FINAL STUDY REPORT

Study Title: Optimising Treatment with TNF Inhibitors in Rheumatoid Arthritis

REC Ref/ CTA No: 10/H0720/69

ISRCTN: ISRCTN28955701

Chief Investigator: Prof David L Scott

Sponsor: Arthritis Research UK

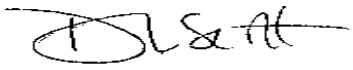
List of Principal Investigators and Sites	Professor Gabrielle Kingsley, Professor Andrew P Cope, Caroline Dore, Ailsa Bosworth, Dr Kimme L Hyrich & Professor Deborah Symmons
List of Publications (or plans for publications) including those for patients (if applicable)	JB Galloway, GH Kingsley, Ma M, B Lorente-Canovas, D Walker, I Pande, A Cope, DG Scott, CJ Doré, F Ibrahim, DL Scott **Optimising Treatment with TNF Inhibitors in Rheumatoid Arthritis: Is Dose Tapering Practical In Optimal Responders? The OPTTIRA Trial** Abstract was accepted as poster presentation at Rheumatology conference in April 2015
Study Start and End Dates	21/04/2011 07/07/2014
Study Design	OPTTIRA is randomised controlled, open label, multi-centre, proof of principle trial. After the first 6 months, follow-up continues as an open exploratory phase in patients with established RA, who have achieved a good response to standard doses of TNF inhibitors and are receiving disease modifying anti-rheumatic drugs (DMARDs).
No. of Patients (planned and analysed)	Number of patients planned to recruit was 99 subjects. The number recruited was 103 subjects and 97 patients analysed
Main inclusion/exclusion criteria	*Inclusion criteria* a. RA by American College of Rheumatology and EULAR criteria b. Etanercept or Adalimumab treatment for at least 6 months (a break of up to 4 consecutive weeks is permitted). c. Taking at least one DMARD from the list and within the standard dose range (given in protocol Appendix 2). d. Stable clinical response for at least 12 weeks as defined by: i. A DAS28 value of ≤ 3.2 at least 12 weeks prior to screening (at least two consecutive DAS28 values of ≤ 3.2 are needed, one at screening and one at least 12 weeks prior to screening) ii. During this period, if one or more DAS28 values

	is between 2.6 and 3.2, there should NOT be an increase in DAS28 value of > 0.6 iii. During this period, if DAS28 values are < 2.6 an increase in DAS28 value of > 0.6 is permissible. e. Patient considers he or she has achieved a suitable response to TNF inhibitors. f. Supervising rheumatologist considers further improvements are unlikely on the patient's current treatment regimen. g. At least 18 years of age. h. Willing and able to give informed consent. *Exclusion criteria* a. Serious concurrent illness (e.g. terminal cancer). b. Prednisolone at more than 10mg daily (for doses > 10mg daily, a 4 week washout period is required). c. Recently received IM/IA steroids (12 week washout required) d. Pregnancy, breast-feeding or women of child-bearing potential not using adequate contraception
Investigational Medicinal Product(s) (including comparator, if applicable), mode of administration and batch number(s)	Two investigational medicinal products, both from the Tumour Necrosis Factor alpha (TNF-α) inhibitors. **Etanercept** *ATC code: L04AB01* *Trade Name: Enbrel* Etanercept is available in prefilled syringes or pens in strengths of 25 and 50mg. 25mg. Etanercept administered twice weekly is the recommended dose for patients with rheumatoid arthritis. Alternatively, 50mg Etanercept administered once weekly has been shown to be an approved dose. In this trial, patients should only self administer 50mg subcutaneously (pen or syringe) according to the dosing regime detailed **Adalimumab** *ATC code: L04AB04* *Trade name: Humira* Adalimumab is available as a 40mg solution for injection in pre-filled syringes or pens. The recommended dose of Adalimumab for adult patients with rheumatoid arthritis is 40mg. Adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with Adalimumab. In this trial, patients will self administer 40mg (pen or syringe) subcutaneously according to the dosing regime detailed in attached in table one.

Duration of Treatment	Patients will receive trial treatment for 12 months after been randomised to the trial.
Primary and Secondary Objective(s)	The primary outcome of the trial was to test the principal hypothesis that tapering treatment to a minimum of one third of the initial "induction" dose does not adversely affect disease control. Secondary objective was to undertake exploratory extension trials. These will increase the number of patients who have undertaken dose tapering and determine if it is possible to reduce TNF-inhibitors to very low doses or to stop treatment entirely.
Endpoints/ Outcome Measure(s)	The development of a flare, defined as an increase in DAS28 scores $\geq$ 0.6 resulting in a DAS28 value of >3.2 is the primary outcome measure. It was measured at baseline, 3, 6, 9 and 12 months. All secondary outcome measures listed below was measured at baseline,3, 6 and 12 months, except for adverse event and DAS28 scores and individual components that were measured quarterly (baseline, 3, 6, 9 and 12 months). a. DAS28 scores and individual components b. Health Assessment Questionnaire (HAQ) scores c. Adverse events d. EuroQol scores e. SF-36 Questionnaire f. FACIT-F (Functional Assessment of Chronic Illness Therapy – Fatigue) Questionnaire g. Plain x-rays of the hands and feet scored by Larsen's method (to provide preliminary data)
Statistical Methods	The main statistical analyses will estimate the time to flare for patients randomised to control, 33% taper or 66% taper. Each tapering group will be compared with the control group. Separate analyses will be performed for the Proof of Principle Phase (0-6 months) and for the Exploratory Phase (6- 12 months). Time to flare survival analysis was used as it allows accounting for lost-to follow up or withdrawn patients since their time at risk would be included up to the point of drop-out. Therefore, there was no imputation method necessary for the primary outcome (time to flare analyses). There was also very few lost to follow-up patients. Methods that take account of the longitudinal nature of the data. For secondary analyses that involve the change in mean a mixed models will be used to estimate the effect of treatment including baseline values as a covariate. Working correlation matrices will

	be unstructured, which is not unduly restrictive given that measurements were taken at three time points. The sandwich estimator of covariance matrix will be used in order to obtain appropriate (consistent) estimates of precision. All analyses were based on an intention-to-treat basis to reflect the randomisation process, except for enrolled patients who were found to be ineligible or who withdraw consent at baseline visit and so never receive any treatment, and for whom no data are available. All statistical tests was two-tailed. P-values and/or confidence intervals was presented as appropriate.
Conclusions	Good responses to TNFis are maintained after TNFis doses are tapered by one-third. Tapering by two-thirds results in more flares, but these respond to restarting TNFis and did not adversely affect disability progression.

Authorised by: Professor David Scott

Signature: 

Date: 06/07/2015