EU Clinical Trials Register

Clinical trial results:

Optimal utilisation of biologic drugs in Behçet's Disease: a randomised controlled trial of infliximab (IFX) verses alpha interferon (aIFN), with genotyping and metabolomic profiling, towards a stratified medicines approach to treatment.

Summary

EudraCT number	2014-005390-36
Trial protocol	GB
Global end of trial date	21 September 2020

Results information

Result version number	v1 (current)
This version publication date	10 October 2021
First version publication date	10 October 2021

Trial information

Trial identification

Sponsor protocol code	UoL001109

Additional study identifiers

ISRCTN number	ISRCTN49793874
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Liverpool
Sponsor organisation address	Clinical Directorate 2nd Floor, Block C, Waterhouse Building 3 Brownlow Street, Liverpool, United Kingdom, L69 3GL
Public contact	Miss Charlotte Rawcliffe, Liverpool Clinical Trials Centre, +44 151 794 8167, c.rawcliffe@liverpool.ac.uk
Scientific contact	Miss Charlotte Rawcliffe, Liverpool Clinical Trials Centre, +44 151 794 8167, c.rawcliffe@liverpool.ac.uk

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	20 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2020
Global end of trial reached?	Yes
Global end of trial date	21 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to underpin clinically effective prescribing of the biologic drugs infliximab (IFX) and alpha interferon (aIFN) for Behçet's Disease (BD).

The primary objective of the study is to undertake a randomised controlled trial to compare IFX versus aIFN in patients with BD who are unresponsive to standard oral therapy.

Protection of trial subjects:

Consent was obtained prior to each patient participating in the trial, after a full explanation had been given of the treatment options, including the conventional and generally accepted methods of treatment. Age and stage-of-development specific Patient Information and Consent Leaflets were also implemented and patient assent obtained where appropriate. The right of patients to refuse their consent to participate in the trial without giving reasons would have been respected.

The study also had a Trial Steering Committee (TSC) and Independent Safety and Data Monitoring Committee (ISDMC). The ISDMC was responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial and for monitoring the overall progress and conduct of the clinical trial.

The TSC was responsible for monitoring and supervising the progress of the trial, considering recommendations from the IDSMC and advising the TMG on all aspects of the trial.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	01 July 2015
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: 79
Worldwide total number of subjects	79
EEA total number of subjects	79

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	78
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place over 43 months from 8recruiting centres, the first patient was randomised on 21st June 2016 and the last patient was randomised on 18th February 2020.

Pre-assignment

Screening details:

161 patients were screened prior to randomisation. 82 patients did not enter the study, 58 of which were due to not meeting the inclusion/exclusion criteria, 4 declined to participate and 10 were due to 'Other' reasons.

Period 1

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

Blinding implementation details:

There was partial blinding in this study. Assessing clinicians were blinded to therapy, documenting the disease activity and potential AEs. Patients, nurses and the clinician responsible for prescribing the study drug were not blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Infliximab

Arm description:

Infliximab Intravenous Infusion (Remicade)

Arm type	Experimental
Investigational medicinal product name	Infliximab
Investigational medicinal product code	L04AB02
Other name	Infliximab Intravenous Infusion
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Patients received Remicade at a standard dose of 5mg/kg at weeks 0, 2 and 6 as loading then every 8 weeks for the remaining length of the trial.

Arm title	Alpha interferon

Arm description:

Alpha interferon (Roferon-A) pre-filled syringes

Arm type	Experimental
Investigational medicinal product name	Interferon alfa-2a
Investigational medicinal product code	L03AB04
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received Remicade at a standard dose of 5mg/kg at weeks 0, 2 and 6 as loading then every 8 weeks for the remaining length of the trial.

Number of subjects in period 1[1]	Infliximab	Alpha interferon
Started	37	37
Completed	31	29
Not completed	6	8
Adverse event, non-fatal	1	2
Other	3	2
Clinician decision (Not adverse event)	1	2
Inadequate response	1	1
Reason missing	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 5 Patients withdrew consent and data are presented on 74 patients included in the final statistical analysis report.

Baseline characteristics

Reporting groups

Reporting group title	Infliximab
Reporting group description:	
Infliximab Intravenous Infusion (Remicade)	
Reporting group title	Alpha interferon
Reporting group description:	
Alpha interferon (Roferon-A) pre-filled syringes	

Reporting group values	Infliximab	Alpha interferon	Total
Number of subjects	37	37	74
Age categorical			
Number of patients to fall into the age categories defined below.			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	38.9	39.3	
inter-quartile range (Q1-Q3)	31.8 to 48.7	31.6 to 46.5	-
Gender categorical			
Units: Subjects			
Female	24	26	50
Male	13	11	24
Ethnicity			
Units: Subjects			
White - British	34	30	64
Caribbean	0	1	1
Black - Other	1	0	1
Other	0	1	1
White - European	1	1	2
White - Other	0	2	2
White and Black Caribbean	0	1	1
Pakistani	1	1	2
Smoking Status			
Units: Subjects			
Missing	0	1	1
Current Smoker	8	6	14
Ex-smoker	17	9	26

Never smoked	12	21	33
Alcohol Status Units: Subjects			
Missing	0	1	1
None	14	11	25
Sporadic	18	18	36
Regular	5	7	12
Steriod Use Units: Subjects			
Missing	1	0	1
No	18	18	36
Yes	18	19	37
Ocular Units: Subjects			
Missing	11	8	19
Primary	10	7	17
Other	16	22	38
Oral Units: Subjects			
Missing	12	7	19
Primary	12	15	27
Other	13	15	28
Genital Units: Subjects			
Missing	12	7	19
Primary	11	14	25
Other	14	16	30
Musculoskeletal Units: Subjects			
Missing	16	13	29
Primary	10	10	20
Other	11	14	25
Previous septic arthritis in the last 12 months Units: Subjects			
No	37	37	74
Previous septic arthritis in prosthetic joint ever Units: Subjects			
No	37	37	74
Malignancy Units: Subjects			
No	36	37	73
Yes	1	0	1
Urine catheter Units: Subjects			
No	37	37	74
Heart Failure Units: Subjects			
No	37	37	74
Skin Rash Units: Subjects			

No	23	23	46
Yes	14	14	28

End points

End points reporting groups

Reporting group title	Infliximab
Reporting group description:	
Infliximab Intravenous Infusion (Remicade)	
Reporting group title	Alpha interferon
Reporting group description:	
Alpha interferon (Roferon-A) pre-filled syringes	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Set on the Intention to treat principle retaining patients in their randomised groups irrespective of any protocol deviations.	

Primary: Modified Behçet's Disease Activity Index (BDAI) after 3 months of treatment

End point title	Modified Behçet's Disease Activity Index (BDAI) after 3 months of treatment
End point description:	
End point type	Primary
End point timeframe:	
Baseline to 3 months of treatment	

End point values	Infliximab	Alpha interferon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: Score				
median (inter-quartile range (Q1-Q3))	-2 (-3.5 to -0.5)	-2 (-4 to 0)		

Statistical analyses

Statistical analysis title	mod BDAI - baseline to 3 months
Statistical analysis description:	
A Bayesian Linear Regression Model	
Comparison groups	Infliximab v Alpha interferon
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Method	Bayesian Linear Regression
Parameter estimate	alone parameter
Point estimate	0.13

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.19
upper limit	0.46
Variability estimate	Standard error of the mean
Dispersion value	0.25

Secondary: Modified Behçet's Disease Activity Index (BDAI) after 6 months of treatment

End point title	Modified Behçet's Disease Activity Index (BDAI) after 6 months of treatment

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months of treatment.

End point values	Infliximab	Alpha interferon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: BDAI				
median (inter-quartile range (Q1-Q3))	-1.5 (-4 to 0)	-3 (-5.25 to -1)		

Statistical analyses

Statistical analysis title	Modified BDAI - baseline to 6 months
Comparison groups	Infliximab v Alpha interferon
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority[1]
Method	Bayesian Linear Regression
Parameter estimate	Model parameter
Point estimate	0.05
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.3
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[1] - Bayesian linear regression Model

Secondary: Original BDAI after 3 months of treatment

End point title	Original BDAI after 3 months of treatment
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 3 months	

End point values	Infliximab	Alpha interferon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: BDAI				
median (inter-quartile range (Q1-Q3))	-1 (-2 to 0.5)	-1 (-2 to 0)		

Statistical analyses

Statistical analysis title	Original BDAI -Baseline to 3 month
Comparison groups	Alpha interferon v Infliximab
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Method	Bayesian Linear Regression
Parameter estimate	Linear regression parameter
Point estimate	0.12
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.2
upper limit	0.44
Variability estimate	Standard error of the mean
Dispersion value	0.25

Secondary: Significant improvement in vitreous haze after 3 months

End point title	Significant improvement in vitreous haze after 3 months
End point description:	
End point type	Secondary
End point timeframe:	
3 months of treatment.	

End point values	Infliximab	Alpha interferon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	37		
Units: Vitreous haze score				
number (not applicable)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Significant improvement in ulcer severity score (USS) after 3 and 6 months of treatment

End point title	Significant improvement in ulcer severity score (USS) after 3 and 6 months of treatment
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 3 months	

End point values	Infliximab	Alpha interferon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	25		
Units: Ulcer severity score				
median (inter-quartile range (Q1-Q3))	-13.0 (-25.0 to 0)	-7.0 (-21.0 to 0)		

Statistical analyses

Statistical analysis title	Ulcer severity score
Comparison groups	Infliximab v Alpha interferon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.76
Method	Fisher exact
Parameter estimate	Exact test - non aplicable

Notes:

[2] - Test performed is a Fisher exact test based on patients with at least 20% reduction.

Secondary: Significant improvement in number of genital ulcers after 3 and 6 months of treatment

End point title	Significant improvement in number of genital ulcers after 3 and 6 months of treatment
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 3 months	

End point values	Infliximab	Alpha interferon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: genital ulcers				
median (inter-quartile range (Q1-Q3))	-17 (-24 to 0)	-11 (-29 to 0)		

Statistical analyses

Statistical analysis title	genital ulcers, baseline to 3 months
Comparison groups	Infliximab v Alpha interferon
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 1
Method	Fisher exact
Parameter estimate	Exact test - no parameter estimate

Notes:

[3] - Fisher test performed on proportion with at least 20% reduction

Secondary: Significant improvement in Likert pain score after 3 and 6 months of treatment

End point title	Significant improvement in Likert pain score after 3 and 6 months of treatment
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 3 months	

End point values	Infliximab	Alpha interferon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	16		
Units: Likert pain score				
median (inter-quartile range (Q1-Q3))	-1 (-2 to 0)	-0.5 (-2.5 to 1.0)		

Statistical analyses

Statistical analysis title	Likert paint score - baseline to 3 months
Statistical analysis description:	
Analysis conducted using a fishers test based on the proportion with at least 20% improvement.	
Comparison groups	Infliximab v Alpha interferon
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Exact test - no parameter specified

Secondary: Use of prednisolone (or equivalent glucocorticoid) at 6 months

End point title	Use of prednisolone (or equivalent glucocorticoid) at 6 months
End point description:	
Analyses performed on the	
End point type	Secondary
End point timeframe:	
Baseline to 6 months	

End point values	Infliximab	Alpha interferon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	37		
Units: Patients	12	11		

Statistical analyses

Statistical analysis title	Use of prednisolone
Statistical analysis description:	
Analysis conducted using a logistical regression model including treatment, timepoints and a treatment by timepoints interaction	
Comparison groups	Infliximab v Alpha interferon

Number of subjects included in analysis	74
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.891
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	30.477
Variability estimate	Standard error of the mean
Dispersion value	1.629

Secondary: Quality of life scores at 3 and 6 months compared to baseline

End point title	Quality of life scores at 3 and 6 months compared to baseline
End point description:	

End point type	Secondary
End point timeframe:	
Baseline to 3 months	

End point values	Infliximab	Alpha interferon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	29		
Units: EQ5D VAS				
median (inter-quartile range (Q1-Q3))	10 (0 to 20)	10 (-5 to 20)		

Statistical analyses

Statistical analysis title	Quality ofLife (EQ5D)
Comparison groups	Infliximab v Alpha interferon
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8318
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Exact test - no parameter specified

Secondary: Physician's Global Assessment of disease activity at 3 and 6 months

End point title	Physician's Global Assessment of disease activity at 3 and 6 months
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 3 months	

End point values	Infliximab	Alpha interferon		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	29		
Units: Disease Activity score				
median (inter-quartile range (Q1-Q3))	-2.0 (-4.0 to -1.0)	-1.0 (-3.0 to 0.0)		

Statistical analyses

Statistical analysis title	Clinician perception disease activity
Comparison groups	Infliximab v Alpha interferon
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.421
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	non-parametric test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Full study period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5

Reporting groups

Reporting group title	Infliximab
Reporting group description: -	
Reporting group title	aIFN

Reporting group description: -

Serious adverse events	Infliximab	aIFN	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 37 (8.11%)	2 / 37 (5.41%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 37 (2.70%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure inadequately controlled			
subjects affected / exposed	1 / 37 (2.70%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 37 (2.70%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	0 / 37 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 37 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection bacterial			
subjects affected / exposed	1 / 37 (2.70%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Infliximab	aIFN	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 37 (32.43%)	17 / 37 (45.95%)	
Investigations			
ALT Increased			
subjects affected / exposed	1 / 37 (2.70%)	3 / 37 (8.11%)	
occurrences (all)	2	8	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 37 (8.11%)	4 / 37 (10.81%)	
occurrences (all)	3	4	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 37 (5.41%)	10 / 37 (27.03%)	
occurrences (all)	3	14	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	2 / 37 (5.41%)	4 / 37 (10.81%)	
occurrences (all)	3	6	
flu like symptoms			
subjects affected / exposed	2 / 37 (5.41%)	5 / 37 (13.51%)	
occurrences (all)	3	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 37 (5.41%)	6 / 37 (16.22%)	
occurrences (all)	2	6	
Nausea			
subjects affected / exposed	2 / 37 (5.41%)	3 / 37 (8.11%)	
occurrences (all)	3	4	
Vomiting			
subjects affected / exposed	2 / 37 (5.41%)	3 / 37 (8.11%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Chest Infection			
subjects affected / exposed	2 / 37 (5.41%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Infections and infestations			
Chest Infection			
subjects affected / exposed	3 / 37 (8.11%)	0 / 37 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2015	Several changes to the protocol as part of the MHRA approval, to include; • A change to the wording of the main exclusion criteria (section 1 and section 5.2) and precautions required (section 7.7.2) to detail the requirements for participants of child bearing potential to use effective contraception. • A change to the schedule of assessments (section 8) and changes to the glossary were made. • Patient information sheet was amended to reduce the amount of blood sample required.
17 December 2015	• General - updated trial start date. • Sections 1 and 5.2 – corrections to the objectives of the trial and confirmation of the number of trial sites. • Exclusion criteria updated to include Multiple Sclerosis and HIV patients. • Section 4.1 – overall design updated to reflect timing of assessments as per standard care practice. • Section 4.3 – secondary end points changes to genital ulcer measure with a reduction of 20% considered to be clinically significant. • Section 6 – Enrolment/baseline update to screening log information. Update to randomisation instructions relating to the online enrolment and randomisation system TARDIS. • Section 6.1- screening assessments to be completed within 35 days prior to the first dose of treatment. HIV added. • Section 6.1- symptom directed assessment removed from baseline assessment and the inclusion of a chest X-ray. Addition of screening for alterations in mood/suicide ideation (as known to be a side effect of Roferon treatment). • Section 7- Study treatment, the standardised use of methotrexate has been removed from the trial for clarity. Concomitant immunosuppressants will now be administered at the clinician discretion on a case by case basis. • Section 8.1 amendments were made to the schedule of assessments. • Section 8.2 Electronic CRF updated relating to assessment of efficacy. • Section 8.4.2.2. Further information detailing the collection of urine samples for metabolomics analyses. • Section 8.7. Trial closure has been amended as being when the last patient has completed their final study visit. • Section 9.2. Updated procedure for generating randomisation code lists. • Section 13. Update to clarify the method of data capture as utilising electronic CRF's. • Quality control procedures at site for primary and secondary endpoints as a consequence of the use of an eCRF platform at sites. • The removal of minimisation techniques for randomisation. • Section 16. Oversight committee members' inf

25 January 2016	Several changes to the protocol as part of the MHRA approval, to include; • A change to the wording of the overall design (section 4.1) as per the ISDMC recommendation. New wording; This is a randomised, two-arm, parallel, open-label design comparing the efficacies of infliximab vs alpha interferon. The population is patients with refractory disease eligible for the first biologic drug. • Primary outcome wording changed to match section 9 of the protocol. New wording; Primary Outcome: Modified Behçet's Disease Activity Index (BDAI) after 3 months of treatment (Week 12 visit), with 20% change in means being defined as the zone of equivalence of treatment.
28 October 2016	• Change to randomisation directions. • Section 7.2.2 – "Target dose of azathioprine is 2.5 mg/kg" added as per ISDMC recommendation. • Section 7.2.1 – Update to provide sites with more information about the IMP. • Section 7.3.2 – Wording added as per ISDMC recommendation "Immunosuppressant's will be discontinued in Arm B". • Section 8.1 – Schedule of assessments – New column added to detail the assessments required at Week 36 for patients who swap treatment arms at 12 weeks. • Section 8.2 – Wording changed to include the mandatory visit (Week 36) for patients who swap treatment at Week 12. • Section 8.4.3.2 – Change to amount of urine to be collected at each visit. • Section 9.2 - Additional details were provided in order to make the randomisation procedure more clearly to the reader. • Section 9.3.2 - Week 26 replaced with Week 24. • Section 9.6.1 - Priors were given explicitly as this was missed in the previous version of the protocol. • Section 9.6.2 - Corrected sample amount and added "at each trial visit" to make the collection clearer • Changes to Remicade SmPC. • Changes to Roferon SmPC for notification purposes only • Update to Staff members. Patient Information Sheet • IRAS number added – to comply with HRA guidance. • New wording to make clear that urine sample is required at visit Week 36 if patients swap treatment at Week 12. Informed Consent Form • IRAS number added – to comply with HRA guidance. • New wording to make clear that urine sample is required at visit Week 36 if patients swap treatment at Week 12. GP Letter • IRAS number added – to comply with HRA guidance

16 May 2017	Exclusion Criteria added (section 5.2) • Point 8 Evidence for active Tuberculosis (TB testing using local standard practise) • New Wording Section 6.1 – If in the opinion of the Principle Investigator, the patient requires a biologic drug, whether a prior immunosuppressive agent has been given or not, that the patient will be eligible for a biologic under normal standard of care and SSBEH_D054/01 Bio Behçet's Final Statistical Analysis Report 20/09/2021 Page 14 of 73 therefore may be included in the trial. (Patients previously receiving a prior biologic agent will, currently, not be eligible for the trial) If, in the opinion of the Principle Investigator, the disease is so severe that the benefit of starting the biologic before receiving all screening test results outweighs the risk of not starting it, that patient will remain eligible for the trial, in line with normal practise. • New Wording Section 4.1 – This is a randomised, two-arm, parallel design comparing the efficacies of the infliximab vs alpha interferon. (Previous Wording – This is a randomised, two-arm, parallel, open label design comparing the efficacies of infliximab vs alpha interferon • New Wording Section 6.1 – Section 6.1 Eligibility assessments for entry into the trial will be performed within 42 days prior to the first dose of treatment.(Previous Wording- Eligibility assessments for entry into the trial will be performed within 35 days prior to the first dose of treatment). • Changes to the wording randomisation procedure – New Wording After a patient has been screened and their details entered onto MACRO 4 database by the trial site the randomisation can be performed on the TARDIS website. The clinician must confirm eligibility by signing a paper eligibility Case Report Form (CRF) which trial site staff will email or fax to LCTU along with a copy of the Informed Consent Form. This will confirm eligibility of the patient along with the stratification factors, which will

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The primary outcome is conducted using a Bayesian approach using priors derived from clinical expertise. As such, the primary outcome is assessed based on a posterior distribution which accounts for both prior information and study data.

Notes: