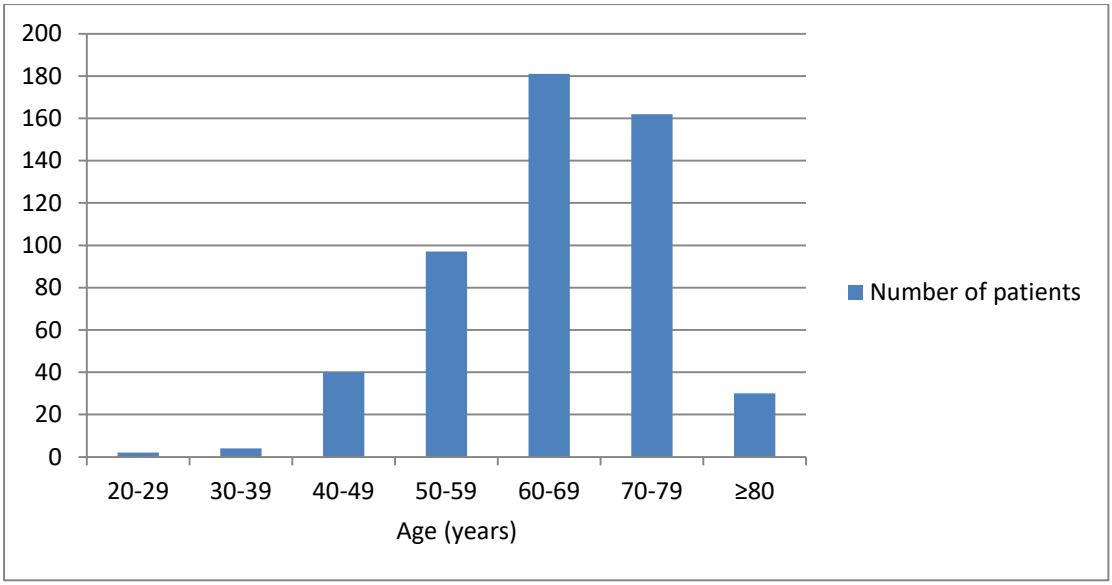
Corticosteroids	45 (8.7%)	
Statins	140 (27.1%)	
Other (insulin, oestrogen etc.)	304 (58.9%)	

Table 3. Baseline clinical characteristics of all the randomised UKGTS patients (n=516)

The baseline characteristics of all the UKGTS participants that attended at least one post-allocation visit (n=483) are shown below in Table 4.

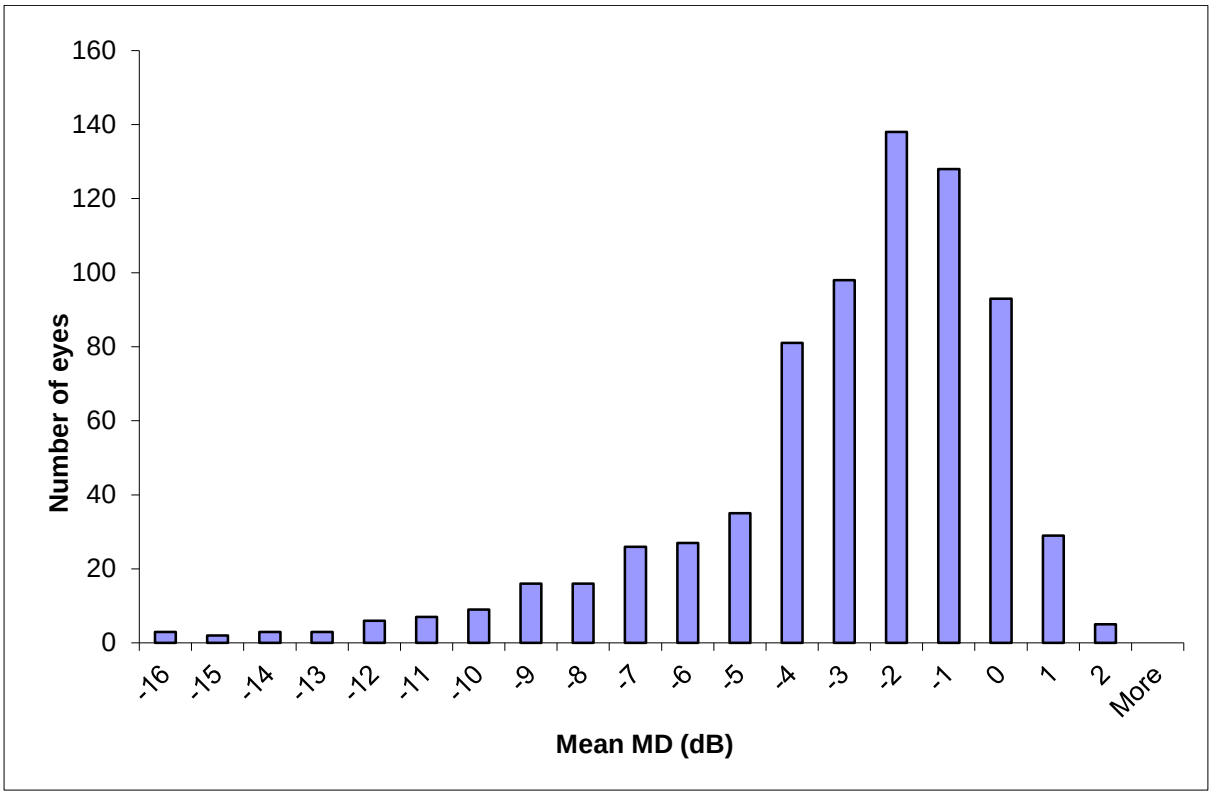
	(n=483)	
	n (%)	Mean ±SD
Systolic blood pressure (mm/Hg)		136 ± 20
Diastolic blood pressure (mm/Hg)		81 ± 11
*Hypertension:		
Receiving treatment, or Systolic >160mmHg, or Diastolic >95mmHg	279 (57.8%)	
*History of:		
General arteriosclerosis (stroke, angina and intermittent claudication)	38 (7.9%)	
Vasospasm, migraine and Raynaud's phenomenon	229 (47.4%)	

The age distribution of all the UKGTS patients at baseline is shown below.



Two visual fields were performed in each eye at the post-allocation baseline visit. In the case of the right eyes, the mean difference (± SD) between the two baseline VFs was 0.16 ± 1.22, with the first VF being more sensitive than the second. In the left eyes, which were tested after the right eyes, this difference was only slightly larger at 0.31 ± 1.16,

The histogram below represents the mean MD (average MD from the two baseline visual fields for each eye) for all the UKGTS eligible eyes (n=771). The median (IQR) for the mean MD was -2.79dB (-4.64 to -1.50).



The baseline characteristics of the better MD versus worse MD eyes are shown in Table 5 below.

	Better MD (n = 483)		Worse MD (n = 483)	
	n (%)	Mean ± SD [median (IQ range)]	n (%)	Mean ± SD [median (IQ range)]
Number of right eyes	189 (39.1%)		294 (60.9%)	
Axial length		24.11 ± 1.29		24.03 ± 1.59
*GAT IOP (mm/Hg):		19.9 ± 4.6		18.9 ± 4.0
<15	59 (12.2%)		72 (14.9%)	
15-19	195 (40.3%)		213 (44.1%)	
20-24	155 (32.1%)		159 (32.9%)	
25-29	65 (13.5%)		38 (7.9%)	
≥30	9 (1.9%)		1 (0.2%)	
CCT (mm)		542 ± 34		542 ± 34
PXF present	0 (0%)		1 (0.2%)	

Table 5. Baseline characteristics of the better MD versus worse MD eyes in the UKGTS (GAT: Goldmann applanation tonometry, CCT: Central corneal thickness, PXF: Pseudoexfoliation)

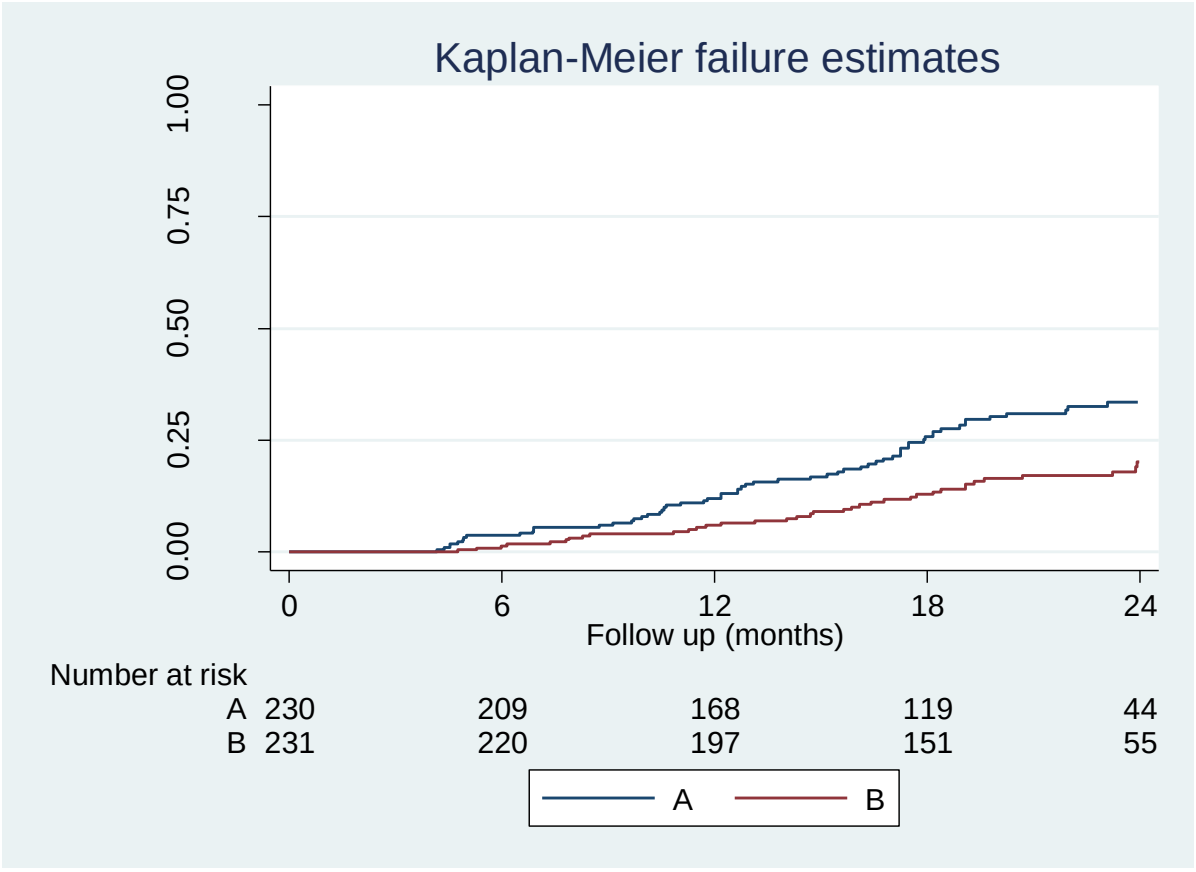
Right eyes appear more likely to be associated with a worse MD at baseline. Also, over half of the better and worse MD eyes demonstrated an IOP of less than 20mmHg at baseline. Axial length and central corneal thickness were very similar between the two eyes, while pseudoexfoliation (PXF) was very rare in our cohort, with only one eye noted to have PXF in the worse MD group.

Outcomes:

In January 2011, the Data and Safety Monitoring Committee (DSMC) requested an interim analysis. This revealed a significant difference between treatment arms and the DSMC requested that the trial be terminated. Patients were scheduled for exit visits over the following 6 months.

Primary Outcome:

Survival analysis showed a statistically significant difference in the time from baseline to the event of confirmed VF progression between the two groups (Group A and Group B) over 24 months following entry to the trial (p=0.0012). The adjusted Hazard Ratio by site was 0.498 (95% CI 0.332, 0.747).



Ancillary analyses:

The IOP change from the pre-allocation visit to the first visit post-allocation in Groups A and B is shown in Table 6 below.

	Group A	Group B
IOP before allocated treatment	19.4 ± 4.7	19.0 ± 4.6
IOP at 1st visit post-allocation	18.8 ± 5.2	14.5 ± 3.3

Table 6. IOP (±SD) before and at the 1st visit after the treatment in Groups A and B

Harms: As shown in Table 7 below, only 7 patients showed a possible or established reaction to a study drug for which they had to be withdrawn from the study. No serious adverse

events definitely related to the study intervention were noted. 2 cases of life-threatening events were reported and included an asthma attack and a suspected stroke.

	(n = 127) n (%)
Reasons:	
Adverse reaction to study drug (possible or established)	7 (5.5%)
Ill health	32 (25.2%)
Death	7 (5.5%)
Ocular co-morbidity*	11 (8.7%)
Other	70 (55.1%)

Table 7. Reasons for loss to follow-up in the UKGTS (*includes cataract, angle closure or uveitis)

Discussion:

Outcome: The UKGTS is the first randomised, placebo-controlled trial to show the efficacy of medical treatment in reducing VF deterioration in OAG.

Limitations and generalizability: The intensive testing and visit schedule contributed to a high attrition rate (almost 25%), potentially limiting the generalisability of the findings. Patient masking may have been imperfect because of the effects on IOP, eyelash growth and iris colour change, but the extent of masking at the end of the study has yet to be analysed.

Agreement between baseline VFs: A good agreement was found between the first and second VFs performed by each participant at the post-allocation baseline visit, suggesting that performing duplicate VFs on the same day might be compatible with clinical practice. The first VF had slightly higher sensitivity than the second in each eye. The difference suggests a possible fatigue effect, however, the discrepancy may be explained by the Humphrey software exclusions for learning (92 of the second baseline VFs automatically excluded by the software, when a significant learning effect determined by the software).

Interpretation of trial design novelties: The UKGTS has the shortest observation period of all OAG therapeutic trials with a VF outcome to date. This was achieved simply by inflating the sample size so that differences in the rate of incident deterioration between treatment groups could be identified at the 2-year time point, based on the outcome of the EMGT.

However, the trial was designed to assess novel data analysis methods, which may further reduce the trial duration or sample size required to identify treatment effects; these design features are related to VF test frequency and interval, selected to maximize the accuracy of estimates of the VF deterioration velocity, and to the inclusion of quantitative imaging of ONH and RNFL structure.

VF tests were clustered at the beginning and end of the 24-month observation period. Statistical modelling demonstrates that clustering increases the precision of estimates of the velocity of deterioration. Additional tests were clustered at the 18-month time point to assess whether trial durations can be reduced further. Additional VF tests were performed following an 'event' endpoint to mitigate potential bias in the velocity estimate introduced by censoring the VF series at an event endpoint. Statistical models have been established for analysing longitudinal data with repeated measures of outcome variables, such as mixed models and generalised estimating equations. Bayesian approaches can also be adopted in order to fit models that are hard to fit within a traditional frequentist framework. However the application of such models for longitudinal data is non-trivial, particularly in VF analysis, because the data variability characteristics change with disease severity and autocorrelation within the time series of repeated measures needs to be considered. The outcome of the UKGTS will be used to compare the relative power of survival analysis and disease velocity-based analyses to identify treatment effects.

Several clinical trials in OHT and OAG have included structural endpoints, based on subjectively-identified change in stereoscopic ONH photographs. The OHTS included quantitative imaging in a subset of patients. The UKGTS is the first clinical trial in OAG to include quantitative imaging in all participants. Structural outcomes were not trial endpoints, so that treatment effects on visual function could be assessed without the censoring effect of endpoints based on structural deterioration. However, it is possible to assess whether the inclusion of structural measures as joint outcomes increases statistical power to identify treatment effects and risk factors; statistical methods have been developed to enable the modelling of joint outcomes and have shown promise in the analysis of longitudinal VF and imaging data in glaucoma.

Other information:

Trial registration number: ISRCTN96423140

Protocol: The full trial protocol can be accessed in Ophthalmology (PMID: 22986112)

Funding: The trial was funded by an unrestricted Investigator-Initiated Research Grant from Pfizer Inc., with additional funding from the NIHR BRC for Ophthalmology and equipment loans from Heidelberg Engineering GhbH, Carl Zeiss Meditec Inc and OptoVue Inc. The trial sponsor was Moorfields Eye Hospital NHS Foundation Trust. The sponsor or funding organization had no role in the design or conduct of this research.