Moorfields Eye Hospital NHS
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Full title of trial	Prospective non-randomised exploratory study to assess the safety and efficacy of Eylea in cystoid macular oedema associated with Retinitis Pigmentosa
Short title	Aflibercept for Macular Oedema with Underlying Retinitis Pigmentosa (AMOUR) study
Version and date of protocol	Version 2.0 26th November2015
Sponsor:	Moorfields Eye Hospital NHS Foundation Trust
Sponsor protocol number	MICM1014
Funder (s) :	Bayer PLC
EudraCT no	2015-003723-65
ACTIVE IMP(s):	Aflibercept (Eylea)
PLACEBO IMP(s):	N/A
Phase of trial	Therapeutic exploratory trial (phase II)
Sites(s)	Single site – Moorfields Eye Hospital

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Statistical Analysis Plan (SAP)

This document has been developed in accordance with the approved MEH SOP documents developed by the Research & Development department at Moorfields.

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Prospective non-randomised exploratory study to assess the safety and efficacy of Eylea in cystoid macular oedema associated with Retinitis Pigmentosa (MICM1014 – The AMOUR study)

SAP SIGN-OFF SHEET

Trial Forms	Version Number	Version Date
MICM1014_SAP_Final_v1.0_08062016.pdf	1.0	08/06/2016

I have reviewed the trial's SAP and approved the use of the above documents

Name	Position	Signature	Date
	Delegated Statistician		__ __ / __ __ / __ __ __ __
	Trial Statistician		__ __ / __ __ / __ __ __ __
	Chief Investigator		__ __ / __ __ / __ __ __ __

Comments

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1. Summary

1.1 Primary research question (formal testing will not be conducted)

The aim of the AMOUR study is to assess the efficacy and safety of Eylea in patients with Retinitis Pigmentosa associated with cystoid macular oedema.

1.2 Study design

Therapeutic exploratory trial (phase II), prospective, non-randomised, single site exploratory trial in patients with Retinitis Pigmentosa associated with cystoid macula oedema.

1.2.1 Treatment arm details

Eylea 2 mg (0.05mL) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 4-12 weeks depending on whether there is evidence of OCT stability in the view of the investigator (i.e. there is no further reduction in macular fluid compared to the previous visit).

1.3 Unit of analysis

Only one eye per patient will be included in the study (the study eye). Unilateral or Bilateral CMO (the worse eye only will be treated – defined as the eye with a greater central macular thickness (CMT) on OCT).

2. Outcome measures

In all sections below, baseline refers to the time of baseline visit.

2.1 Primary outcome measure:

The primary outcome is the mean Central Macular Thickness (CMT) at 12 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

2.2 Secondary outcome measures

2.2.1 To report mean Central Macular Thickness (CMT) at 6 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months

2.2.2 To report mean change in Central Macular Thickness (CMT) as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months

2.2.3 To report the mean BCVA ETDRS letter score at 6 and 12 months in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months

2.2.4 To report the mean change in BCVA ETDRS letter score in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months

2.2.5 To report mean macular volume at 6 and 12 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months

2.2.6 To report mean change in macular volume as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months

2.2.7 To report all AEs and SAEs at any time point during the 12 month study of using intravitreal Eylea in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema

2.2.8 To report the mean retinal sensitivity at 6 and 12 months using Microperimetry in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months

2.2.9 To report the mean change in retinal sensitivity using Microperimetry in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months

2.2.10 To report the mean number of intravitreal injections administered in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months

3. CRFs, data collection, data validation and management

3.1 CRFs and variables

Full details of data collection and timing are described in the trial protocol. A copy of the CRF is held in the Trial Master File.

3.2 Data coding

Variable coding lists are available from the applications manager.

3.3 Data Entry

The completed CRFs will be checked for completion by the research nurse / trial manager. The delegated authorised individual will then enter data onto the trial database created by the R&D IT team. Data entry will be carried out within 1 week of CRF completion. The data entry clerk will double data enter for at least 10% of all data randomly, plus 100% of primary outcome data (Central Macular Thickness (CMT) at 12 months after baseline). The first and second data entries will be compared for completion and consistency checks will be performed. The error rate will be calculated and errors will be corrected as necessary.

3.4 Data verification

Data verification, consistency and range checks are performed at data entry to the trial database, as well as checks for missing data (a complete list of these checks can be found in the Trial Master File).
Additional range, consistency and missing data checks will be performed, as appropriate, when the analysis is performed (and when the datasets for analysis are constructed). All variables will be examined for unusual, outlying, unlabelled or inconsistent values. Any problems with trial data will be queried with the Trial Managers or Data Entry Clerks, as appropriate. If possible, data queries will be resolved; although it is accepted that due to administrative reasons and data availability a small number of problems may continue to exist. This will be minimised, any outliers remaining after the extensive data verification processes will continue to be reported and not replaced as missing.

3.5 Management of datasets

At the time of analysis a copy of each dataset will be made and moved to a designated area of CTU network (data locked) by the CTU Applications Manager. If necessary, new data can be entered on the main, unfrozen copy of the dataset. If any outstanding data queries are resolved during the analysis that relate to data in the frozen dataset (eg problems that are found during analysis or amended CRFs that are returned to CTU), the main and the locked datasets should both be changed under the oversight of the Trial Manager. If any outstanding data queries are resolved while the analysis files are being prepared (i.e. when only a practice dataset has so far been copied), the changes need only be made to the main datasets and an updated, locked copy made available on the CTU statisticians' area.

4. Sample size calculation

This is an exploratory study which aims to assess the safety and efficacy of Eylea in patients with RP and CMO. We have chosen a sample size of 30 patients which is justified on the basis that 30 subjects will provide an estimate of the mean change in CMT from baseline to 12 months with reasonable precision as advocated by Browne (1995) and Hertzog (2008).

5. Data Analysis

5.1 Analysis Principles

5.1.1 ITT or PP

Data will be analysed based on the ITT principle.

5.1.2 Significance levels of tests

No statistical tests will be performed. All confidence intervals will be 95% and two sided.

5.1.3 Recruitment, randomisation and follow-up (to be prepared by research manager)

Recruitment and follow-up will be summarised in a CONSORT flow-diagram.

5.1.4 Follow-up and losses to follow-up: missing data

It is inevitable that some patients may be lost to follow-up. If data are missing for any patients, reasons for missingness may be important and these will be examined using logistic regression of covariates (i.e. gender, age and ethnicity and all other variables listed in Table 1) and on an indicator of missingness.

5.1.5 Adjustment for design factors

No adjustment for design factors will be made.

5.1.6 Masking in the analysis stage

Not applicable as this is an open-label non-randomised study.

5.2 Planned Analysis

Summary statistics for the primary and all secondary endpoints will be presented using mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables.

5.2.1 Baseline characteristics

Baseline characteristics will be summarised using mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables.

5.2.2 Primary Endpoint Analysis

The mean Central Macular Thickness (CMT) at 12 months after baseline will be estimated with a 95% confidence interval.

5.2.3 Secondary Endpoint Analysis

Summary statistics for all secondary outcomes will be presented. Where appropriate, the standard error and two-sided 95% confidence interval will also be presented alongside these. For the case of any outcome measures which are presented as a proportion, a 95% confidence interval will be computed by the exact binomial method.

5.2.4 Subgroup Analyses

No subgroup analyses will be performed.

5.2.5 Sensitivity and other planned analyses

No sensitivity or planned analyses will be performed.

5.3 Toxicity / Symptoms **(to be prepared by CI/research manager)**

All adverse events will be reported in full detail.

Appendix 1: Dummy tables for AMOUR

In all tables, missing data will be reported when applicable.

Figure 1. Consort flow chart (to be prepared by CI/research manager)

Table 1. Non-Ocular Baseline Characteristics

	Eylea (N=)
Number of Patients (Eyes), n (%)	
Male / Female, n (%)	
Age (years), Mean(SD)/Median(IQR)	
Ethnicity, n (%): White Asian Mixed Other	

Table 2. Ocular Baseline Characteristics

	Eylea (N=)
Duration of CMO (weeks), Mean (SD)/Median (IQR)	
Lens status, n (%): Aphakic Pseudophakic Phakic	
ETDRS BCVA, Mean (SD)	
Colour vision, Mean (SD)/Median (IQR)	
Contrast sensitivity, Mean (SD)/Median (IQR)	
IOP (mmHg), Mean (SD)	
Central macular thickness on OCT, Mean (SD)	
Macular Volume on OCT, Mean (SD)	
Mean Retinal sensitivity on microperimetry, Mean (SD)/Median (IQR)	

BCVA = best corrected visual acuity; OHT = ocular hypertension; IOP = intraocular pressure; mmHg = millimetre of mercury

Table 3. Primary outcome measures

	Eylea (N=)	95% CI
Central Macular thickness on SDOCT, Mean (SD) at 12 months		

ETDRS = early treatment diabetic retinopathy study; BCVA = best corrected visual acuity; CI = confidence interval

Table 4. Secondary outcome measures

	Eylea (N =)	95% CI
Central Macular thickness on SDOCT, Mean (SD) at 6 months		
Change in Central Macular thickness on SDOCT from - Baseline to 12 months, Mean (SD) - Baseline to 6 months, Mean (SD)		
ETDRS BCVA, Mean (SD) at 6 months		
ETDRS BCVA, Mean (SD) at 12 months		
Change in ETDRS BCVA from - Baseline to 12 months, Mean (SD) - Baseline to 6 months, Mean (SD)		
Macular Volume on SDOCT, Mean (SD) at 6 months		
Macular Volume on SDOCT, Mean (SD) at 12 months		
Change in Macular Volume on SDOCT from - Baseline to 12 months, Mean (SD) - Baseline to 6 months, Mean (SD)		
Retinal Sensitivity, Mean (SD) at 6 months		
Retinal Sensitivity, Mean (SD) at 12 months		
Change in Retinal Sensitivity from - Baseline to 12 months, Mean (SD) - Baseline to 6 months, Mean (SD)		
Total number of injections received over the study period (12 months), Mean (SD) /Median (IQR)		

BCVA = best-corrected visual acuity; CMT = central macular thickness; OCT = Optical coherence tomography

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Table 5. Ocular and Non-Ocular Adverse Events (AEs) and Serious Adverse Events (SAEs) – at 6 months and 12 months (to be prepared by CI/research manager)

I can confirm that I have written this form and take full responsibility its contents.

Print: **Date:**

Signed: _____ _____ _____

I can confirm that I have reviewed this form and take full responsibility its contents.

Print: **Date:**

Signed: _____ _____ _____