Clinical trial results:
Optimising Treatment With Tumour Necrosis Factor Inhibitors In Rheumatoid Arthritis: Is Dose Tapering Practical In Good Responders? A “Proof Of Principle” And Exploratory Trial. (OPTTIRA)

Summary

EudraCT number	2010-020738-24
Trial protocol	GB
Global end of trial date	07 July 2014

Results information

Result version number	v1 (current)
This version publication date	15 March 2019
First version publication date	15 March 2019
Summary attachment (see zip file)	Summary Report (End of Trial Final Study Report-OPTTIRA Study_July 2015.pdf)

Trial information

Trial identification

Sponsor protocol code	Version 1.2 (20/06/2011)

Additional study identifiers

ISRCTN number	ISRCTN28955701
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Professor David Scott, King's College London, +44 02078485200, kch-tr.opttira@nhs.net
Scientific contact	Professor David Scott, King's College London, +44 02078485200, kch-tr.opttira@nhs.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2014
Global end of trial reached?	Yes
Global end of trial date	07 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study investigates whether in it is possible to reduce the dose of or even stop TNF-inhibitors without adversely affecting the control of this disease. This will be assessed by looking at:
a. The risk of disease flares (using the disease activity score with a 28 tender and swollen joint count (DAS28). An increase of disease activity score (DAS28) of 0.6 or more represents adversely affecting disease control and is considered a flare)
b. If flares are reversed by reverting to the original TNF inhibitor dosage
c. If either tapering group show worse key RA assessments including disease activity (DAS28) and disability as measured by health assessment questionnaire (HAQ) scores
d. Structural damage (plain hand and fe

Protection of trial subjects:

Participants had their DMARD monitoring performed as part of the trial's safety monitoring which has been designed to fit with routine clinical practice,

Background therapy:

Patients will continue to receive the DMARDs prescribed prior to trial entry at standard doses . They will be taking either Etanercept OR Adalimumab

Evidence for comparator: -

Actual start date of recruitment	05 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 97
Worldwide total number of subjects	97
EEA total number of subjects	97

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	97
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from multiple centers across the UK between 2011 and 2014

Pre-assignment

Screening details:

Patients already on TNF inhibitors (failure to respond to two DMARDs) and have a sustained good response. Patients must be taking Etanercept or Adalimumab at standard doses (50mg/week and 40mg/fortnight respectively) and at least one concomit

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 - TNF inhibitor tapered to 66% of initial dose

Arm description:

Experimental group 1 – patients have their TNF inhibitor tapered to 66% of initial dose by reducing frequency of dosing.
Month 1 to 6 - TNF inhibitor tapered to 66% of initial dose.
Month 7 to 12 - Time between injections increased on each occasion until injections are stopped completely.

Arm type	Experimental
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

50mg subcutaneously reducing as detailed in trial protocol.

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

During the "Proof of Principle" phase (months 0 – 6) patients will self administer Adalimumab subcutaneously at a dose of 40mg according to the protocol regime.
During the Exploratory Phase (months 7 - 12) patients in the experimental groups will increase the time between injections until injections are stopped completely

Arm title	Group 2 - TNF inhibitor tapered to 33%

Arm description:

Experimental group 2 - patients have their TNF inhibitor tapered to 33% of initial dose.
Months 1 to 6 - patients have their TNF inhibitor tapered to 33% of initial dose.
Months 7 to 12 - During the Exploratory Phase (months 7 - 12) patients in the experimental groups will increase the time between injections on each occasion until injections are stopped completely.

Arm type	Experimental

Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

50mg subcutaneously reducing as detailed in trial protocol. reducing to 33% of original dose.

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

During the "Proof of Principle" phase (months 0 – 6) patients will self administer Adalimumab subcutaneously at a dose of 40mg according to the protocol regime.
During the Exploratory Phase (months 7 - 12) patients in the experimental groups will increase the time between injections until injections are stopped completely

Arm title	Group 3 Control Group

Arm description:

Control group – patients continue on standard doses as prescribed prior to trial entry.

Arm type	Control
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

50mg subcutaneously weekly as routine standard of care.

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Adalimumab subcutaneously at a dose of 40mg as per routine standard of care.

Number of subjects in period 1	Group 1 - TNF inhibitor tapered to 66% of initial dose	Group 2 - TNF inhibitor tapered to 33%	Group 3 Control Group
Started	21	26	50
Completed	21	26	50

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	97	97	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	97	97	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	72	72	
Male	25	25	

End points

End points reporting groups

Reporting group title	Group 1 - TNF inhibitor tapered to 66% of initial dose

Reporting group description:

Experimental group 1 – patients have their TNF inhibitor tapered to 66% of initial dose by reducing frequency of dosing.
Month 1 to 6 - TNF inhibitor tapered to 66% of initial dose.
Month 7 to 12 - Time between injections increased on each occasion until injections are stopped completely.

Reporting group title	Group 2 - TNF inhibitor tapered to 33%

Reporting group description:

Experimental group 2 - patients have their TNF inhibitor tapered to 33% of initial dose.
Months 1 to 6 - patients have their TNF inhibitor tapered to 33% of initial dose.
Months 7 to 12 - During the Exploratory Phase (months 7 - 12) patients in the experimental groups will increase the time between injections on each occasion until injections are stopped completely.

Reporting group title	Group 3 Control Group

Reporting group description:

Control group – patients continue on standard doses as prescribed prior to trial entry.

Primary: Development of flares

End point title	Development of flares[1]

End point description:

Development of flares, defined as an increase in DAS28 scores ≥ 0.6 [44].

End point type	Primary

End point timeframe:

0 to 12 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: See attached chart for results

End point values	Group 1 - TNF inhibitor tapered to 66% of initial dose	Group 2 - TNF inhibitor tapered to 33%	Group 3 Control Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	26	50	
Units: whole	21	26	50	

Attachments (see zip file)	Secondary Outcomes/Secondary outcomes.pdf Flare Rates/Flare Rates.pdf Adverse Event Data/Adverse Event data.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Outcome measures

End point title	Secondary Outcome measures

End point description:

DAS28 (tender and swollen joint counts, patient global (VAS), ESR) and Extended Joint Count 68/66
Simple disease activity score (SDAI) and clinical disease activity score (CDAI) [45]
Health Assessment Questionnaire (HAQ) scores [46]
Adverse events
EuroQol scores [47]
SF-36
Plain x-rays of the hands and feet scored by Larsen's and van der Heijdi Sharpe Modified Scores (to provide preliminary data)
Analysis of serum, immunological and gene expression profiles

End point type	Secondary

End point timeframe:

0-12 months

End point values	Group 1 - TNF inhibitor tapered to 66% of initial dose	Group 2 - TNF inhibitor tapered to 33%	Group 3 Control Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	26	50	
Units: whole	21	26	50	

Attachments (see zip file)	Consort Flowchart/OPTTIRA additional file 2.pdf Dosing Schedules/OPTTIRA additional files.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

0-12 MONTHS

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Whole Trial

Reporting group description:

All participants received either Etanacept or Adalimumab

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Please see uploaded Adverse Event chart.

Serious adverse events	Whole Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 97 (4.12%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Collapse - reason unidentified			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Otitis externa			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Whole Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 97 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2011	Amendment to remove the requirementfor additional Clinical Trial labelling for the IMPs and NIMPs. Also to request return of excess TNF inhibitors at month 12 to patients (re-labelled with the routine dosing instructions) to avoid destruction and wastage of expensive IMPs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28968858