<u>CONFIDENTIAL</u>

BIO BEHÇET'S
Optimal utilisation of biologic drugs in Behçet's Disease: a randomised controlled trial of infliximab vs alpha interferon, with genotyping and metabolomic profiling, towards a stratified medicines approach to treatment.

Study Sponsor:

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Study Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Signature: _____   Date: 25/07/17

Professor Robert John Moots
Chief Investigator
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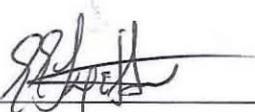Signature: _____   Date: 27/07/17

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Signed on behalf of Liverpool Clinical Trials Unit
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General Information

This document describes the BIO Behçet's trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Cancer Research UK Liverpool Cancer Trials Unit (LCTU)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via LCTU.

Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, LCTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004

UK Registration

This study will have National Research Ethics Service (NRES) approval and hold a Clinical Trials Authorisation issued by the Medicines and Healthcare Products Regulatory Agency (MHRA). Each centre must also undergo Site Specific Assessment by the relevant Trust Research and Development department (or Local Research Ethics Committee for Non-NHS Sites) and NHS sites must be granted Research and Development Approval from each Trust where the trial will be carried out.

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Glossary

AE	Adverse Event
aIFN	alpha Interferon
AR	Adverse Reaction
BD	Behçet's Disease
BDAI	Behçet's Disease Activity Index
CI	Chief Investigator
CRF	Case Report Form
CRP	C-reactive protein
CTIMP	Clinical Trial of an Investigational Medical Product
CTU	Clinical Trials Unit
eCRF	Electronic Case Report Form
ESR	Erythrocyte Sedimentation Rate
GP	General Practitioner
IB	Investigator's Brochure
ICBD	International Criteria for Behçet's Disease
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IFNL3	Interferon, Lambda 3
IFNL4	Interferon, Lambda 4
IFX	Infliximab
IMP	Investigational Medicinal Product
ISG	International Study Group
LCTU	Liverpool Clinical Trials Unit
LREC	Local Research Ethics Committee
MREC	Multi-centre Research Ethics Committee
NHS	National Health Service
PI	Principal Investigator
QoL	Quality of Life
R&D	Research & Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SNP	Single-Nucleotide Polymorphism
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
WOCBP	Women of Child Bearing Potential

1   PROTOCOL SUMMARY

Title: Bio Behçet's - Optimal utilisation of biologic drugs in Behçet's disease (BD): a randomised controlled trial of infliximab vs alpha interferon, with genotyping and metabolomic profiling, towards a stratified medicines approach to treatment.

Phase: III

Sample Size: 100 patients are to be enrolled in total.

Main Inclusion Criteria:

The inclusion criteria are adult individuals who are:
1. Diagnosed to have BD by International Study Group (ISG) criteria or International Criteria for Behçet's disease (ICBD),
2. Have refractory disease as defined by the UK Centres of Excellence criteria (failure to respond to steroid and/or immunosuppressive therapy with significant or major organ-threatening disease) and therefore qualify for biologic therapy with either infliximab or alpha interferon. A summary drugs pathway is attached as Appendix A. Patients will have failed to respond to or have been intolerant of azathioprine at a dose of >2mg/kg (or comparable drug) and/or prednisolone at a dose of >40mg/day typically for more than three months, or with evidence of either organ threatening disease or unacceptable adverse events from immunosuppressive medication.
3. Able to give informed consent.
4. Have not previously received a biologic agent, and
5. Aged over 18 years.

Main Exclusion Criteria

1. Have a contraindication to either infliximab or alpha interferon (e.g. active infection, severe liver disease, neutropenia or previous malignancy).
2. Are likely to not comply: for example cannot attend assessments because of excessive travel requirements.
3. Express a strong preference for one of the two potential therapies.
4. Have severe heart failure.
5. Have been diagnosed with Multiple Sclerosis.
6. Have evidence of infection with HIV
7. a) Women of Child Bearing Potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy for the study duration plus 6 months.
   b) Women who are pregnant or breastfeeding.
   c) Sexually active fertile men not using effective birth control if their partners are WOCBP.

Reproductive Status of Trial Participants
Definition of WOCBP:

WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who are not post-menopausal (see definition below).

Post-menopause is defined as:

- Women who have had amenorrhea for 12 consecutive months (without another cause) and who have a documented serum follicle-stimulating hormone (FSH) level > 35 mIU/mL.
- Women who have irregular menstrual periods and a documented serum FSH level > 35 mIU/mL.
- Women who are taking Hormone Replacement Therapy (HRT).

The following women are WOCBP:

- Women using the following methods to prevent pregnancy: Oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as intrauterine devices or barrier methods (diaphragm, condoms, spermicides).
- Women who are practicing abstinence.
- Women who have a partner who is sterile (e.g. due to vasectomy).

WOCBP entering the trial must:

- Be using an acceptable method of contraception to avoid pregnancy throughout the study and for up to 6 months after the last dose of study drug in such a manner that the risk of pregnancy is minimised. The decision about the appropriate methods to be used to prevent pregnancy should be determined by discussions with the study subject.
- Have a negative serum or urine pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of HCG) within 0 to 72 hours before the first dose of study drug.
- Not be breast-feeding.

Sexually active fertile men entering the trial must use effective birth control if their partners are WOCBP for the duration of the trial plus 6 months.

Number of Sites: 6 (2 UK Behçet's Centres of Excellence and 4 satellite sites)

Study Duration: 4 years

Description of Agent/ Intervention:

1. Infliximab: Remicade 5mg/kg intravenous infusion at time 0, 2, 6 and then 8 weekly (6 weekly for eye disease).
2. Interferon alpha: Roferon-A subcutaneous injection in tapering dose starting at 3 million units once daily for three days, then 6 million units once daily (male with body weight more than 80 kg) or

4.5 million units once daily (female, or male with weight less than 80 kg). Dose tapered down every 2-4 weeks according to defined clinical criteria to 3 million units twice a week, over the period of the trial.

Objectives:

The aim of the study is to create the evidence base to underpin clinically effective prescribing of the biologic drugs infliximab and alpha interferon for BD.

The objectives of the study are to:

1. Undertake a randomised controlled trial to compare infliximab versus alpha interferon in patients with BD who are unresponsive to standard oral therapy.
2. Examine whether Interferon, Lambda 3 (IFNL3) and Interferon, Lambda 4 (IFNL4) Single-Nucleotide Polymorphisms (SNPs) can predict response to aIFN and/or IFX in BD.
3. Examine the potential for urine metabolomics to act as biomarker for drug response to infliximab and/or alpha interferon in BD.

Schematic of Study Design:
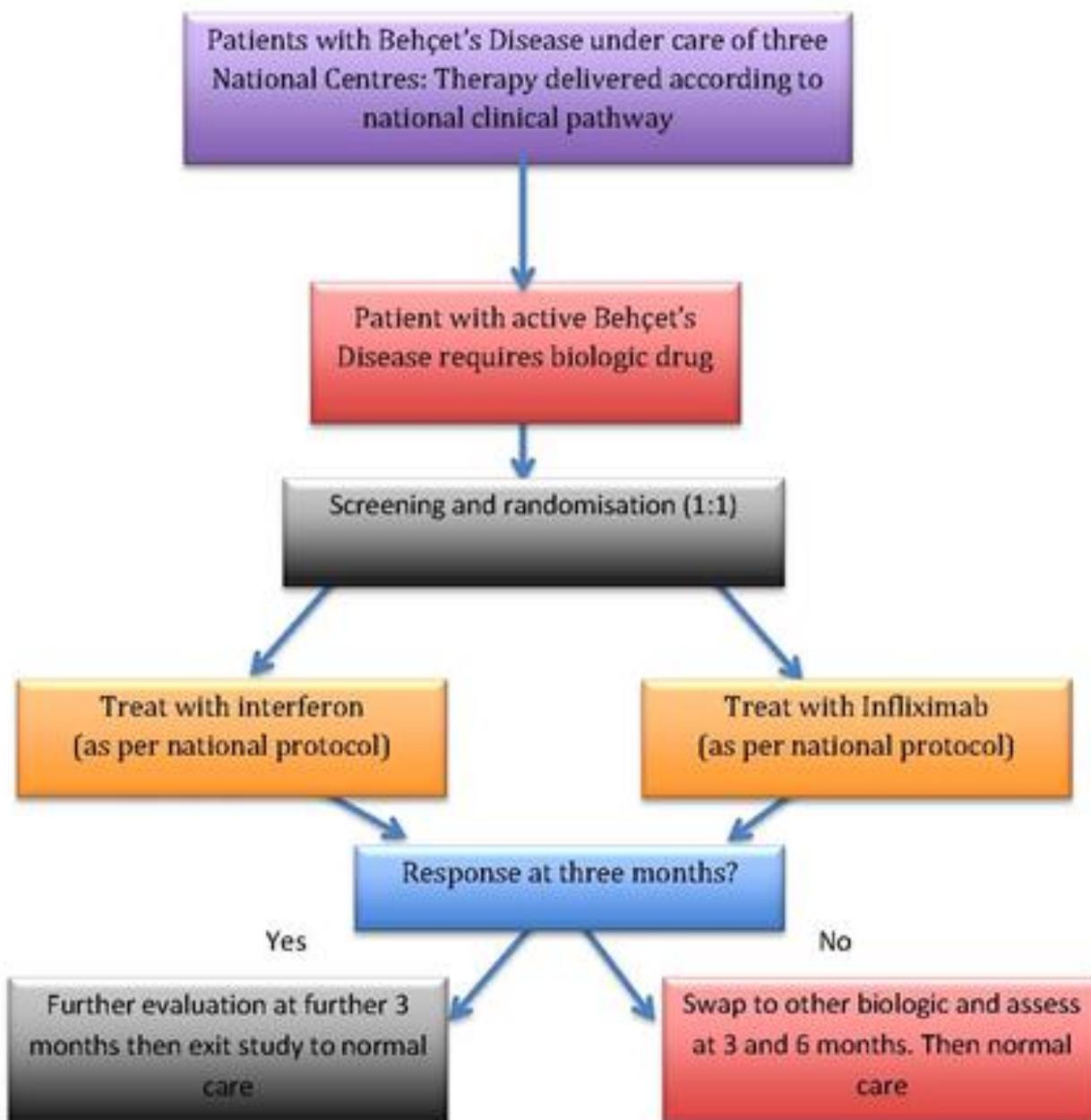
- Biologic drugs already funded (nationally commissioned agreed drug pathway)
- Rescue medication with steroid - as required clinically and specified in protocol
- Swap biologic if no response at three months
- Outcomes measured by standard (validated) organ-specific/composite BD scores
- Blood for genotyping ILFNL3 and 4 SNPs and urine for metabolomics taken at screening and randomisation stage (for later analyses: not influencing randomisation)
- Responders continue on drug, with funding continuing from National Centres in line with normal care

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BIO BEHÇET'S

2   BACKGROUND INFORMATION

2.1   Introduction

Behçet's Disease (BD; also called Behçet's Syndrome) is a systemic inflammatory vasculitis of unknown aetiology, characterised by recurrent episodes of acute inflammation in a variety of organs, typically including mucus ulceration in the mouth and genitally, but also manifestations in other organs from the skin to the eyes, where it can cause blindness [6,30]. It is a very rare disease in the UK (with less than 800 individuals thought to be affected) but more prevalent in the "silk route" countries from Japan across to Southern Europe. There is considerable variation in its clinical presentation between and within individuals and there appears to be differences in disease manifestations and response to therapy in patients in UK compared to those in Southern European or Far East countries. Whilst little is known about the underlying pathophysiological processes, recent years have witnessed the successful application of biologic therapies, with good outcomes in patients who had not previously responded to standard therapy with steroids and/or immunosuppressants such as azathioprine [15,22,34]. Much of the evidence base for biologic therapy has arisen from case series or other uncontrolled trials performed in countries outside the UK - where the phenotype appears to differ. For example, more severe ocular disease is reported in patients in Turkey and Japan compared to the UK, where mucocutaneous manifestations are more prevalent. Accordingly, most trials have reported effects on ocular disease. Very little data is available to inform useful systematic reviews and most guidelines therefore stem from expert-based consensus [13].

The recent establishment of National Centres of Excellence for BD in England [1] has led to the creation of a national cohort of patients, with agreed pathways for assessment and treatment by multidisciplinary teams comprising the specialist and support staff needed to cover the wide spectrum of organ involvement and the ability to fund biologic therapy when indicated. All are participating in this application, in addition to other centres with large BD cohorts. Whilst all biologics with good evidence for use in BD can be funded, the UK Centres (in line with experts in other countries) consider that only two such drugs (infliximab and alpha interferon) have sufficient evidence for use as first line biologics in refractory disease. Biologics such as alemtuzumab, whilst used with success in the UK BD Centres, are reserved for patients refractory to infliximab and alpha interferon because of a less favourable adverse event profile and the prolonged lymphopaenia that inevitably occurs. Other biologics, such as the IL-17 inhibitor secukinumab, have been trialled in BD but have either been found to be ineffective, or are at too early stages of development to be considered as first line biologics.

Infliximab is a mouse/human chimeric monoclonal antibody originally developed for use in rheumatoid arthritis that works by neutralising Tumour Necrosis Factor (TNF) alpha. Its long term safety record is well established in rheumatoid arthritis [2] and utility in BD reported in typically uncontrolled studies in countries outside the UK [22]. In 2011, Arida et al conducted an extensive PubMed/Medline search on the published experience of 375 patients treated with a TNF-inhibitor for BD [5] and with a variety of organ systems involved. Of these, the vast majority (325) were treated with infliximab and all had been inadequately controlled with, or were intolerant to, other immunosuppressive regimens such as glucocorticoids, azathioprine and ciclosporin. Sustained organ-specific, clinical responses were evident in 90%, 89%, 100%, and 91% of patients with resistant mucocutaneous, ocular, gastrointestinal, and central nervous system involvement, respectively. None of those trials were randomised or placebo controlled.

Alpha interferon is used in a number of inflammatory and rheumatic disorders including BD, well summarised by Yazici in 2010 [16]. Much of the reported experience of

alpha interferon in BD originates from uncontrolled studies in patients with ocular disease. Kotter et al reported in 2003 an open, non-randomised, uncontrolled prospective study using aIFN in 50 patients with inflammatory eye disease due to BD [17]. An overall ocular response rate of 92% was reported, with rapid response: the posterior uveitis score of the affected eye falling by 46% per week and full remission achieved by week 24. A retrospective single centre uncontrolled series reported by Bodaghi et al [8] of ocular BD also reported a high response rate of 82.6%, with other groups reporting similar findings. Reports of controlled trials of alpha interferon and efficacy in extraocular disease are limited. Alpsoy et al [4] published a randomized placebo-controlled study of 50 patients with mucocutaneous BD randomised to alpha interferon or placebo, reporting that alpha interferon was effective in the management of mucocutaneous lesions, with a trend to improvement of joint symptoms. The formulation of and dosing regimes for alpha interferon has varied between these studies: most utilising the preparation Roferon, with short half-life and more frequent administration. The subsequent development of pegylated alpha interferon (Viraferon Peg) [32], allowed dosing once a week. However, a recent UK prospective trial evaluating Viraferon Peg in BD reported only modest benefit, with responses far less than that for Roferon [20]. The UK BD Centres therefore now choose Roferon as their interferon preparation.

Measuring Clinical Activity: BD is characterised by the potential for multiple organ involvement with many different clinical manifestations. Because of the extreme clinical variability of the manifestations of BD attempts have been made to measure the overall clinical activity of the disease but, as yet, an international standard has not been adopted. Mumcu et al. [21] summarized the various methods used to measure the overall clinical activity. The International Scientific Committee on BD produced the "Behçet's Disease Current Activity Form" (BDCAF) with investigators from five countries participating [19]. Thirty dichotomous questions reduce down to a disease activity score (BDAI) lying between 0 and 12, but then transformed to a 0-20 scale. In Iran, the Iranian BD Dynamic Measure is used [25] The Behçet's Syndrome Activity Scale (BSAS) was developed as a patient reported outcome measure (PROM) and correlates with the BDCAF [9]. A Behçet's Disease-specific Quality of Life measure (BD-QoL) was derived by the Psychometric Group in the Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds University; it consists of thirty easily answered dichotomized questions [11]. Various other disease activity measurements have been proposed for specific organ symptoms. The intention here is to use a slightly modified form of the BDAI as the primary outcome for the proposed clinical trial as this is a verified measure of the overall severity of the disease.

Genetic and Metabolomic Biomarkers: Three genome wide association studies in patients with hepatitis C virus genotype 1 infection implicated SNPs in the vicinity of the IFNL3 (IL28B) gene on chromosome 19q13.13 with response to alpha interferon therapy [10,28,29]. Patients with the CC genotype at rs12979860 had higher response rates to alpha interferon [31]. A recent parallel sequencing study [27] was able to show that rs4803221 and rs7248668 predicted failure to respond better than rs12979860. IFNL3 encodes a lambda type of infliximab, while the SNP at rs12979860, affects interferon-stimulated gene production as part of the innate immune response, but the actual mechanism is unclear [3]. Despite this, treatment algorithms incorporating IFNL3 genotyping are now used in many clinics for the treatment of hepatitis C [18]. A recent study [23] has shown that rs12979860 is in linkage disequilibrium with a frameshift variant, ss469415590[ΔG], which also creates a new gene, IFNL4, reduced expression of which may be associated with reduced responsiveness of cells to alpha interferon 8 (aIFN8). Whether the same SNPs affect response to alpha interferon in other diseases is unclear, but given the role of the innate immune system in the pathogenesis of BD [12], it is biologically plausible that a similar effect to that seen in hepatitis C with alpha interferon, may be operating in BD. This is a hypothesis we intend to test as part of this trial. As yet there have been no convincing genetic predictors identified through genome wide association studies as determinants of response to infliximab.

Nuclear Magnetic Resonance (NMR)-based metabolomics allows the examination of the changes in hundreds or thousands of low-molecular-weight metabolites in an intact tissue or biofluid and offers several distinct advantages in a clinical setting since it can be carried out on standard preparations of blood cells, serum, plasma or urine. Pattern recognition techniques are applied to the NMR spectra of samples taken from individuals. Metabolomic analysis was able to distinguish between patients with rheumatoid arthritis who responded to anti-TNF therapy compared to those that did not with a sensitivity of 88.7% and a specificity of 85.9% [14]. We have previously shown that metabolomic analysis of vitreous humour could separate with high sensitivity and specificity samples from patients with two inflammatory conditions, lens-induced uveitis and idiopathic chronic uveitis with urea and oxaloacetate levels associated with the different conditions [33]. It is intended to carry out similar analysis in patients with BD.

The assessment of biomarkers as part of this trial may not only help in identifying determinants of response, but will also provide insights into the potential mechanisms of actions of these biologics in BD patients.

2.2   Rationale

BD is associated with significant morbidity and mortality in the UK and abroad. It can take up to 12 years to diagnose, leads to blindness and stroke, often does not respond to simple immunosuppressive therapy and, as we have previously reported, has a major impact on quality of life [7]. Although the biologic drugs infliximab and alpha interferon have been reported to be effective in refractory BD they are expensive (infliximab £20,000/yr and alpha interferon [Roferon] £4,000/yr), have not been subjected to rigorously undertaken randomised controlled trials compared directly against each other for efficacy and safety. Evidence for their efficacy rather arises from uncontrolled studies other countries, where the disease appears to differ from that presenting in the UK [13]. Funding for biologic drugs for BD in England is held by the three National Centres of Excellence, from specialised commissioning [1]. Whilst generally considered effective, the national centres anecdotally observe efficacy rates for the UK to differ from that reported in other countries, with variable and unpredictable responses. Currently, clinicians in the UK therefore currently make therapeutic decisions on choice of biologic therapy for BD with an extremely poor evidence base. This may not only be bad from a clinical perspective, but also could represent a waste of resources and funding for the NHS if both drugs were equally effective. Therefore, the identification of a biomarker(s) predicting response to biologic drug is also needed. A polymorphism in the IFNL3 (IL28B) is predictive of reduction in viral load in response to alpha interferon in hepatitis B or C infections [10,24,26]. As similar alpha interferon mediated pathways of innate immunity are involved in BD, the potential effect of IFNL3 SNP will therefore be addressed in BD, to determine the potential influence on response to therapy with alpha interferon. Urine samples from patients will be assessed by metabolomic analysis and profiles compared to treatment response.

2.3   Objectives

The aim of the study is to create the evidence base to underpin clinically effective prescribing of the biologic drugs infliximab and alpha interferon for BD.

The objectives of the study are to:

1. Undertake a randomised controlled trial to compare infliximab versus alpha interferon in patients with BD who are unresponsive to standard oral therapy.
2. Examine whether IFNL3 and IFNL4 SNPs can predict response to alpha interferon and/or infliximab in BD.

3. Examine the potential for urine metabolomics to act as biomarker for drug response to infliximab and/or alpha interferon in BD.

2.4   Potential Risks and Benefits

2.4.1   Potential Risks

This is a pragmatically designed trial that follows normal clinical practice in the UK Behçet's Centres of Excellence. We anticipate minimal, if any, risks to participants as they would qualify for the study biologic agents (infliximab or alpha interferon) as part of their normal clinical care in the UK.

2.4.2   Known Potential Benefits

In this study we will evaluate these two first-line biologic drugs for BD in a normal clinical setting: in patients who are refractory to standard oral immunosuppressives. Both drugs are widely used both for BD and for many other conditions and have been so for more than a decade, with well-established long–term safety records. While there are no direct benefits to participants of the study (as a biologic drug would be provided in normal practice), there are huge potential benefits to patients with BD and to society as a whole in the future, as this study may provide novel insights into pathophysiological mechanisms and allow the more rational and cost effective use of these agents. The potential for cost saving should the two drugs prove comparable, and with biomarker directed targeting is considerable.

3   SELECTION OF CENTRES/CLINICIANS

Each participating centre (and investigator) has been identified on the basis of:
a. Having at least one lead clinician with a specific interest in, and responsibility for, supervising and managing patients with BD.
b. Showing enthusiasm to participate in the study.
c. Ensuring that sufficient time, staff and adequate facilities are available for the trial.
d. Providing information to all supporting staff members involved with the trial or with other elements of the patient's management.
e. Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibilities of the study, including signing up to Good Clinical Practice (GCP) and other regulatory documentation.

3.1   Centre/Clinician Inclusion Criteria

a. Positive Site Specific Assessment (SSA) by Local NHS Research & Development (R&D) offices
b. Local HRA approval
c. Signed Research Site Agreement
d. Receipt of evidence of completion of (a) & (b) by LCTU
e. Completion and return of 'Signature and Delegation Log' to LCTU
f. Curriculum Vitae (CV) including a record of International Conference for Harmonisation (ICH) of GCP training – Principal Investigator (PI)
g. CV including a record of ICH GCP training – Other personnel on the delegation log
h. Clinical Study Protocol Receipt Form
i. Investigator Brochure's Receipt Form
j. Local laboratory accreditation/Quality Check
k. Local laboratory reference ranges
l. Patient information sheet (PIS), consent form (CF) and GP letter on trust headed paper
m. Local Pharmacy Practice Form

3.2   Centre/Clinician Exclusion Criteria

Those centres that do not fulfil the above inclusion criteria will not be permitted to participate in the trial.

4   TRIAL DESIGN

4.1   Overall Design

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. Patients will be recruited from the national and regional Behçet's Centres and randomised to the two arms of the trial with stratification by centre. A total of 100 patients will be randomised on a 1:1 ratio for arms. Recruitment will take approximately 36 months. Assessments will be made at baseline, 12, 24 and 36 weeks. The end of study will be when the final patient completes their 6-month follow-up assessment.

4.2   Primary Endpoint

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.

4.3   Secondary Endpoints

1)   Modified BDAI after 6 months of treatment (Week 24 visit).
2)   Original BDAI after 3 and 6 months of treatment (Week 12 and Week 24 visits).
3)   Significant improvement in organ systems after 3 and 6 months (Week 12 and Week 24 visits) assessed by:
    a.   Ocular: reduction in vitreous haze using the SUN consensus group grading scale and best corrected visual acuity change (using the LogMAR chart at 4 meters) from baseline. A reduction of 2 or more in vitreous haze and a difference of 15 letters or more in best corrected visual acuity are considered to be clinically significant.
    b.   Oral ulcer activity: change in ulcer severity score (USS). An improvement of 20% is considered to be clinically meaningful.
    c.   Change in number of genital ulcers: a reduction of 20% is considered to be clinical significant.
    d.   Musculoskeletal: Likert pain score assessed by Arthritis pain 10cm LIKERT scale on Rheumatology and Flare Data Collection Form (an improvement of 20% is considered to be clinically meaningful).
4)   Adverse events in each group.
5)   Reduction in dose of prednisolone (or equivalent glucocorticoid) at 3 months (Week 12 visit): a clinically meaningful reduction is considered to be 50% of baseline or dose of <15mg/day prednisolone.
6)   Reduction in dose of prednisolone (or equivalent glucocorticoid) at 6 months (Week 24 visit): a clinically meaningful reduction is considered to be 50% of baseline or dose of <7.5mg/day prednisolone.
7)   Quality of life scores at 3 and 6 months (Week 12 and Week 24 visits) compared to baseline. The QoL instruments used will be EQ-5D and BD-QoL: a reduction of 20% would be of clinical importance.
8)   Physician's Global Assessment of disease activity (a 7 point Likert Scale completed as part of [but assessed independently of] the BDAI) at 3 and 6 months (Week 12 and Week 24 visits) (a change of 2 points is considered to be clinically meaningful).

5   STUDY POPULATION

The population studied will be drawn from patients attending the five UK Behçet's Centres of Excellence. There are an estimated 800 patients with BD in England. The Behçet's Centres, established by National Specialist Commissioning in 2012 are funded to serve these patients by providing a comprehensive service for diagnosis and management, including full funding for biologic drugs in patients with refractory disease who are intolerant of, or inadequate responders to therapy with corticosteroids and/or immunosuppressants. Each centre runs weekly multidisciplinary clinics for patients with BD, attended by consultants in oral medicine, ophthalmology, neurology, dermatology, GUM medicine or gynaecology and rheumatology; supported by a specialist nurse, clinical psychologist and support worker.

5.1   Inclusion Criteria

The inclusion criteria are adult individuals who are:
1.   Diagnosed to have BD by ISG criteria or ICBD.
2.   Have refractory disease as defined by the UK Centres of Excellence criteria (failure to respond to steroid and/or immunosuppressive therapy with significant or major organ-threatening disease) and therefore qualify for biologic therapy with either infliximab or alpha interferon. Patients will have failed to respond to or have been intolerant of azathioprine at a dose of >2mg/kg (or comparable drug) and/or prednisolone at a dose of >40mg/day typically for more than three months, or with evidence of either organ threatening disease or unacceptable adverse events from immunosuppressive medication.
3.   Able to give informed consent.
4.   Have not previously received a biologic agent.
5.   Aged over 18 years.

5.2   Exclusion Criteria

1.   Have a contraindication to either infliximab or alpha interferon (e.g. active infection, severe liver disease, neutropenia, previous malignancy).
2.   Are likely to not comply (e.g. cannot attend for assessments because of excessive travel requirements).
3.   Express a strong preference for one of the two potential therapies.
4.   Have severe heart failure that would contraindicate the use of infliximab
5.   Have been diagnosed with multiple sclerosis,
6.   Have evidence of infection with HIV
7.   a) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the study duration plus 6 months.
      b) Women who are pregnant or breastfeeding.
      c) Sexually active fertile men not using effective birth control if their partners are WOCBP.

5.3   Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial treatment, follow-up, sample collection and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any Adverse Event (AE) are resolved or the subject's condition becomes stable. Follow-up of these patients will be continued through the trial research practitioners, the lead investigator at each centre and,

where these are unsuccessful, through the patient's GP. The trials unit may use the patient's routine electronic NHS health care records gathered from the NHS Information Centre if follow-up data is not available from the patient's hospital or GP.

5.3.1   Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP.

MACRO and TARDIS training should be provided to the new centre's staff, along with individual accounts to access these databases. The patient will have to sign a new consent form at the new centre, and until this occurs, the patient remains the responsibility of the original centre. The LCTU should be notified in writing about each patient transfer that occurs on the study.

5.3.2   Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:
  a. The patient withdraws consent.
  b. The PI considers it to not be in the interest of the patient to remain in the study.
  c. Lack of treatment efficacy or unacceptable toxicity.
  d. A contraindication to infliximab or alpha interferon therapy arises.
  e. The disease is not controlled by either of the biologic agents under evaluation and different agent is required.
  f. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 5.3.3). Following withdrawal from trial treatment, patients will be treated according to usual local clinical practice. Reasons for withdrawal must be recorded on the eCRF in the MACRO database.

Patients withdrawn will not be substituted.

5.3.3   Withdrawal from Trial Completely

Patients who autonomously withdraw from the trial for reasons other than those listed above, have previously consented to follow-up in the trial. Data up to this time can be included in the trial if anonymised. Such patients may need to reaffirm that they consent to follow-up through usual NHS mechanisms. If the patient explicitly states their wish not to contribute further data to the study, the LCTU should be informed in writing by the responsible physician and an End of Study eCRF should be completed on the MACRO database; follow-up data will not be sought for these patients.

6 ENROLMENT AND RANDOMISATION

6.1 Screening

Screening will be performed upon a patient's possible eligibility for the study after the patient has consented to trial participation, and must be documented on the electronic screening log located on the LCTU web portal. Screening details should be entered onto the portal, which will automatically generate a screening number and a confirmation email with the details sent to centre staff. The screening log can be printed at any time off the portal to allow for storage in the Investigator Site File. All potential patients identified must be document on the screening log, including individuals who decide not to participate in or are unsuitable for the study.

Patient hospital notes should be screened by the research team prior to the patient being approached to ensure inclusion/exclusion criteria are met.

Eligibility assessments for entry into the trial will be performed within 35 days prior to the first dose of treatment.

The following screening assessments should be performed once a patient is considered eligible to take part in the study:

- Written informed consent
- Complete medical history
- Concomitant medication
- Pregnancy test (WOCBP only)
- Complete physical examination
- Demographics (height, weight)
- Quality of life questionnaires (EQ-5D-5L and BD QoL)
- BDAI
- FBC
- Biochemical profile (liver, bone and renal)
- ESR
- CRP
- *Serology for Hepatitis B and C
- *HIV screening
- DNA blood sample
- Blood sample for bio-banking
- Urine sample for bio-banking
- Routine clinical assessment (eyes, ulcers (mouth/genital), musculoskeletal, skin and systemic problems)
- Steroid use (primary outcome)
- Visual acuity (LogMAR chart)
- Intraocular inflammation (SUN grading)
- Burden of skin rash
- Musculoskeletal LIKERT pain score
- Oral ulcer severity score
- Genital ulcer severity score
- PHQ-9 questionnaire

*Not to be carried out if evidence of completion within the last 6 months.

It is also anticipated that participants will have had a chest x-ray within the past 6 months as part of their standard of care of assessment for potential biologic drug therapy.
Patients who fulfil the screening requirements will be eligible for enrolment.

6.2   Randomisation

Patients who have provided written informed consent and meet eligibility criteria will be randomised by trained staff on site who have delegated authority (as per the delegation log) to one of two treatment arms (infliximab or interferon alpha) in the ratio of 1:1, using block randomisation and will be stratified by centre. Randomisation and data storage will be controlled centrally by the LCTU

Randomisation will take place via a web based tool called the Treatment Allocation Randomisation System (TARDIS).

After a patient has been screened and their details entered onto MACRO 4 database by the trial sitethe randomisation can be performed on the TARDIS website. The clinician will be prompted to confirm eligibility of the patient along with the stratification factors, which will enable randomisation to one of the two treatment arms.

Once the patient is randomised, an enrolment confirmation email will be sent to site personnel detailing the patients MACRO ID, trial number, initials, date of birth and date enrolled.

RANDOMISATION

Web site: www.lctu.org.uk/tardis

Available 24 hours per day, 7 days a week

Trial treatment should begin within 14 days of randomisation.

7 TRIAL TREATMENT/S

7.1 Introduction

BIO Behçet's is considered to be a Type A (no higher risk than that of standard medical care) study. Patients will be randomised equally between the two Investigational Medicinal products (IMPs) on the study, intravenous infliximab (Remicade - Arm A) and subcutaneous alpha interferon (Roferon-a - Arm B), with both drugs being equally recommended in the national drug pathway for the treatment of refractory Behçet's disease.

7.2 Arm A

7.2.1 Formulation, Packaging, Labelling, Storage and Stability

Infliximab Intravenous Infusion (Remicade®)

Please refer to the current Summary of Product Characteristics (SmPC) document on the electronic Medicines Compendium:

https://www.medicines.org.uk/emc/

Remicade will be used in this study and will be supplied from local stock. No additional labelling by site pharmacy is required. No accountability is required. Sites should store Remicade as per instructions and temperature monitoring should be carried out in accordance with local policy.

Remicade must be handled according to the instructions within the corresponding SmPC (please refer to the current Remicade SmPC supplied by the appropriate manufacturer and to any local policies which may apply).

The cost of the IMP is covered by the National Behçet's Centres, centres can be billed as per standard practice.
.

Patients will continue with concomitant immunosuppressant such as methotrexate or azathioprine unless otherwise clinically indicated.

7.2.2 Preparation, Dosage and Administration of Study Treatment/s

Patients in arm A will receive 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.

Remicade will be administered according to the standard preparation and infusion procedures of each investigational centre. Refer to the specific package inserts and local policy for preparation, administration (including the use of flushes) and storage guidelines.

Concomitant immunosupressants

Concomitant immunosupressants such as methotrexate or azathioprine can be used at the prescribing clinicians' discretion according to normal clinical practice. Target dose of azathioprine is 2.5mg/kg.

All drugs will be dispensed from hospital stocks using the usual prescribing and dispensing practices. Annex 13 labelling will not be applied and no accountability records will be kept.

7.2.3   Dose Modifications

No dose modification should be used for arm A. Remicade will be given as per guidelines for the National Centres of Excellence for Behçet's Disease. The drug will be discontinued in the event of severe infection, major infusion reaction or inefficacy at the 3 month primary end point.

7.3   Arm B

7.3.1   Formulation, Packaging, Labelling, Storage and Stability

Alpha interferon (Roferon-A®) pre-filled syringes

Please refer to the current SmPC document on the electronic Medicines Compendium:

https://www.medicines.org.uk/emc/

Roferon will be used in this study and will be supplied from local stock. No additional labelling by site pharmacy is required. No accountability is required. Sites should store Roferon as per instructions and temperature monitoring should be carried out in accordance with local policy.

Roferon must be handled according to the instructions within the corresponding SmPC (please refer to the current Roferon SmPC supplied by the appropriate manufacturer and to any local policies which may apply).

The cost of the IMP is covered by the National Behçet's Centres, centres can be billed as per standard practice.
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7.3.2   Preparation, Dosage and Administration of Study Treatment/s

A decreasing dose of Roferon-A will be given to patients randomised to Arm B. All doses will be given subcutaneously. The following dosing schedule will be followed:

Dose	Frequency	Duration
• 3 million units	• daily	• 3 days
• 6 million units**	• daily	• 2 - 4 weeks
• 4.5 million units	• daily	• 2 – 4 weeks
• 3 million units	• daily	• 2 – 4 weeks
• 3 million units	• 3 times a week	• 2 – 4 weeks
• 3 million units	• Twice weekly	• To trial end

** The 6 million units dose will only be administered to males weighing over 80 kg with major organ threatening disease (e.g. severe eye involvement). Males of less than 80kg and females will start with 4.5 million units once daily to minimise the development of side effects.

Immunosuppressants to be discontinued in Arm B.

In the absence of an adverse event, tapering down will occur at four-weekly intervals. The development of an AE (such as leukopaenia, persistent fever, raised liver function tests [ALT or AST greater than three times the upper limit of normal], persistent unacceptable fatigue, flu-like symptoms or severe depression) will prompt a reduction in dose and/or frequency according to the schedule above.

Roferon–A pre filled syringes will be dispensed from hospital stocks using the usual prescribing and dispensing practises. Annex 13 labelling will not be applied and no accountability records will be kept.

7.3.3   Dose Modifications

Roferon-A will be administered according to the standard national centre drug pathway. The drug will be discontinued in the event of a severe AE or inefficacy at the 3 month primary endpoint.

7.4   Unblinding

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

7.5   Accountability Procedures for Study Treatment/s

The Principal Investigator (PI) is fully responsible for the IMPs at the site. Dispensing of medication may be delegated to a hospital pharmacy as locally applicable. The person responsible for dispensing the medication will be responsible for maintaining adequate control of the IMPs and for documenting all transactions relating to them. IMPs must be stored in a safe and secure place (only accessible to authorized personnel), and proper dispensing arrangements must be made. As this study is considered Type A risk, no accountability documentation above normal practice will be kept.

7.6   Assessment of Compliance with Study Treatment/s

Remicade is administered in hospital. Details of infusions will be captured on the eCRF,

For Roferon-A, data regarding dose of treatment prescribed and taken at home will be recorded on the eCRF, thus allowing assessment of compliance with the treatment regime. At each visit, treatment diaries will be provided to patients to record compliance with home treatment regimens and asked if they had any difficulties with the previous period of treatment. Patients will be instructed to contact the PI/research nurse for advice as soon as possible in the event of any problems and the treatment diary will provide a reminder of this.

7.7 Concomitant Medications

Normal standard of care therapies will be used. Patients receiving Roferon-A will be prescribed paracetamol for the first three days of therapy if the patient is experiencing flu-like symptoms. Such symptoms, if present, typically resolve after three days.

7.7.1 Medications Permitted

All medications required for normal standard clinical care of the patient, unless specifically contraindicated in patients taking infliximab or interferon alpha will be permitted.

7.7.2 Medications Not Permitted/ Precautions Required

Roferon-A may affect the oxidative metabolic process by reducing the activity of hepatic microsomal cytochrome enzymes in the P450 group. Although the clinical relevance is still unclear, this should be taken into account when prescribing concomitant therapy with drugs metabolized by this route.

WOCBP must use an acceptable method to avoid pregnancy for the study duration plus 6 months. Sexually active fertile men must use effective birth control for the duration of the trial plus 6 months if their partners are WOCBP.

Administration of live vaccine is not recommended during Remicade administration,

Please refer to the current SmPCs for each IMP for any other relevant prohibited/not recommended concomitant medications.

Remicade https://www.medicines.org.uk/emc/medicine/3236
Roferon-A https://www.medicines.org.uk/emc/medicine/4319

7.7.3 Data on Concomitant Medication

In line with standard care, any concomitant medication will be recorded at each study visit.

7.8 Overdoses

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported to the LCTU as soon as site becoming aware of the event.

7.9 Co-enrolment Guidelines

Patients in this trial will not be eligible for entry into another CTIMP study for the duration of the trial.

8   ASSESSMENTS AND PROCEDURES

8.1   Schedule of Trial Procedures

Time (weeks)		0	12 weeks	24 weeks	36 weeks***
	Screening	Randomisation/ Baseline*		End of trial	End of trial
Informed written consent	x				
Assessment of eligibility criteria	x				
Review of medical history	x				
Review of concomitant medications	x	x	x	x	x
Pregnancy test	x	x	x	x	x
Randomisation		x			
Compliance with study intervention			x	x	x
Height	x				
Weight	x	x	x	x	x
Heart rate, respiratory rate, blood pressure	x	x	x	x	x
EQ-5D-5L Health Questionnaire		x	x	x	x
BD QoL questionnaire		x	x	x	x
BDAI		x	x	x	x
Collection of 9ml blood for translational research		x			
Collection of (3 x 1ml) urine for translational research		x	x	x	x
Laboratory assessments (FBC)	x	x	x	x	x
Laboratory assessments - Biochemical Profile -(liver, bone and renal)	x	x	x	x	x
Laboratory assessments (ESR)	x		x	x	x
Laboratory assessments (CRP)	x		x	x	x
Laboratory assessments (Hep B and C Serology)	**x				
HIV screening	**x				
Assessment of adverse events	x		x	x	x
*Routine clinical assessment (eyes, ulcers [mouth/genital], musculoskeletal, skin and systemic problems) as clinically indicated	x	x	x	x	x
Steroid Use	x	x	x	x	x
*Visual acuity (using LogMAR chart)	x	x	x	x	x
*Intraocular inflammation (SUN grading)	x	x	x	x	x
*Burden of skin rash	x	x	x	x	x
*Musculoskeletal LIKERT pain score	x	x	x	x	x
*Genital Ulcer Severity Score	x	x	x	x	x
*Oral Ulcer Severity Score	x	x	x	x	x
PHQ-9 Questionnaire	x	x	x	x	x

*To be performed at Baseline, then a symptom-directed approach is to be used for follow up visits (Week 12,Week 24 and week 36).
**Not to be completed if already carried out up to 6 months earlier
*** Week 36 – for patients that swap treatment at week 12
Study intervention to be administered as per protocol

8.2   Procedures for Assessing Efficacy

Assessments for efficacy will be completed at Baseline, Week 12, Week 24 and week 36 (for patients that swap treatment at week 12), together with any other unscheduled visits as indicated clinically.

Measurements will be entered onto the eCRF. As the same items are measured in normal clinical care at the centres, data will continue to be collected after the trial has ended, providing an opportunity to gain information over a longer time period.

Assessment of efficacy will comprise of:
1) BDAI.
2) Assessment of ocular vitreous haze (using the SUN consensus group grading scale),
3) Best corrected visual acuity (using LogMAR chart).
4) Oral Ulcer Severity Score.
5) Genital Ulcer Severity Score.
6) Musculoskeletal pain (assessed by Arthritis pain 10cm LIKERT scale on Rheumatology and Flare Data Collection Form).
7) Quality of life scores (EQ-5D-5L and BD-QoL - measured at baseline, Week 12 and Week 26).
8) Physician's Global Assessment of disease activity (a 7 point LIKERT Scale completed as part of [but assessed independently to] the BDAI at Baseline, Week 12 and Week 26.

8.3   Procedures for Assessing Safety

Safety will be assessed through the reporting of adverse events as described in Section 10. Formal toxicity assessments will be performed at each study visit as described in Section 8.

8.4   Other Assessments

8.4.1   Quality of Life and Health Economics

Potential changes in quality of life at Week 12 and Week 26 from baseline will be estimated by the instruments EQ-5D-5L and BD-QoL. Overall changes will be measured, together with changes in the individual domains that constitute the overall score. A change of 20% will be deemed to be clinically important.

The health economic implications of the study will be calculated based on the acquisition costs of the two IMPs, costs of administration (including infusion for infliximab and training for delivery of self-administered injections for alpha interferon) and the cost of monitoring and management of potential adverse events. This will be calculated considering the pre-trial utilisation of these two drugs by the UK centres of excellence compared to projected use after the trial. For example, should both IMPs prove to be not significantly different, with respect to efficacy, it is anticipated that the lower priced IMP will be used as first line biologic and cost savings for that scenario will be calculated.

8.4.2   Mood Questionnaire

The Patient Health Questionnaire-9 (PHQ-9) should be completed by the patients at all visits (including screening). The PHQ-9 is the 9-item depression module from the full Patient

Health Questionnaire (PHQ). The PHQ is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders. The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day). Questionnaires will be provided by the LCTU to the trial site via the LCTU portal. Completed forms should be entered onto MACRO by sites. Guidelines on how to instruct the patient to complete the questionnaire as well as how to determine the scores will be provided with each instrument. Guidance on scoring questionnaires is also provided in Appendix E.

8.4.3   Translational

8.4.3.1   Genotyping for IFNL3 and IFNL4 SNPs:

A 9ml blood sample will be collected at baseline and then transported using Royal Mail SafeBoxes to the Wolfson Centre for Personalised Medicine, University of Liverpool. Following this, DNA will be extracted and four SNPs will be genotyped including rs12979860, rs4803221, rs7248668 and ss469415590[ΔG]). This will be carried out by a trained technician with RealTime Polymerase Chain Reaction (PCR) utilising a 7900HT Fast Real Time PCR System (Applied Biosystems). Test specific Standard Operating Procedures (SOPs) will be written prior to the start of genotyping and strict Quality Control (QC) measures will be followed to ensure systematic validation of the genotype results.

The genotypic analysis will be an exploratory analysis to determine whether any of the SNPs show an effect of efficacy of alpha interferon based on primary and secondary outcomes. If a strong effect is found for a particular SNP with one of the study outcomes or a trend is observed over several of the outcomes, the SNP with the highest predictive value will be tested in approximately 200 other patients (based on power calculations) where DNA is available from Alfred Mahr and our collaborators. These samples will have been taken from patients who have previously been recruited from both observational studies and part of clinical practice; consequently there will be documented evidence of whether and how they responded to alpha interferon.

8.4.3.2   Metabolomic analysis:

3 x1ml urine sample will be collected at Baseline, Week 12, Week 24 and Week 36, snap frozen and stored at -80℃ and then transported to the Centre for Translational Medicine, The University of Birmingham in batches. After thawing, urine samples will be centrifuged at 13,000g, prepared using a standard protocol and loaded into a standard 5-mm NMR tube for spectroscopy. One-dimensional (1-D) 1H spectra will be acquired at 300°K using a standard spin-echo pulse sequence with water suppression using excitation sculpting on a Bruker DRX 500 MHz NMR spectrometer equipped with a cryoprobe. Glutamine levels will be measured using high-performance ionexchange chromatography. Xanthurenic acid levels will be measured using a fluorometric method.

Lists of metabolites providing the greatest discrimination between groups will be identified using multivariate analyses and metabolites identified using an NMR database (Human Metabolome Database version 2.5) and Chenomx NMR suite.

Test specific SOPs will be written prior to the start of the metabolic analysis and we will adhere to strict QC measures to ensure proper validation of genotype results.

8.5   Sub-studies

No sub-studies are planned at present.

8.6 Loss to Follow-up

If any of the trial patients are lost to follow up, contact will initially be attempted through the PI at each centre. If the PI at the trial centre is not the patient's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. Where all of these attempts are unsuccessful, the patient's GP will be asked to provide follow-up information to the recruiting centre. The trials unit may use the patient's routine electronic NHS health care records gathered from the NHS Information Centre if follow-up data is not available from the patient's hospital or GP.

8.7 Trial Closure

Investigators will be informed when patient recruitment is to cease.

Trial enrolment may be stopped at a site when the total requested number of subjects for the trial has been obtained.

The IDSMC may recommend to the TSC that the trial be stopped prematurely. Such premature termination/suspension of the trial will be notified to the MHRA and MREC as required.

The trial will be considered formally "closed" when the last patient has completed their final study assessment.

9   STATISTICAL CONSIDERATIONS

9.1   Introduction

Behçet's Disease is a rare disease with only a limited number of patients available for a trial and so a Bayesian approach has been taken.

9.2   Method of Randomisation

Stratified block randomisation will be used based on randomly permuted blocks with random block sizes of 2 and 4.The randomisation code list will be generated by the LCTU trial statistician with the software package STATA using 'ralloc' statement. The trial is open-labelled. The stratification factor included in the design is Centre. Data from the eCRFs will be entered onto a MACRO4 database with extensive data validation checks alerting all missing data to be queried. Missing data will be monitored and strategies developed to minimise its occurrence. Central statistical data monitoring will summarise missing or inconsistent data periodically.

9.3   Outcome Measures

9.3.1   Primary

- 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.

9.3.2   Secondary

- Modified BDAI after 6 months of treatment (Week 24 visit).
- Original BDAI after 3 and 6 months of treatment (Week 12 and Week 26 visits)
- Significant improvement in organ systems after 3 and 6 months (Week 12 and Week 24 visits) assessed by:
    - Ocular: reduction in vitreous haze using the SUN consensus group grading scale and best corrected visual acuity change (using the LogMAR chart at 4 meters) from baseline. A reduction of 2 or more in vitreous haze and a difference of 15 letters or more in best corrected visual acuity are considered to be clinically significant.
    - Oral ulcer activity: change in ulcer severity score (USS). An improvement of 20% is considered to be clinically meaningful.
    - Change in number of genital ulcers: a reduction of 20% is considered to be clinical significant.
    - Musculoskeletal: Likert pain score assessed by Arthritis pain 10cm LIKERT scale on Rheumatology and Flare Data Collection Form (an improvement of 20% is considered to be clinically meaningful).
- Adverse events in each group.
- Reduction in dose of prednisolone (or equivalent glucocorticoid) at 3 months (Week 12 visit): a clinically meaningful reduction is considered to be 50% of baseline or dose of <15mg/day prednisolone.

- Reduction in dose of prednisolone (or equivalent glucocorticoid) at 6months (Week 24 visit): a clinically meaningful reduction is considered to be 50% of baseline or dose of <7.5mg/day prednisolone.
- Quality of Life (QoL) scores at 3 and 6 months (Week 12 and Week 24 visits) compared to Baseline. The QoL instruments used will be EQ-5D and BD-QoL: a reduction of 20% would be of clinical importance.
- Physician's Global Assessment of disease activity (a 7 point Likert Scale completed as part of [but assessed independently of] the BDAI) at 3 and 6 months (Week 12 and Week 24 visits) (a change of 2 points is considered to be clinically meaningful).

9.4   Sample Size

The primary outcome will be a modified version of the BDAI after three months of therapy, which will range from 0 to 30 for a patient.

If a traditional frequentist equivalence design were to be used, then based on equivalence being defined as the difference in means being less than 20% (i.e. 20% of mean BDAI of 10 = 2), then for significance level, 0.20 and power 90%, a sample size of 176 (88 per arm) is required. (Here we have assumed standard deviation of 4 for BDAI at 3 months, a difference in means of 0.5, in accordance with the opinions of the international experts recruited for the Bayesian design. Also baseline measurements have not been taken into account which would be expected to reduce the sample size to some extent). As the recruitment of this number of patients is not feasible, the Bayesian design is adopted.

Bayesian design: Analysis of the data obtained from the small survey of international experts described in Section 4 (Research Design), gives a prior distribution of the difference in mean vales of BDAI as $N(0.52, 1.062)$ and less than 24% difference in means to define equivalence. The mode for the latter was 20% and this value is used in the sample size calculation as it fits better with FDA guidelines.

If the difference in means, D, of BDAI at 3-months is considered without the use of baseline BDAI, then assuming the above prior for D and a normal distribution, $N(10, 42)$ for the distribution of the 3-month BDAI scores. For a sample size of 45 per arm the Bayesian power based on an equi-tailed 80% credible interval for testing for equivalence is 0.71.

To be more accurate, a simulation exercise was carried out using R and WinBUGS to establish the sample size for the Analysis of Covariance Model. For one arm, random baseline and 3-month BDAI scores were generated from a bivariate normal distribution with mean vector (12, 10), variances 4.0 for both, and correlation r. For the other arm, random baseline and 3-month BDAI scores were generated from a bivariate normal distribution with mean vector (12, 10+m), variances 4.0 for both, and correlation r. For each simulation r was randomly chosen from a uniform distribution on (0.05, 0.5) and m from a $N(0.52, 1.062)$ distribution. For a sample size of 45 per arm, testing for equivalence using an 80% equi-tailed credible interval calculated from the posterior distribution, Bayesian power of 91% was obtained. When a 90% credible interval was used, the Bayesian power dropped to 73%.

Using this design with the 80% credible interval, a sample size of 45 patients per arm was deemed suitable, which allowing for 10% drop-out, requires 100 patients to be recruited.

9.5   Interim Monitoring and Analyses

There will be no formal interim analyses. However informal interim analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an Independent Data Monitoring and Safety Committee (ISDMC). These analyses will be performed at the Liverpool Clinical Trials Unit. The ISDMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the ISDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The ISDMC will make recommendations to the Trial Steering Committee (TSC, see section 16) as to the continuation of the trial.

9.6   Analysis Plan

9.6.1   Primary outcome

The parameter of interest is the difference, D, in the mean BDAI scores for infliximab and alpha interferon. A Bayesian Analysis of Covariance model will be used:

$$y = \beta_0 + \beta_1 \times x + \alpha \times tr + \varepsilon,$$

where y = BDAI at 3-months, x = baseline BDAI, tr = 0 if a patient is in the infliximab group and tr = 1 if a patient is in the alpha interferon group. β_0, β_1 and α are the parameters to be estimated and ε is the error term with variance σ^2 (to be estimated). The parameter of particular interest is α as it measures the difference between the two treatment groups. Prior distributions will be placed on β_0, β_1, α and σ^2 WinBUGS will be used to fit the model.

Prior information
Vague priors for β_0 and β_1 were set as following a normal distribution with mean 0 and a larger variance (i.e. ~ N (0.0, 100000)). The prior distribution for σ was set as a uniform distribution with limits of 0 and 3 respectively (i.e. ~ U (0, 3)).

The prior distribution for alpha is based on data obtained from a small group of international BD experts using the question:

> *On the assumption that the average BDAI score for patients treated with infliximab is 10, share out 100 points on the following scale on how better or worse alpha interferon is compared to infliximab at relieving/controlling BD symptoms.*

	Alpha-Interferon Better					Alpha-Interferon Worse				
Scale:	21%+	16-20%	11-15%	6-10%	0-5%	0-5%	6-10%	11-15%	16-20%	21%+
e.g.	0	0	10	20	3	20	10	10	0	0

The experts' answers revealed a mean of 0.053 and a variance equal to 0.0126. The results are also shown on the table and plot below.

Table 1: Results from experts' survey

Difference	expert1	expert2	expert3	expert4	expert5	expert6
-25	0	0	0	0	0	0
-18	0	0	5	0	0	0
-13	10	0	10	5	5	0
-8	10	0	15	20	10	5
-3	15	0	20	20	10	10
3	30	5	20	5	10	20
8	15	15	15	25	10	30
13	15	20	10	25	10	20
18	5	30	5	0	10	10
25	0	30	0	0	35	5

Figure 1: Prior distribution
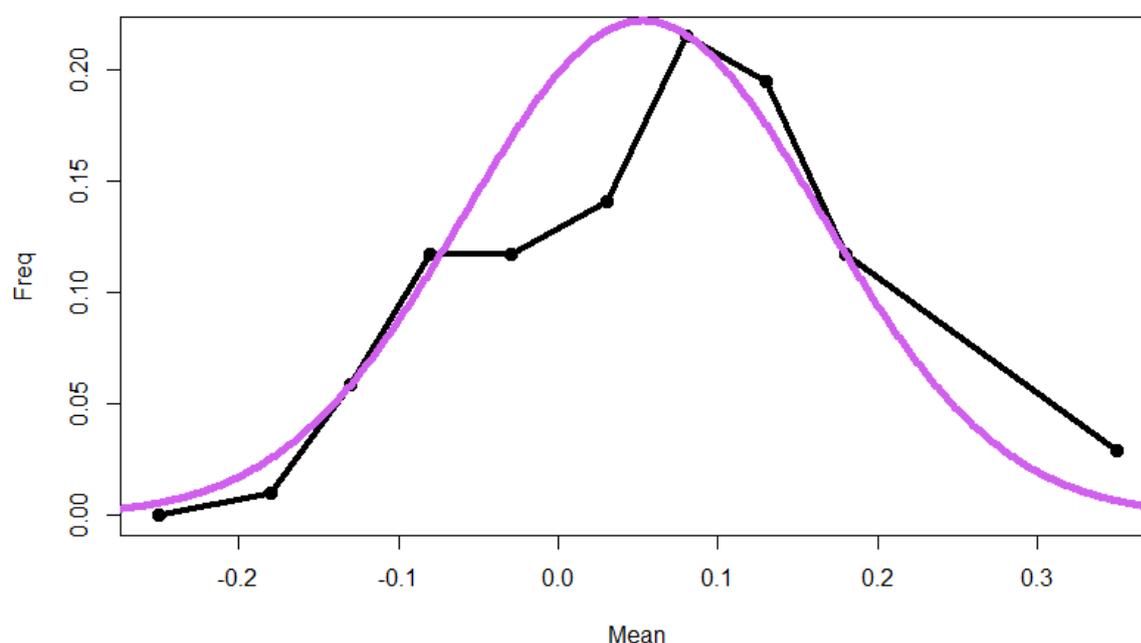
A second question will assess where a point of equivalence between the two drugs is reached. The question posed is:

Suppose you are generally prescribing just one of the two drugs (infliximab or alpha interferon) at the moment. If you were told that the efficacies of infliximab and alpha interferon are exactly the same, then presumably you would not change to prescribing the other drug. However, if you were told that the other drug is 40% more efficacious than the one you are currently prescribing, then you would presumably change. Somewhere between 0% and 40% you would probably change from prescribing the current drug to the other. What % would this be? (Ignore any other factors such as cost of drug. Percentages are based on a mean of 10 for the BDAI.)

The responses to the second question will inform the boundaries as to where infliximab and alpha interferon can be considered to be equivalent and also where one is superior to the other.

Let the equivalence boundary be given by γ. Then the equi-tailed, 80% Bayesian credible region $[\alpha_L, \alpha_U]$ obtained from the posterior distribution for α will be used to describe the difference in efficacy for the two treatments, guided by the following:

> if $[\alpha_L, \alpha_U]$ lies between $[-\gamma, \gamma]$, then
> equivalent if $\alpha_U < -\gamma$, then infliximab
> superior
> if $\alpha_U < -\gamma$ and $\alpha_U < \gamma$, then infliximab could be equivalent or
> superior if $\alpha_U < -\gamma$ and $\alpha_U > \gamma$, then equipoise
> if $\alpha_U > -\gamma$ and $\alpha_U > \gamma$, then alpha interferon could be equivalent
> or superior if $\alpha_L > \gamma$, then alpha inerferon superior

9.6.2   Secondary outcomes

As listed in section 9.3.2.

As this trial is for a very rare disease, clinical decisions and recommendations will be based on the analyses of both the primary outcome and all the secondary outcomes, weighing up the evidence in the true spirit of statistics, but keeping in mind the problems of multiple testing and over interpretation.

The ITT principal will be used for the primary analysis. Secondary sensitivity analyses will be carried out on: (i) all patients including the data for both arms for patients who switched treatment (the Analysis of Covariance model can cope with this), (ii) those patients who responded to treatment whether it was their original treatment or the one to which they may have switched, (iii) all patients who remained on their original treatment and complied with the protocol. Data on the number of patients who switch treatments and their reasons for doing so will be recorded and analysed. Another sensitivity analysis will carried out investigating the effect of the prior distributions in the Bayesian analysis, especially on the parameter of prime interest (the difference in means between treatments) where results using a vague prior will be compared to those using the prior based on expert opinion.

The ISDMC will review safety and the data after 12 patients have had their 3-month follow-up visit and again when 45 patients have had their 3-month follow-up visit. In addition the ISDMC will meet before the trial commences and at least yearly during the course of the trial. No specific stopping rules will be applied but the ISDMC will recommend continuation or stopping of the trial based on safety data and efficacy data based on the primary and secondary outcomes. The recommendation to stop the trial should only be made if the reasons for stopping would convince clinical experts in BD.

A single statistical analysis plan will be produced during the course of the trial. This document will detail how the final analysis and interim analysis shall be carried out as well as including all relevant information for inspection by the IDSMC. This document will be approved by the Trial Steering Committee (TSC) and the IDSMC prior to any analysis being carried out.

Separate protocols and statistical analysis plans will be produced for the second two objectives of the study (genotyping and metabolomics). In brief for these:

Genotyping for IFNL3 and IFNL4 SNPs: DNA will be extracted from all blood samples which will be transported at the time of recruitment to the Wolfson Centre for Personalised Medicine using Royal Mail SafeBoxes. Genotying for 4 SNPs will be undertaken (rs12979860, rs4803221 and rs7248668 and ss469415590[ΔG]) using RealTime Polymerase Chain Reaction (PCR) utilising a 7900HT Fast Real Time PCR System (Applied Biosystems). Genotyping will be performed in by a trained technician. Test specific SOPs will be written prior to the start of genotyping and we will adhere to strict QC measures to ensure proper validation of genotype results. This will be an exploratory analysis to determine whether any of the SNPs show an effect with respect of the efficacy of alpha interferon based on the primary and secondary outcomes. If a strong effect is found for a SNP based on one of the primary and secondary outcomes, or as a "trend" over several of the outcomes, the SNP with the highest predictive value will be tested in approximately 200 other patients (based on power calculations) where DNA is available from Alfred Mahr and our collaborators. These patients have been recruited in observational studies and as part of clinical practice, and have documented evidence of whether and how they responded to alpha interferon.

Metabolomic analysis: (3 x1 ml) urine samples will be taken from patients at each trial visit and snap frozen and stored at $-80^{0}C$ before transporting the Birmingham in batches. After thawing, urine samples will were centrifuged at 13,000g and prepared using a standard protocol and loaded into a standard 5-mm NMR tube for spectroscopy. One-dimensional (1-D) 1H spectra will be acquired at 300°K using a standard spin-echo pulse sequence with water suppression using excitation sculpting on a Bruker DRX 500 MHz NMR spectrometer equipped with a cryoprobe. Glutamine levels will be measured in the urine samples using high-performance ionexchange chromatography. Xanthurenic acid levels measured using a fluorometric method.

Lists of metabolites providing the greatest discrimination between groups will be identified using multivariate analyses and metabolites identified using an NMR database (Human Metabolome Database version 2.5) and Chenomx NMR suite.

Test specific SOPs will be written prior to the start of the metabolic analysis and we will adhere to strict QC measures to ensure proper validation of genotype results.

Rationale for mechanistic studies
The mechanistic studies are designed to: (a) lead to important developments in the elucidation of the as yet unknown pathophysiological processes underlying BD, (b) clarify the role of two inflammatory pathways involved in a variety of manifestations of the disease and responses (or not) to two distinct biologic drugs that target different inflammatory processes and, (c) identify the potential usefulness of two promising novel biomarkers to facilitate cost-effective targeting of therapy, derived from the greater mechanistic understanding of disease process that (a) and (b) will provide. Assuming the frequency of the CC genotype is 55%, then the power is approximately 75% for detecting a difference in response of 20% (CC genotype 95% v non-CC genotype 75%, giving an overall response rate of approximately 85%) using a one sided test and significance level 0.2. This high significance level is inevitable for a sample size of 45. However, if the overall response rate is 80%, then a difference in response rate of 35% (CC genotype 95% v non-CC genotype 60%) could be detected with 75% power with a 2-sided test and significance level 0.05. To strengthen further the power of the analyses, patient response will also be classified on an ordinal scale of "no response", "poor response", "good response" according to BDAI score. Results from techniques such as ordinal logistic regression might then be more conclusive.

10   PHARMACOVIGILANCE

10.1   Terms and Definitions

The following definitions have been adapted from European Directive 2001/20/EC and ICH GCP E6

Adverse Event (AE)

An AE is defined as any untoward medical occurrence [i.e. any unfavourable or unintended sign including abnormal laboratory results), symptom or disease] in a research participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)

An AR is defined as any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)

A UAR is defined as any adverse reaction of which the nature and severity is not consistent with the information about the medicinal product in question set out in:

a) In the case of a product with a marketing authorization, in the summary of product characteristics for that product
b) In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR):

An SAE or SAR is defined as any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

a) Results in death
b) Is life-threatening* (subject at immediate risk of death)
c) Requires in-patient hospitalisation or prolongation of existing hospitalisation**
d) Results in persistent or significant disability or incapacity, or
e) Consists of a congenital anomaly or birth defect
f) Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon

appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory anomalies that require clinical intervention or further investigation (unless they are associated with an already reported clinical event)
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

10.2.2 Do Not Include

- Medical or surgical procedures- the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

10.2.3 Reporting of Pregnancy

If a patient or their partner becomes pregnant during treatment or in the six months following treatment, a completed Pregnancy Report Form must be faxed to the LCTU within 24 hours of learning of its occurrence. (Should you need a copy of the Pregnancy Report Form please contact the trial coordinator.)

On pregnancy outcome, the final Pregnancy Report Form should be faxed to the LCTU 28 days after the outcome. The final Pregnancy Report Form is used to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up information on this form also includes an assessment of the possible relationship to the trial medication of any pregnancy outcome.

Pregnancy outcomes should also be collected for the female partners of male patients participating in the trial. Consent to report information regarding these pregnancy outcomes should be obtained from the mother prior to completion and faxing of the final Pregnancy Report Form. Any SAE experienced during pregnancy must be reported on the SAE form.

The LCTU will report all pregnancies to the trial Sponsor, MHRA and MREC.

Pregnancies must be reported by faxing a completed Pregnancy Report Form sent within 24 hours of becoming aware of the event to the Liverpool Clinical Trials Unit
Fax. No. 0151 794 8930

**Pregnancy outcomes must be reported by faxing a completed final Pregnancy Report Form 28 days following the outcome to the
Liverpool Clinical Trials Unit Fax. No. 0151 794 8930**

10.3   Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below. Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Definition of Severity of Adverse Events:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities
Life threatening
Death

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.4   Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table below.
If any doubt about the causality exists the local investigator should inform the LCTU who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Definitions of Causality:

Relationship	Description
None	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Highly Probable	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "highly probable" is an Adverse Drug Reaction.
All events judged by the investigator to be possibly, probably, or highly probably related to the IMP, graded as serious and **unexpected** for list of Expected Adverse Events (see Reference Safely Information section 10.6) should be reported as a SUSAR.

10.6 Reference Safety Information

The Reference Safety Information (RSI) to be used for this trial is as follows:

- Infliximab Intravenous Infusion (Remicade®) 100 mg powder for concentrate for solution for infusion: Section 4.8 of the Summary of Product Characteristics (SmPC).

- Roferon-A 6 million international units (IU) solution for injection in pre-filled syringe: Section 4.8 of the Summary of Product Characteristics (SmPC).

- Roferon-A 4.5 million international units (IU) solution for injection in pre-filled syringe: Section 4.8 of the Summary of Product Characteristics (SmPC).

- Roferon-A 3 million international units (IU) solution for injection in pre-filled syringe: Section 4.8 of the Summary of Product Characteristics (SmPC).

10.7 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.8 Reporting Procedures

All adverse events should be reported from the point of consent until 8 weeks post the last dose of treatment. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the LCTU in the first instance.

10.8.1 Non serious ARs/AEs

All such events, whether expected or not, should be recorded directly onto an Adverse Event Form within the LCTU Pharmacovigilance MACRO database or on a hard copy Adverse Event form, at the study visits for which a toxicity assessment is required (see section 8.1).

Detailed AE completion guidelines will be provided for reference and training will also be given at the site initiation meetings.

10.7.2 Serious ARs/AEs/SUSARs

SARs, SAEs and SUSARs should be reported within **24 hours** of the local site becoming aware of the event by recording the information directly onto a Serious Adverse Event Form within the LCTU Pharmacovigilance MACRO database or on a hard copy Serious Adverse Event form.

For sites wishing to report data electronically, detailed SAE completion guidelines will be provided for reference and training will also be given at the site initiation meetings.

Steps for electronic reporting:

i. The online SAE form should be completed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team. The responsible investigator should check the SAE form, make changes as appropriate and sign as soon as possible. The initial report shall be followed by detailed, written reports. When an SAE form has been added an email is sent to the person completing the form, the Principal Investigator at the site and the LCTU trial team.

ii. Once data has been entered onto MACRO it will be available immediately to the LCTU (who will be notified by email when an SAE is entered).

iii. The responsible investigator must notify their R&D department of the event (as per standard local procedure).

iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

v. Follow-up information is noted on the same SAE form within the LCTU Pharmacovigilance MACRO database. The SAE type drop down question at the top of the form should be changed to 'follow-up'. Extra, annotated information and/or copies of test results may be provided separately.

vi. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence.

The Investigator must institute appropriate therapeutic action and follow-up measures in accordance with Good Medical Practice but should notify the study co-ordinator of such actions.

Additional informed should be added to the Pharmacovigilance MACRO database within 5 days if the reaction/event has not resolved at the time of reporting.

The minimum dataset required for a preliminary report should include the following:

Section A
- Patient trial number and initials.
- Days since last dose of trial treatment

Section B
- Date of onset of event.
- Outcome (i.e. current status).
- Overall diagnosis of event and symptoms, with CTCAE grade.

Section C
- Any changes in drug treatment

Section D
- Serious criteria
- Section E
- Trial Medication and concurrent drug information
- Sign-off details
- Section F (Investigator completes)
- Causality
- Sign-off details

Steps for hard copy reporting via fax:

i. The hard copy SAE form should be completed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team and faxed to the LCTU immediately. The responsible investigator should check the SAE form, make changes as appropriate, sign and then re-fax to the LCTU as soon as possible. The initial report shall be followed by detailed, written reports.

ii. Send the SAE form by fax (within 24 hours) to the LCTU:

<div align="center">

Fax Number: 0151 794 8930
Tel: 0151 794 8974

</div>

iii. The responsible investigator must notify their R&D department of the event (as per standard local procedure).

iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

v. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the LCTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

vi. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence.

On reporting an SAE to the LCTU (by either method), research sites will receive an acknowledgement of receipt, either via email or fax. If a receipt has not been received with 2 hours of reporting the SAE, please telephone the LCTU trial team on 0151 794 8974.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Chief Investigator and the LCTU is undertaking duties delegated by the trial Sponsor, University of Liverpool and is responsible for the reporting of SUSARs and other SARs to the Sponsor, MHRA and MREC within the following timelines:

- Fatal or life threatening SUSARs within 7 days after receiving the initial information.
- All other SUSARs with 15 days after receiving the information.

The Chief Investigator and the LCTU will inform all investigators of SUSARs as they occur.

Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & and Development Office.

All SUSARs are managed in accordance with the LCTU Pharmacovigilance SOPs and the study Pharmacovigilance plan.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
  a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
  b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
  c. A major safety finding from a newly completed animal study (such as carcinogenicity).
  d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

Annual Reporting to MHRA and MREC

From September 2011, the Sponsor will submit an annual Development Safety Update Report (DSUR) to the MHRA and MREC.

The DSUR will present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period relating to the Investigational Medicinal Product it will cover the following 4 areas:

1) Examine whether the information obtained by the sponsor during the reporting period is   in accord with previous knowledge of the investigational drug's safety

2) Describe new safety issues that could have an impact on the protection of clinical trial subjects.
3) Summarise the current understanding and management of identified and potential risks.
4) Provide an update on the status of the clinical investigation/development programme and study results.

10.9   Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.

All SAEs must be reported immediately by the investigator to the LCTU on an SAE form unless the SAE is specified in the protocol, IB or SPC as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

11   ETHICAL CONSIDERATIONS

11.1   Ethical Considerations

The trial will be conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments (Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

The study will be conducted in accordance with the EU Directive 2001/20/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 and the principles of Good Clinical Practice.

Patients will be asked to consent that data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

This study may be terminated at the request of the Chief Investigator, Independent Safety and Data Monitoring Committee, Independent Ethics Committee or the MHRA if, during the course of the study, concerns about the safety of further dosing emerge.

The Chief Investigator will update the ethics committee of any new information related to the study drug when appropriate.

11.2   Ethical Approval

The trial protocol has received the favourable opinion of the Multi-centre Research Ethics Committee (MREC) but must undergo site specific assessment (SSA) by completing section C of the REC application form and submitting all sections of this form to the NHS R&D offices. A copy of local Research & Development (R&D) approval and of the PIS and CF on local headed paper should be forwarded to LCTU prior to site green light.

Consent should be obtained prior to each patient participating in the trial, after a full explanation has 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 should also be implemented and patient assent obtained where appropriate. The right of patients to refuse their consent to participate in the trial without giving reasons must be respected.

After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing the further treatment.

11.3   Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in LCTU coordinated trials. In obtaining and documenting informed

consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with appropriate experience. An appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. A contact point where further information about the trial may be obtained will be provided.

After being given adequate time to consider the information, the patient will be asked to sign the informed consent document. A copy of the informed consent document will be given to the patient for their records and a copy placed in the medical records, with the original retained in the Investigator Site File.

The patient may withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

11.4   Study Discontinuation

The reason for discontinuation of study treatment/study should be clearly documented and the End of Study Treatment form completed.

12   REGULATORY APPROVAL

This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The CTA reference is to be confirmed.

13   TRIAL MONITORING

Central and site monitoring is conducted to ensure protection of patients participating in the trial, trial procedures, trial intervention administration, and laboratory and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements. A risk assessment will be carried out to determine the level of monitoring required, and a subsequent monitoring plan will be developed to document who will conduct the central (and potentially site) monitoring, at what frequency monitoring will be carried out and the level of detail at which monitoring will be conducted.

13.1   Risk Assessment

In accordance with the LCTU Standard Operating Procedure a risk assessment has been completed in partnership with:

- Representatives of the Trial Sponsor (University of Liverpool)
- Chief Investigator
- Trial Coordinator
- Trial Statistician

In conducting this risk assessment, the contributors considered the risks associated with the trial IMP(s)/intervention(s) for the IMP(s)/intervention being investigated, risks related to the design and methods of the trial (including risks to participant, safety and rights, as well as reliability of results), organisational and trial hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment is assigned according to the following categories:

- Type A = No higher than the risk of standard medical care
- Type B = Somewhat higher than the risk of standard medical care
- Type C = Markedly higher than the risk of standard medical care

This trial is considered to be a Type A = No higher than the risk of standard medical care.

13.2   Source Documents

Source Data
Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).

Source Documents
Original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions
certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial (ICH E6, 1.52).

In order to resolve possible discrepancies between information appearing in the eCRF and any other patient related documents, it is important to know what constitutes the source

document and therefore the source data for all information in the eCRF. Data recorded on the eCRF should be consistent and verifiable with source data in source documents other than the eCRF (e.g. medical record, laboratory reports and nurses' notes). Each participating site should maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

For data where no prior record exists and which are recorded directly on the eCRF (e.g. inclusion/exclusion criteria, adverse events and Quality of life questionnaires), the eCRF will be considered the **source document**, unless otherwise indicated by the investigator.

In addition to the above, date(s) of conducting informed consent including date of provision of patient information, trial screening number, trial number, study treatment and the fact that the patient is participating in a clinical trial should be added to the patient's medical record contemporaneously.

13.3 Data Capture Methods

Trial data will be captured using electronic Case Report Forms (eCRFs), transcribed to a MACRO Database. This database is designed and maintained by the LCTU. The eCRF is the primary data collection instrument for the study. All data requested on the eCRF must be recorded and all missing data must be explained.

All eCRFs are entered directly into a MACRO database that can be accessed via a secure webpage by research site staff and the clinical trial co-ordinator at LCTU. The client application is secured with a unique username/password combination allocated to each delegated member of the research team. When data is entered into an eCRF it is electronically stamped with the date, time and the person who entered it. If data is changed on an eCRF, it is electronically stamped with the change and will be accompanied with the date, time, person and a reason for making the change or correction. The previous value is recorded in an audit trail for each data item.

Each eCRF contains specific validation checks on the data being entered. If any values are outside what is expected, or data is missing, this is flagged up and will be raised as a discrepancy on the main database system. Regular reports will be generated to identify discrepancies in the data, and allow for follow up. Comprehensive guidelines for eCRF data entry will be provided to all staff who have been delegated the responsibility for data collection. Where the site is unable to upload data using the eCRF a backup paper CRF will be available to use and accessed from the LCTU portal. In such cases the site research staff will enter the data onto the trial MACRO database following the assessment.

Electronic and paper screening logs will be kept in clinics to record the number of patients declining participation and when volunteered the reason given. All data will be kept in a secure locked location on NHS premises. All routine eCRFs should be completed and within 14 days of the study visit occurring.

Paper versions of the CRFs will be available for download from the LCTU website http://www.lctu.org.uk. These will be used as an aid to research staff. To ensure current versions of CRFs are used, please print pages directly from the LCTU website as and when they are needed. Quality Control (QC) processes including on site source data verification for primary and secondary endpoints will be put in place in line with the eCRF platform. With the exception of AE and SAE forms, paper copies of eCRFs should not be forwarded on to the LCTU.

13.4   Monitoring at LCTU

There are a number of monitoring features in place at the LCTU to ensure reliability and validity of the trial data.

13.4.1   Green Light Process

The Green Light Process in place at the LCTU ensures that all regulatory and ethical approvals are in place, all contracts/agreements signed and all trial-specific and ICH GCP training received for site research staff before a site is opened to the trial and able to perform randomisations.

13.4.2   Site Research Staff

All site research staff involved in the trial must be included on the delegation log. The PI at each site signs off on the delegation log only those staff members he/she feels are able and competent to complete the assigned tasks. The delegation log provides clearly defined delegation of responsibility thus ensuring site research staff are aware of their responsibilities, and is continuously checked (as part of the data management plan) against staff named on CRFs, SAE reports and randomisation forms.

The TC ensures that as a minimum the PI, a research nurse, and a member of pharmacy staff at site have trial-specific training (on the protocol, SAE reporting and consent process) all of which is provided at site initiation (either on site or by teleconference) by the TC. The PI is responsible for ensuring site staff named on the delegation log but not present at site initiation receive trial-specific training (on the protocol, SAE reporting and consent process). Sites are supplied with copies of training aids presented at site initiation to provide a constant reminder of key trial issues. Delegated site research staff must also submit their CV and provide the date of their last ICH GCP training. In order to ensure that site research staff maintain up to date ICH GCP training (recommended to be renewed approximately every 2 years by the study Sponsor), an automated email reminder is sent to site research staff when their next ICH GCP training is due. Non-NHS staff must have honorary NHS contracts and evidence of CRB checks must be obtained for staff (when necessary by UK law).

Automated 6-monthly email reminders (from site opening) are sent to sites requesting that an updated delegation log is faxed to LCTU. On receipt of updated delegation logs, the TC ensures that new staff members have submitted their CVs and date of last ICH GCP training.

13.4.3   Oversight Committees

The ISDMC is an independent multidisciplinary group consisting of at least one statistician and at least one clinician that, collectively, have experience in the management of Behçet's disease and in the conduct of randomised clinical trials. They are 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 as outlined in the ISDMC charter.

The TSC is limited and includes an independent Chairman and two additional independent expert members (one being a statistician) and a lay/consumer representative, along with members of the TMG. Among other things, the TSC takes responsibility for monitoring and supervising the progress of the trial, considering recommendations from the IDSMC and advising the TMG on all aspects of the trial as outlined in the TSC charter.

13.4.4   Safety Reports

Regular safety reports are generated by the TC/delegate for review by the TMG, which allows monitoring of SAE and ADR reporting rates across sites. The IDSMC also regularly review AE and SAE reporting, and the TC prepares annual Development Safety Update Reports (DSURs) for submission to the MHRA and REC. Any concerns raised by the IDSMC or TMG, or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the TC/Trial Team to carry out site visits if there is suspicion of unreported AEs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines (as outlined in the pharmacovigilance plan) is noted at a given site.

13.4.5   Randomisation

The TC verifies that key site research staff have attended trial-specific training relating to eligibility screening and the informed consent and randomisation processes. Prior to randomisation, the TC/delegate will carry out a check of all consent forms sent to the LCTU. This includes checking that the patient is eligible, the correct versions of the PIS and Informed Consent Form (ICF) have been used and the patient and clinician signatures are present and dated on the same day. In addition, a check will be made to confirm that the site who are performing the randomisation have actually been granted trial green light.

Research staff at each centre participating in the study will receive appropriate randomisation training prior to performing randomisation checks and there is always office cover to ensure the randomisation procedures are carried out correctly. The TC maintains a record of any randomisation errors that occur and notifies the trial statistician as they occur. Randomisation problems are monitored by the TMG on a regular basis, and if it is noted that a particular site is making consistent errors in the consent, randomisation processes, additional training will be provided by the TC/delegate to rectify the problem.

13.4.6   Patient Confidentiality

All LCTU and research staff at each centre have received ICH GCP training and are thus aware of the importance of patient confidentiality. The TC/DM consistently check that the CRFs sent to LCTU are all anonymised and are identifiable only by trial number (except for signed consent forms, which are stored in a locked cabinet in the LCTU). The TC/Trial Team will monitor site performance on maintaining patient confidentiality (as outlined above) and will provide additional training if a particular site sends any patient identifiers to LCTU (other than on the signed consent form).

13.4.7   Recruitment

The TC will produce regular recruitment reports, to allow the TMG to review recruitment across sites. Slow or inconsistent recruitment will trigger further action centrally. The TC/Trial Team may liaise directly with site staff in order to query reasons for slow recruitment and try to resolve any problems that could impact recruitment. TC will check that the trial is being actively promoted at sites, and site recruitment schedules will be reviewed during the course of the trial as necessary.

13.4.8   Protocol Violations/Deviations

All protocol violations and deviations are recorded by the TC/Trial Team in the trial site status database, and are included in the regular IDSMC reports and central monitoring reports. Details of all protocol violations and deviations are provided to the TMG which

includes Sponsor representation, within the central monitoring report, for their review. Any violations and deviations that are considered to be a potential serious breach would be forwarded immediately to the Sponsor for their assessment. The TMG will discuss and decide proposed actions for sites that are making consistent protocol violations or deviations.

13.4.9   Withdrawals, Losses to Follow Up and Missing Data

The TC will produce reports on withdrawals, losses to follow-up and the quantity of missing CRFs/data across sites for review by the NIHR business meeting, TMG, TSC and IDSMC. Identified problems will be discussed and remedial action taken as necessary.

As outlined in the data management plan, the TC/DM will check that the withdrawal CRF is completed for all withdrawn patients (including the reasons for withdrawal). The TC will compare withdrawal rates and reasons for withdrawal across centres, paying particular attention to withdrawals close to date of randomisation. If a certain site experiences an excessive rate of withdrawals, additional training on the informed consent procedure will be provided.

13.4.10 Data Management Plan

Data entered onto the eCRF MACRO database will be centrally monitored by the LCTU to ensure that data collected are consistent with adherence to the trial protocol. The MACRO database used for this trial includes validation features which will alert the user to certain inconsistent or missing data on data entry. If any problems are identified via automated validation or central monitoring, a query is raised within the MACRO database and emailed to site. A complete log of discrepancies and data amendments is automatically generated by MACRO, including the date of each change, the reason for the change and the person who made the change, thus providing a complete audit trail. Automated email reminders are generated by the database if follow up data from a scheduled patient visit is overdue.

Additional site training will be carried out if recurring problems are noted with data from a certain site, such as consistently incorrect or incomplete data, a backlog of unresolved queries, or unacceptable time delays in completing eCRFs.

13.4.11 Statistical Monitoring

Central statistical monitoring is carried out by the trial statistician prior to the production of each IDSMC report. The statistician checks trial numbers to ensure there are no duplicated or missing numbers, and that randomisation dates for consecutive trial numbers are in the correct order. Eligibility criteria and informed consent are checked to ensure all are documented and satisfied. Monitoring is used to highlight suspicions of fraudulent data (by carrying out range checks for unusual values, checking for consistency within participants and comparing data across sites to highlight inconsistencies), as well as providing a record of the degree of missing CRFs and follow up visits, and missing baseline and outcome data. Safety and withdrawal data are also reviewed for completeness.

If there is compelling evidence to suggest that data from a particular site may be fraudulent, the TC may request a site visit to carry out source document verification of patient case notes and other source documentation.

13.4.12 LCTU Staff

All LCTU staff will receive regular ICH GCP training, have in-house training records and

undergo regular Individual Performance Review (IPR) sessions, all of which are used to ensure that appropriate training is received and any problems identified and resolved in a timely fashion.

13.5   Clinical Site Monitoring

13.5.1   Direct Access to Data

Site monitoring may be deemed to be necessary as a result of central data checks. In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Each PI therefore permits trial related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents. As this also affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

13.5.2   Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Case report forms will be labelled with patient initials and unique trial screening and/or trial number. Blood samples and will be transferred to the Wolfson Centre for Personalised Medicine, University of Liverpool laboratory and urine samples transferred to the Centre for Translational Medicine, The University of Birmingham. They will be identifiable by unique trial number only. Consent forms sent to the LCTU as part of the randomisation process may contain patient identifiers for the purpose of monitoring as described in the trial risk assessment. Such information will be stored in secure, locked cabinets.

The LCTU will request consent from all patients to obtain information from the NHS Information Centre (Medical Research Information Service) to follow patients' progress if this is not available from their hospital or General Practitioner.

13.5.3   Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol have been/will be implemented within relevant institutions with responsibility for this trial. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The Bio- Behçet's Investigational sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit and inspection by competent or IEC. Such audits/inspections may take place at any site where trial related activity is taking place (the Sponsor's site(s), Cancer Research UK (CR-UK) Liverpool Cancer Trials Unit or at any investigator's site including laboratories, pharmacies etc.)

The site staff should assist in all aspects of audit/inspection and be fully cognisant of the LCTU communication strategy for multicentre trials. This includes management systems for the green light process prior to site opening, conforming to the total Quality Management System currently operating within the LCTU.

13.6   Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until the LCTU informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The LCTU undertakes to store all data related to completed eCRFs except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the LCTU by recruiting centres. This requires that name data will be transferred to the LCTU, which is explained in the PISC. The LCTU will preserve the confidentiality of participants taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

14   INDEMNITY

This trial sponsored by the University of Liverpool (UoL) and co-ordinated by the LCTU in the University of Liverpool. The University of Liverpool has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical trial, including but not limited to the authorship of the Clinical Trial Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15   FINANCIAL ARRANGEMENTS

This is a non-commercial trial, and no direct payments are available to cover the costs associated with patient recruitment, treatment administration, follow-up visits, data collection or travel expenses.

16   TRIAL OVERSIGHT COMMITTEES

16.1   Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the LCTU Clinical Trials Unit. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year.

16.2   Trial Steering Committee (TSC)

The TSC will consist of the TMG plus the following members:

Dr David Jayne   -   Independent Chairman
Thomas Jaki   -   Independent Statistician
Professor Dorian Haskard -   Independent in the field of Bechet's Disease
Ms Rachael Benson   -   Independent Lay Representative
Prof Robert Moots   -   Chief Investigator
Elizabeth Blennerhassett -   Trial Co-ordinator

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

16.3   Independent Data and Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) will consist of the following independent members:

Dr Christoph Deuter   -   Independent Chairman
James Wason   -   Independent Statistician
Hasan Yazici   -   Independent in the field of Bechet's Disease -

The ISDMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The ISDMC will first convene prior to trial opening and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 9.

The ISDMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study.

17   PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18   PROTOCOL AMENDMENTS

18.1   Version 1 (18/DEC/2014)

Original Approved version

18.2   Version 2 (03/FEB/2015)

The original submission to Ethics was sent with Protocol Version 1 dated 18th December 2014. The resubmission was sent with Protocol Version 2 dated 03rd February 2015. Version 2 of this protocol was not document controlled at the time, the date and version number details were not changed on the Protocol 2 document and the exclusion point 5 was added and reviewed by sponsor (confirmed via the IRAS system). Following this, the Document Controller has amended Protocol version 2 to reflect the correct date (03/Feb/2015) and added it to the Document Management System.

18.3   Version 3 (17/DEC/2016)

Main changes as follows:

- General – updated start date.
- Sections 1 and 5.2 – correction 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 Endpoints: change to genital ulcer measure - a reduction of 20% is considered to be clinically significant.
- Section 6.1 – Screening Assessments: to be completed within 35 days prior to the first dose of treatment. HIV screening added.
- Section 6.1 – symptom directed assessment removed from baseline assessment, and the inclusion of a chest x-ray and screening for alterations in mood/suicide ideation (as this is known to be a side effect for the Roferon-a treatment arm).
- Section 6 – Enrolment/Baseline: update to screening log information. Randomisation: update to randomisation instructions relating to online enrolment and randomisation using the TARDIS system.
- Section 7 – Study Treatment: for clarity, the standardised use of methotrexate has been removed from the trial. Concomitant immunosuppressants will now be administered at the clinician's discretion on a case-by-case basis.
- Section 8.1 – Schedule of Assessments: amendments to the schedule of assessments.
- Section 8.2 - Updated eCRF amendment relating to assessment of efficacy.
- Section 8.4.2.2 - Further details regarding the collection of urine samples for metabolomics analyses.
- Section 8.7 - Trial Closure: change to the definition of trial closure. 'The trial is considered formally closed when the database is locked' has now been changed to 'when the last patient has completed their final study assessment.
- Section 9.2 – Method of Randomisation: updated procedure for the generation of the randomisation code lists.

- Section 13 – Updated to include (1) the use of electronic Case Report Forms (eCRFs) for this trial, (2) Quality Control (QC) procedures at site for primary and secondary endpoints as consequence of the use of an eCRF platform at sites and (3) the removal of minimisation techniques for randomisation with this trial.
- Section 16 – Oversight Committees: committee members updated.

18.4   Version 4 (25/JAN/2016)

The following changes have been applied:

- There is a change to the wording of the Main Exclusion (section 1), Exclusion Criteria (section 5.2) and Medications not Permitted/Precautions Required (section 7.7.2) to detail the requirement for participants of child bearing potential to use effective contraception. A change to the Schedule of Assessments (section 8) has been made and the additions of three terms in the glossary.
- Section 7.7.2 – addition of comment 'Administration of live vaccine is not recommended during Remicade administration'.
- Section 7.7.2 – addition of SmPC web links.
- Section 8 – change to Schedule of Assessments, omitting compulsory data collection at weeks 2, 4 and 6.

18.5   Version 5 (TBC)The following changes have been applied:

- There is a change to the wording of the overall design
- There is a change to the wording of the primary and secondary outcomes
- Section 7.2.2 - addition of comment 'Target dose of azathioprine is 2.5mg/kg'
- Section 7.3.2 – addition of comment 'Immunosuprressants to be discontinued in Arm B'
- Section 8.1 – addition of week 36 visit, for patients that swap treatment arms at week 12
- Section 8.2 - addition of week 36 visit, for patients that swap treatment arms at week 12
- Section 8.4.3.2. – Urine samples – 3ml collected at each visit (not 1ml as previously stated)
- Section 9.2 – Additional details provided in order to make the randomisation procedure more clearly to the reader
- Section 9.6.1 – Prior information added
- Section 9.6.2 – Corrected sample amount and added "at each trial visit" to make the collection clear

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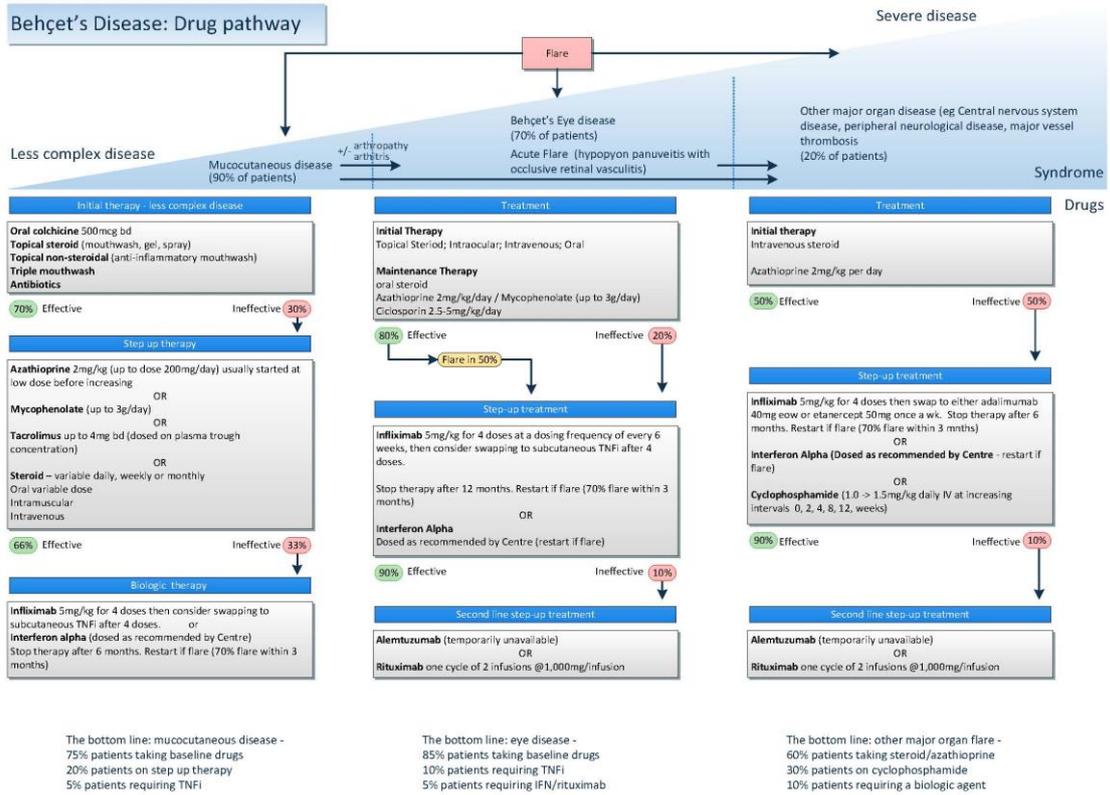
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20   APPENDICES

Appendix A   Patient Drug Pathway

Appendix B   Quality of Life Questionnaires (EQ-5D-5L and BD-QoL)

Appendix C   Patient Self-Reported Mood Questionnaire (PHQ-9)

Appendix D   Behçet's Disease Activity Index (BDAI)

Appendix A: Patient Drug Pathway

Behçet's Disease: Drug pathway

Severe disease

Flare

Less complex disease

+/- arthropathy arthritis

Mucocutaneous disease (90% of patients)

Behçet's Eye disease (70% of patients)

Acute Flare (hypopyon panuveitis with occlusive retinal vasculitis)

Other major organ disease (eg Central nervous system disease, peripheral neurological disease, major vessel thrombosis (20% of patients)

Syndrome

Drugs

Initial therapy - less complex disease

Oral colchicine 500mcg bd
Topical steroid (mouthwash, gel, spray)
Topical non-steroidal (anti-inflammatory mouthwash)
Triple mouthwash
Antibiotics

70% Effective   Ineffective 30%

Step up therapy

Azathioprine 2mg/kg (up to dose 200mg/day) usually started at low dose before increasing
OR
Mycophenolate (up to 3g/day)
OR
Tacrolimus up to 4mg bd (dosed on plasma trough concentration)
OR
Steroid – variable daily, weekly or monthly
Oral variable dose
Intramuscular
Intravenous

66% Effective   Ineffective 33%

Biologic therapy

Infliximab 5mg/kg for 4 doses then consider swapping to subcutaneous TNFi after 4 doses.   or
Interferon alpha (dosed as recommended by Centre)
Stop therapy after 6 months. Restart if flare (70% flare within 3 months)

Treatment

Initial Therapy
Topical Steriod; Intraocular; Intravenous; Oral

Maintenance Therapy
oral steroid
Azathioprine 2mg/kg/day / Mycophenolate (up to 3g/day)
Ciclosporin 2.5-5mg/kg/day

80% Effective   Ineffective 20%

Flare in 50%

Step-up treatment

Infliximab 5mg/kg for 4 doses at a dosing frequency of every 6 weeks, then consider swapping to subcutaneous TNFi after 4 doses.

Stop therapy after 12 months. Restart if flare (70% flare within 3 months)
OR
Interferon Alpha
Dosed as recommended by Centre (restart if flare)

90% Effective   Ineffective 10%

Second line step-up treatment

Alemtuzumab (temporarily unavailable)
OR
Rituximab one cycle of 2 infusions @1,000mg/infusion

Treatment

Initial therapy
Intravenous steroid

Azathioprine 2mg/kg per day

50% Effective   Ineffective 50%

Step-up treatment

Infliximab 5mg/kg for 4 doses then swap to either adalimumab 40mg eow or etanercept 50mg once a wk. Stop therapy after 6 months. Restart if flare (70% flare within 3 mnths)

Interferon Alpha (Dosed as recommended by Centre - restart if flare)
OR
Cyclophosphamide (1.0 -> 1.5mg/kg daily IV at increasing intervals 0, 2, 4, 8, 12, weeks)

90% Effective   Ineffective 10%

Second line step-up treatment

Alemtuzumab (temporarily unavailable)
OR
Rituximab one cycle of 2 infusions @1,000mg/infusion

The bottom line: mucocutaneous disease -
75% patients taking baseline drugs
20% patients on step up therapy
5% patients requiring TNFi

The bottom line: eye disease -
85% patients taking baseline drugs
10% patients requiring TNFi
5% patients requiring IFN/rituximab

The bottom line: other major organ flare -
60% patients taking steroid/azathioprine
30% patients on cyclophosphamide
10% patients requiring a biologic agent

Appendix B: Quality of Life Questionnaires (EQ-5D-5L and BD-QoL)

EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ☐

I have slight problems in walking about ☐

I have moderate problems in walking about ☐

I have severe problems in walking about ☐

I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐

I have moderate problems washing or dressing myself ☐

I have severe problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐

I have slight problems doing my usual activities ☐

I have moderate problems doing my usual activities ☐

I have severe problems doing my usual activities ☐

I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐

I have slight pain or discomfort ☐

I have moderate pain or discomfort ☐

I have severe pain or discomfort ☐

I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐

I am slightly anxious or depressed ☐

I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

2

The best health
you can imagine

- We would like to know how good or bad your health is
  TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the
  box below.

YOUR HEALTH TODAY =

100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

The worst health
you can imagine

3
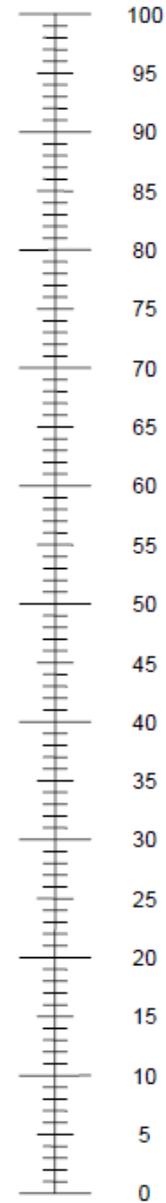
BD-QoL

BD-QoL

Date:

Name:_____ Age:_____ Sex: _____

On the following pages you will find some statements which have been made by people who have Behçet'sDisease
,
Instructions: This questionnaire consists of 30 statements. Please read each statement carefully, and then choose **True** if the statement applies to you and choose **Not True** if it does not apply to you at the moment. Circle the appropriate number.

1. My life revolves around hospital visits
  1 True
  0 Not True
	8. It is difficult to get out of bed
	  1 True
	  0 Not True

2. Nothing interests me
  1 True
  0 Not True
	9. I feel terrible about the way I look
	  1 True
	  0 Not True

3. It's too much effort to go out and see people
  1 True
  0 Not True
	10. Talking is stressful
	  1 True
	  0 Not True

4. Walking is painful
  1 True
  0 Not True
	11. I feel dependent on others
	  1 True
	  0 Not True

5. It takes me longer to do things
  1 True
  0 Not True
	12. I feel older than my years
	  1 True
	  0 Not True

6. I cannot stand for long
  1 True
  0 Not True
	13. It limits the places I can go
	  1 True
	  0 Not True

7. My condition interferes with my life
  1 True
  0 Not True
	14. I find it difficult to take care of the people I am close to
	  1 True 0 Not True

Continue on Back

15. I cannot rely on how I will be tomorrow
    1 True
    0 Not True

16. My condition is drastically affecting my life
    1 True
    0 Not True

17. I often get frustrated
    1 True
    0 Not True

18. I feel like a prisoner in my own home
    1 True
    0 Not True

19. My condition affects important decisions in my life
    1 True
    0 Not True

20. I don't like being touched
    1 True
    0 Not True

21. I cannot speak properly
    1 True
    0 Not True

22. It puts a strain on my personal relationships
    1 True
    0 Not True

23. I feel useless
    1 True
    0 Not True

24. I worry that I hold others back
    1 True
    0 Not True

25. People close to me have lost out because of my condition
    1 True
    0 Not True

26. I feel unable to cope with my condition
    1 True
    0 Not True

27. I have lost contact with people
    1 True
    0 Not True

28. I worry about the effects on others
    1 True
    0 Not True

29. Everything is getting to me today
    1 True
    0 Not True

30. I feel lonely
    1 True
    0 Not True

Appendix C: Patient Self Reported Mood Questionnaire (PHQ-9)

Calculating the Total Score for the PHQ-9
Total scores from the PHQ-9 will be calculated to assess depression severity according to the developer's guidelines (Instruction Manual: Instructions for Patient Health Questionnaire (PHQ) and GAD-7 Measures. Accessed on 2010 Sept 9 from: www.phqscreeners.com). This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. PHQ-9 total score for the nine items ranges from 0 to 27.

PHQ-9 Scoring Example:
In the example below, the Total Score for the PHQ-9 depression severity is 8, where the score is the sum of four items scored "0" (questions: #3, 7, 8, 9), three items scored "1" (questions: #1, 4, 6), one item scored "2" (question #2), and one item scored "3" (question: #5).

PATIENT HEALTH QUESTIONNAIRE - 9 (PHQ - 9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

(Use "✓" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	☒1	2	3
2. Feeling down, depressed, or hopeless	0	1	☒2	3
3. Trouble falling or staying asleep, or sleeping too much	☒0	1	2	3
4. Feeling tired or having little energy	0	☒1	2	3
5. Poor appetite or overeating	0	1	2	☒3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	☒1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	☒0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	☒0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	☒0	1	2	3

Column totals: 0 + 3 + 2 + 3

PHQ-9 TOTAL SCORE: 8

Appendix D: Behçet's Disease Activity Index (BDAI)

ISBD
International Society for Behçet's Disease

BEHÇET'S DISEASE CURRENT ACTIVITY FORM 2006

Date: Name: Sex: M/F
Centre: Telephone   Date of birth:
Country:
Clinician: Address:

All scoring depends on the symptoms present over the **4 weeks** prior to assessment.
Only clinical features that the **clinician feels are due to Behçet's Disease** should be scored.

PATIENT'S PERCEPTION OF DISEASE ACTIVITY
(Ask the patient the following question:)

"Thinking about your Behçet's disease only, which of
these faces expresses how you have been feeling over
the last four weeks? "(Tick one face)

**HEADACHE, MOUTH ULCERS, GENITAL ULCERS, SKIN LESIONS, JOINT INVOLVEMENT AND
GASTROINTESTINAL SYMPTOMS**

Ask the patient the following questions and fill in the related boxes "Over the past 4 weeks have you had?"

(please tick one box per line)

	not at all	Present for up to 4 weeks
Headache		
Mouth Ulceration		
Genital Ulceration		
Erythema		
Skin Pustules		
Joints - Arthralgia		
Joints - Arthritis		
Nausea/vomiting/abdominal pain		
Diarrhoea+altered/frank blood per rectum		

EYE INVOLVEMENT
(Ask questions below)

(please circle)

		Right Eye		Left Eye	
"Over the last 4 weeks have you had?"	a red eye	No	Yes	No	Yes
	a painful eye	No	Yes	No	Yes
	blurred or reduced vision	No	Yes	No	Yes

If any of the above is present: "Is this new"?   No   Yes
(circle the correct answer)