CDAID Trial

A Phase Ib/IIa, Randomised, Double Blind, Placebo-Controlled Trial to Investigate the Safety, Tolerability and Clinical Activity of Humanised Antibody GSK1070806 in the Treatment of Patients with Moderate-to-Severe Crohn's Disease

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Cancer Research UK Clinical Trials Unit @CRCTU

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SIGNATURE PAGE

CDAID Trial Protocol Version 6.0 7th August 2019

This protocol has been approved by:

Name:	Dr Marietta Iacucci	**Trial Role:**	Chief Investigator
Signature:	_____	**Date:**	07 / August / 2019

This protocol describes the CDAID trial and provides information about procedures for patients taking part in the CDAID trial. The protocol should not be used as a guide for treatment of patients not taking part in the CDAID trial.

This protocol was written using CRCTU-PRT-QCD-001, version 1.0b

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
01	13-Mar-2019	5.0	Substantial Amendment	• Schedule of Events – Information regarding endoscopy images added. Information Clarification on when Patient Daily Diary should be completed • Additional information included regarding photographic images and/or video recordings in Sections 3, 5 and 7 • Update of Section 6.2 Emergency Randomisation • Minor typos throughout
02	12-Aug-2019	6.0	Substantial Amendment	• Reduction in sample size from 30 to 21 • Removal of CDAI score from Eligibility Criteria • Clarification of PK and PD sampling. EOI and 4-8hour sample for Visit 3 PD removed. Visit 9 PK removed. • Clarification of screening endoscopy timepoint and biopsy samples • Change to permitted concomitant medications (washout) and prohibited medications • Change of SAE reporting email address • Amendment to CRFs. Removal of SES-CD CRF. Inclusion of Endoscopy Score Form CRF • Removal of 2nd interim analysis point after patient 18

TRIAL SYNOPSIS

Trial Title	A Phase Ib/IIa, Randomised, Double Blind, Placebo-Controlled Trial to Investigate the Safety, Tolerability and Clinical Activity of Humanised Antibody GSK1070806 in the Treatment of Patients with Moderate-to-Severe Crohn's Disease
Trial Design	A randomised, double-blind, placebo-controlled trial in patients with moderate-to-severe active Crohn's disease
Trial Duration	3 years (12-18 months recruitment period)
Patient Population	Adult patients with Crohn's disease
Sample Size	21
Objectives	Primary Objective To evaluate the safety and tolerability of single dose intravenous (IV) administrations of GSK1070806 in patients with moderate to severe Crohn's disease. Secondary Objectives 1. To evaluate the clinical activity of single dose IV administrations of GSK1070806 in patients with moderate to severe Crohn's disease. 2. To evaluate the serum pharmacokinetics (PK) following single dose IV administrations of GSK1070806 in patients with moderate to severe Crohn's disease. 3. To evaluate the proportion of patients with moderate to severe Crohn's disease achieving clinical remission following single dose IV administrations of GSK1070806. 4. Time to clinical response following single dose IV administrations of GSK1070806 in patients with moderate to severe Crohn's disease. 5. To evaluate the effect of GSK1070806 on established biomarkers of disease in patients with moderate to severe Crohn's disease. 6. To evaluate the potential of anti-GSK1070806 antibody formation following administration of GSK1070806 in patients with moderate to severe Crohn's disease.
Outcome Measures	Primary Outcome Measures Safety and tolerability parameters include: adverse events, serious adverse events, clinical laboratory tests, electrocardiograms and vital signs. Frequency, type and severity of infections. Key Secondary Outcome Measure CDAI score over time (refer to Schedule of Events for assessment times).

	Further Secondary Outcome Measures 1. Serum concentrations of GSK1070806 over time and derived PK parameters if feasible AUC(0-τ), Cmax, Tmax and t½. 2. Abdominal pain (AP) over time (refer to Schedule of Events for assessment times) 3. Stool frequency (SF) over time (refer to Schedule of Events for assessment times) 4. Post-treatment (w12) SES-CD endoscopic score. 5. Proportion of patients in clinical remission defined as average daily Stool Frequency ≤ 2.8 and /or average daily Abdominal pain ≤ 1 and CDAI <150. 6. Kinetics of induction of clinical response defined as a ≥ 70 point decrease from baseline CDAI score (or score ≤ 150). 7. Serum C-reactive protein over time (refer to Schedule of Events for assessment times). 8. Faecal calprotectin over time (refer to Schedule of Events for assessment times). 9. Incidence and titers of serum of anti-GSK1070806 antibodies before and after GSK1070806 administration
Main Inclusion and Exclusion Criteria	Inclusion Criteria 1. Written informed consent prior to any of the screening procedures including discontinuation of prohibited medications. (see Section 7.11 for additional information) 2. Patients must have been diagnosed with Crohn's disease at least 3 months prior to Screening Visit 1 3. Patients are required to have endoscopic evidence of active Crohn's disease at Baseline defined by endoscopic appearance: SES-CD excluding the narrowed component of ≥ 6 (or ≥4 for patients with isolated ileal disease). 4. AST and ALT ≤ 2xULN; alkaline phosphatase and bilirubin ≤ 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) 5. Male or female participants aged ≥16 years (up to 80 years) *See Section 4 for complete list of inclusion criteria* Exclusion Criteria 1. Diagnosis of ulcerative or indeterminate colitis Crohn's disease complications: 2. Evidence of an infected abscess by MRI or other examinations 3. Bowel surgery other than appendectomy within 12 weeks prior to screen and/or has planned surgery or deemed likely to need surgery for CD during the trial period 4. Participants with ileostomies, colostomies or rectal pouches 5. Participants with a bowel stricture that is fixed 6. Participants with evidence of short bowel syndrome

	7. Participants requiring enteral or parenteral feeding 8. Deep penetrating ulcers at endoscopy thought to be at risk for perforation. *See Section 4 for complete list of exclusion criteria*
Permitted Concomitant Medication	1. Oral Corticosteroids: For participants receiving prednisone, or equivalent, the dose must be ≤20mg/day for ≥4 weeks prior to screening and planned to remain stable for the duration of the trial. For participants receiving budesonide the dose must be ≤6mg/day for ≥4 weeks prior to screen and planned to remain stable for the duration of the study 2. Immunosuppressant and other Crohn's disease medications: For participants receiving azathioprine, methotrexate, or 6-mercaptopurine for Crohn's disease, the dose must be stable for >8 weeks prior to screening and planned to remain stable for the duration of the study. For participants receiving methotrexate or 5-aminosalicyclic acid for Crohn's disease, the dose must be stable for >4 weeks prior to screening and planned to remain stable for the duration of the study. 3. All other medications including over-the-counter medicines, supplements, vitamins and herbal remedies that each participant is taking at the time of consent will be permitted and recorded. *See Section 7.11 for further concomitant medication information*
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TRIAL SCHEMA

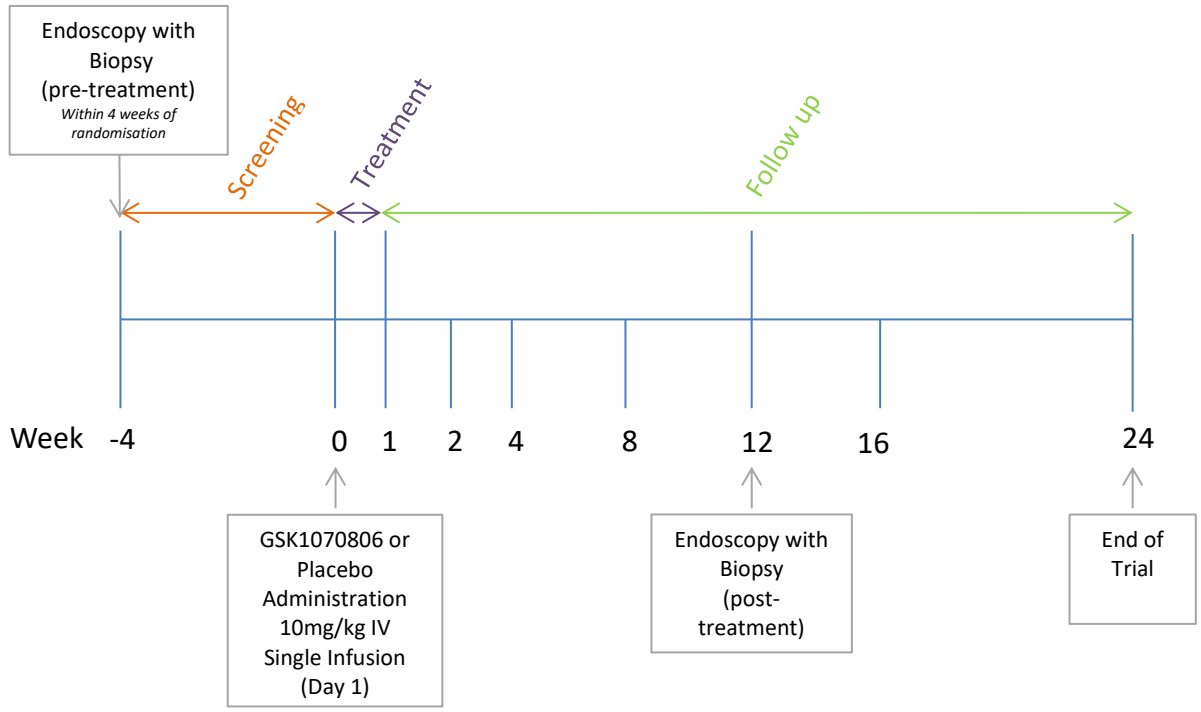

Figure 1 Trial Schema

SCHEDULE OF EVENTS

			Treatment period (Week 1)		Follow-up (+/- 3 days) Days						
Schedule of Assessments	**Screening period**		**Week 1**	**Week 1**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 24**
Time schedule	**Visit 1 ≤ 28 days of Randomisation**	**Visit 2 ≤ 7 days of Day 1**	**Visit 3 Day 1 (Day of Treatment)**	**Visit 3a Day 2[#]**	**Visit 4 Day 7**	**Visit 5 Day 14**	**Visit 6 Day 28**	**Visit 7 Day 56**	**Visit 8 Day 84**	**Visit 9 Day 112**	**Visit 10 Day 168**
Informed Consent	**X**										
Demographics (age, gender, ethnicity)	**X**										
Medical & Crohn's Disease History	**X**										
Inclusion/Exclusion criteria	**X**	**X**									
Randomisation		**X** (up to 7 days before Day 1 of treatment)									
Clinical Assessment[1]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vital Signs[2]	**X**	**X**	**X[2a]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Physical Examination[3]	**X**	**X**	**X**	**X**			**X**	**X**	**X**	**X**	
Serology Screening (HepB, HepC,)	**X**										

			Treatment period (Week 1)		Follow-up (+/- 3 days) Days						
Schedule of Assessments	**Screening period**		**Week 1**	**Week 1**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 24**
Time schedule	**Visit 1 ≤ 28 days of Randomisation**	**Visit 2 ≤ 7 days of Day 1**	**Visit 3 Day 1 (Day of Treatment)**	**Visit 3a Day 2#**	**Visit 4 Day 7**	**Visit 5 Day 14**	**Visit 6 Day 28**	**Visit 7 Day 56**	**Visit 8 Day 84**	**Visit 9 Day 112**	**Visit 10 Day 168**
Influenza Risk Screening[4]	X		X								
Clostridium Difficile Testing	X										
Pregnancy test	X		X				X		X		X
12 Lead ECG[5]	X		X			X					X
Quantiferon GOLD(TB test)[6]	X										
Biochemistry[7]	X	X	X	X	X	X	X	X	X	X	X
Haematology [8]	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics[9]			X	X	X	X	X	X	X		X
Pharmacodynamics sampling[10]			X	X	X	X	X	X	X	X	X
Endoscopy with Biopsy[11]	X								X		
CDAI	X	X	X		X	X	X	X	X	X	X
Immunogenicity Blood sample[12]			X (pre-dose)				X	X	X	X	X
Patient Daily Diary[13]	X	X	X	X	X	X	X	X	X	X	X

			Treatment period (Week 1)		Follow-up (+/- 3 days) Days						
Schedule of Assessments	**Screening period**		**Week 1**	**Week 1**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 24**
Time schedule	**Visit 1 ≤ 28 days of Randomisation**	**Visit 2 ≤ 7 days of Day 1**	**Visit 3 Day 1 (Day of Treatment)**	**Visit 3a Day 2[#]**	**Visit 4 Day 7**	**Visit 5 Day 14**	**Visit 6 Day 28**	**Visit 7 Day 56**	**Visit 8 Day 84**	**Visit 9 Day 112**	**Visit 10 Day 168**
GSK1070806 Drug /Placebo administration[14]			**X**								
Faecal Calprotectin		**X**	**X**				**X**		**X**		**X**
Adverse Event/SAE reporting	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medication Review	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Genetics / pharmacogenetics sample for optional genetic research [15]			**X**								
Additional Research Samples[16]	**X**		**X**		**X**	**X**	**X**	**X**	**X**		**X**

Treatment given	X

 # If patient decides not to attend the clinic in person then a telephone visit is required to confirm patients' health status/record an adverse events. No other assessments are required. This telephone call will need to be conducted by a suitably qualified medical individual i.e. Research nurse or other medical professional.

NB: See specific sections within the protocol for visit window information (Sections 5.2, 7.7, 7.13)

1 **Clinical Assessment – assessment of CDAI score, daily diary and adverse events**

2 **Includes heart rate, blood pressure, oral body temperature (°C), respiratory rate, (all taken in supine position) and weight (kg). Weight is to be measured at Screening Visit 1 and Visit 12. Height (cm) is to be measured at Screening Visit 1.**

2a	On Visit 3 (day of treatment), vital signs are taken pre-dose, at 30 minute intervals (+/-10 minutes) during infusion period and at 30 minute (+/-10 minutes) intervals for period of 3 hours post infusion (removal of needle)
3	The need for a physical examination will be determined by the local Investigator according to clinical need
4	Influenza Risk Screening to be carried out pre-screening (within 7 days of treatment)and prior to treatment at Visit 3 (day of treatment). A review of patients recent medical history – specifically related to any current evidence, or history within the last 14 days, of an influenza-like illness as defined by fever (>38°C) and two or more of the following symptoms; cough, sore throat, runny nose, sneezing, limb/joint pain, headache, vomiting/diarrhoea
5	12 Lead ECG – On Visit 3 (day of treatment), ECG is carried out pre-dose and 60 mins (+/- 10minutes) post infusion
6	TB test- see Appendix 4 – T-Spot.TB
7	Biochemistry - to include Alkaline phosphate (ALP), Alanine transaminase (ALT), aspartate transaminase (AST), albumin, bilirubin, sodium, potassium, urea, creatinine, calcium, total protein, eGFR (calculated by Cockcroft-Gault equation or alternative as per institutional practice – Appendix 7), C-Reactive protein (CRP) (see Section 7.8.8). On Visit 3 (day of treatment), sample to be taken pre-dose and 60 minutes post infusion. Not applicable if Visit 3a is conducted via telephone.
8	Haematology - Full Blood Count (FBC) to include haemoglobin, platelets, red blood cells, white blood cells, haematocrit, mean cell volume, mean cell haemoglobin, neutrophils, lymphocytes, monocytes, eosinophils, basophils, INR, APTT ratio (see Section 7.8.8). On Visit 3 (day of treatment), sample to be taken pre-dose and 60 minutes post infusion. Not applicable if Visit 3a is conducted via telephone.
9	On Visit 3 (day of treatment), sample to be taken pre-dose, end of infusion, 4-8h. Sample at Visit 3a to be taken if patient attends clinic.
10	On Visit 3 (day of treatment) samples to be taken pre-dose. Sample at Visit 3a to be taken if patient attends clinic.
11	Endoscopy will include the capture of photographic images and/or video recordings for central review. See Section 7.8.10. Biopsy samples (for exploratory biomarker analysis) to be collected in accordance Laboratory Manual/shipping instructions (formalin fixed) and shipped to the GlaxoSmithKline Laboratory (USA) within 48 hours of collection. See Laboratory Manual and Section 7.9.1 of protocol for additional information.
12	If a patient develops an Adverse Event which is defined by body system- Immune System Disorder (as per CTCAE v4.0), an additional Immunogenicity sample should be collected where possible if this time period falls outside of the protocol scheduled defined visit/sample collection
13	Screening Visit 1 - Patient Daily Diary issued to the patient and is to be completed 7 consecutive days directly prior to Screening Visit 2. Visit 2 – Visit 9 Patients should bring completed diaries to these visits and be issued new diaries. Visit 10 – Completed diaries collected. No new diary to be issued
14	Includes a 3 hour safety observations AFTER drug infusion
15	This sample can be taken at any time during the study if not taken on Day 1 – one sample only
16	On Visit 3 (day of treatment) sample to be taken at the end of infusion

ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
aTNFα	Anti-TNFα
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CRCTU	Cancer Research UK Clinical Trials Unit
CRF	Case Report Form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic cells
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DoH	Department of Health
DSS	dextran sulphate sodium
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ELF	Enhanced Liver Fibrosis
ELISA	Enzyme Linked Immunosorbent Assay
eRDC	Electronic Remote Data Capture
ESLD	End-stage Liver Disease
FBC	Full Blood Count
FSH	Follicle Stimulating Hormone
FTIH	First Treatment in Human
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GP	General Practitioner
HRS	Hours
HRT	Hormonal Replacement Therapy
IECs	Intestinal Epithelial cells
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
IECs	intestinal epithelial cells
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
IL-18R	IL-18 receptor
INR	International Normalised Ratio
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IV	Intravenous
LFT	Liver Function Test
LPLV	Last Patient Last Visit
MHRA	Medicines and Healthcare Products Regulatory Agency

MINS	Minutes
MRI	Magnetic Resonance Imaging
NaCl	Sodium Chloride
NCI	National Cancer Institute
NIHR	National Institute of Health Research
NSAID	Non-steroidal Anti-Inflammatory Drug
OBS	Observations
PD	Pharmacodynamics
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
PRO	Patient Reported Outcome
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SES-CD	Simple Endoscopic Score for Crohn's Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TNBS	Trinitrobenzene Sulphonic
TNF	Tumour Necrosis Factor
TNFα	Tumour Necrosis Factor alpha
UC	Ulcerative Colitis
UE	Urea and Electrolytes
ULN	Upper Limit of Normal
WHO	World Health Organisation
WOCBP	Woman Of Childbearing Potential

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Crohn's Disease

Crohn's disease (CD) is a chronic systemic disorder involving the gastrointestinal tract. Patients with Inflammatory Bowel Disease (IBD) can present with a range of symptoms including diarrhoea and abdominal pain, tenesmus or rectal bleeding reflecting the anatomic location of disease [Lichtenstein et al, 2009]. CD is characterised by focal, asymmetric, transmural inflammation affecting the small and large intestines (Lichtenstein, Yip et al. 2009).

The incidence and prevalence of CD in western populations is about 50 per 100,000 (Ng, Shi et al. 2018). The most common age for first diagnosis is 15-30 years and in some studies there is a female preponderance. (Lichtenstein, Yip et al. 2009, Cosnes, Gower-Rousseau et al. 2011) (Molodecky, Soon et al. 2012).

CD is heterogeneous in the location of intestinal involvement and disease course. The Montreal classification, attempted to phenotype patients with CD by disease location (ileal, colonic, ileocolonic or isolated upper intestinal) and by evolution (stricturing, penetrating (fistulas and abscesses) or non-stricturing, non-penetrating). Longitudinal studies indicate the anatomic location of disease is relatively stable over time (with about 47% ileal, 28% colonic and 21% ileocolonic at first presentation) and less than 20% of patients with small bowel disease developing colonic disease and vice versa over 10 year follow up (Baumgart and Carding 2007) (Cosnes, Gower-Rousseau et al. 2011). It is increasingly clear that disease behaviour is dynamic over time and patients with predominantly inflammatory disease at diagnosis are very likely to develop either fistulising or stricturing complications during follow up (Cosnes, Gower-Rousseau et al. 2011) (Satsangi, Silverberg et al. 2006) so that CD is progressive. CD evolution relates to disease location. Small bowel involvement is associated with higher rates of penetrating or other complications, whereas colonic disease can remain uncomplicated or inflammatory for many years (Cosnes, Gower-Rousseau et al. 2011).

After the first year from diagnosis, 10–30% of patients with CD have an exacerbation, 15–25% have low activity, and 55–65% are in remission. Around 15–20% of patients with CD have a chronic active course of disease activity, 67–73% have a chronic intermittent course and only 10–13% remain in remission for several years. After 20 years, most patients with CD will have undergone surgery (Ma, Moran et al. 2017) to resect inflamed bowel (not responding to medical treatment), relief of obstruction, abscess drainage or fistula excision and closure. The life expectancy of patients with CD is slightly reduced (Baumgart and Carding 2007).

1.1.2 Measurement of disease activity, disease progression and predictive biomarkers

CD is viewed as a progressive disease with the cumulative effect of cycles of inflammation and resolution leading to structural sequelae, but there is no good measure of progression. The International Program to develop New Indexes in Crohn's Disease group have proposed validation of an instrument called the Crohn's Disease Digestive Damage Score (the Lémann score), to take into account damage location, severity, extent, progression, and reversibility, as measured by diagnostic imaging modalities and the history of surgical resection. Importantly, the score will be diagnostic modality agnostic: for each lesion and location, a modality appropriate for the anatomic site (for example: computed tomography or magnetic resonance imaging enterography, and colonoscopy) will be used (Pariente, Cosnes et al. 2011). In addition, a World Health Organisation (WHO) validated disability score as well as Crohn's disease severity index have been recently proposed, but these are generally not used in trials for drug development.

Clinical features of disease, including the need for corticosteroids, predict development of complications with modest success. Addition of baseline C-Reactive Protein (CRP), serology and a transcriptional signature in CD8 lymphocytes may lead to the development of diagnostic models with better predictive probability for rapid progression. Defining progression as development of strictures and fistulae requiring surgery, a number of serologic markers reflecting immune response to microbial antigens associated with Pseudomonas fluorescens, porin protein C from Escherichia coli, bacterial flagellin, and Saccharomyces cerevisiae have been shown to correlate with progression. In a cross sectional study using banked samples, a combination of serology with a genetic marker (single nucleotide polymorphism in the NOD2 locus) improves the probability of complicated disease behaviour above serology alone (Lichtenstein, Targan et al. 2011). In a small study whole genome expression analysis of CD8 T cells isolated from the blood of with active CD or ulcerative colitis (UC) before commencing treatment identified two distinct subgroups. About 40% of patients with CD or UC displayed a "high risk" pattern of gene expression associated with a greater requirement to introduce immunomodulators or perform surgery and the necessity for more such escalations over a 700 day follow-up period (Lee, Lyons et al. 2011).

1.1.3 Management and treatment of disease

Management of CD is dependent upon severity of disease (Lichtenstein, Yip et al. 2009)(Burger and Travis 2011) (Talley, Abreu et al. 2011). Treatment guidelines for mild disease recommend that sulfasalazine is used as first line treatment for predominantly colonic disease and Budesonide for ileal and ileo-caecal disease. Oral corticosteroids (prednisolone at doses of 40-60 mg per day) are used as second-line therapy for patients with mild disease unresponsive to the above approaches and as first-line agents for patients with moderate-severe disease. AntiTNFα (aTNFα) treatment is indicated for induction of remission in moderate-severe disease who do not enter remission with prednisolone and for maintenance of remission in patients failing conventional therapies. Azathioprine, 6-mercaptopurine and methotrexate are not ideal induction agents because of their slow onset of action but are introduced as maintenance agents for patients with one or more relapses often in combination with biologic therapy. Additional biological agents approved for use in moderate to severe CD include vedolizumab and ustekinumab. A current review has discussed the expanding options for treatment of IBD (Paramsothy, Rosenstein et al. 2018).

Four aTNFα therapies are available (though are not universally approved in all countries): Infliximab is a chimeric monoclonal antibody which binds specifically to human tumour necrosis factor alpha (TNFα); Adalimumab is a fully humanised Immunoglobulin G (IgG1) monoclonal antibody; Certolizumab Pegol is a recombinant, humanized antibody Fab' fragment, with specificity for human tumour necrosis factor alpha (TNFα), conjugated to an approximately 40kDa polyethylene glycol; Golimunab is a fully humanised subcutaneous administered aTNFα approved only for UC. Currently, both infliximab and adalimumab are approved in the European Union as second-line treatments for severe, active CD in patients not responding to or intolerant of conventional therapy. Infliximab and adalimumab appear to have comparable efficacy (Hazlewood, Rezaie et al. 2015). Certolizumab pegol is approved only in the United States and Switzerland as a second-line treatment for moderate-to-severe, active CD in patients not responding to or intolerant of conventional therapy (Feagan, Lemann et al. 2012).

Despite the introduction of aTNFα therapies the management of moderate-severe CD remains challenging. In clinical trial settings when care is taken to select patients with active CD, between 70 and 90% of patients show some clinical improvement by 4 weeks during treatment with an aTNFα with maximal response reached after 12 weeks (Burger and Travis 2011) (Allez, Vermeire et al. 2010). These response rates obscure the fact that full response characterized by clinical remission and tissue healing only occurs in a minority of patients (around 30%). Furthermore, response is not maintained, with a loss of response varying from around 50% per year in placebo controlled trials to slightly more than 10% per year in smaller studies and single-centre studies in which

treatment optimization (including dose escalation and dose interval changes) is allowed. Other factors that may prevent loss of response include steroid premedication, immunosuppressive co-treatments, and maintenance treatment as opposed to episodic treatment (Allez, Vermeire et al. 2010).

Anti-TNFα (aTNFα) agents are approved for severe disease, but with growing recognition of the safety of aTNFα s and the progressive nature of CD, an earlier "top-down" introduction of aTNFα early in the treatment algorithm is being championed. Combined with azathioprine infliximab is better than infliximab alone (SONIC trial) (Colombel, Sandborn et al. 2010). However, this may not be the case with all biologics in IBD, and the need for combination therapy with adalimumab is less convincing (DIAMOND study). Other mechanism of actions that has provided additional biologic therapies in moderate to severe CD include inhibition of α4β7 (vedolizumab) and inhibition of Interleukin (IL) 12/23 p40 (ustekinumab).

Given the low initial and longer term remission rates associated with aTNFα's, there is a high unmet need for new treatment options which are effective in anti-TNFα's primary and secondary non-responders. The drugs with an alternative mechanism of action currently available for these patients are natalizumab (only in the USA), vedolizumab and ustekinumab. Although these drugs are well tolerated, these may be associated with an increased risk for infections, acute hypersensitivity reactions, and hepatotoxicity.

Recent advances in the understanding of the pathophysiology of CD have led to the identification of new therapeutic opportunities. Classic CD has a Th1-type cytokine profile which is pivotal in the orchestration and promotion of the immune response. Th1 development is triggered by microbes that stimulate production of cytokines including IL-18, and IFN γ, which then activate macrophages and the release of IL-1, IL-6 and TNFα. Many of the novel therapies under development for CD aim to inhibit T-cell function differentiation or activation e.g. tocilizumab, ustekinumab (Ito, Takazoe et al. 2004) (Sandborn, Feagan et al. 2007), induce apoptosis of T cells or a particular subset of these cells e.g. Visilizumab (Carpenter, Appelbaum et al. 2002) or inhibit leukocyte migration to sites of inflammation e.g. natalizumab, CCX282-R (Sandborn, Colombel et al. 2005) (Walters, Wang et al. 2010). A number of other classes of drugs are in development in CD including JAK inhibitors, monoclonal antibody to IL23 (anti p19, Risankizumab), antisense SMAD7 (Mongersen). Despite the currently available targeted therapies of aTNFα, vedolizumab, ustekinumab, there is a large unmet need in CDwith considerable morbidity, hospitalisation and repeated surgeries.

1.1.4 Interleukin 18

IL-18 is a member of the IL-1 family of cytokines which was originally described as an interferon gamma (IFN-γ) inducing factor (Okamura, Nagata et al. 1995). The cytokine is produced constitutively in many different cell types, including macrophages, endothelial cells, vascular smooth muscle cells, dendritic cells and Kupffer cells. IL-18 is also produced in adipocytes (Skurk, Kolb et al. 2005), but non-adipocyte cells have been identified as the main source of IL-18 in adipose tissue (Fain, Tichansky et al. 2006). Over the past decade, it has become clear that IL-18 has more widespread functions than induction of IFN-γ. These functions include regulation of gene expression including those for angiogenic factors like vascular endothelial growth factors (Amin, Mansfield et al. 2007), modulation of proliferation of various cell types including immune and nonimmune cells (Tomura, Zhou et al. 1998) (Tominaga, Yoshimoto et al. 2000) (Khan, Peltekian et al. 2008), and regulation of cell migration and metastasis (Jung, Song et al. 2006) (Park, Cheon et al. 2007).

Pro-IL-18, the natural cellular precursor, is cleaved by Caspase-1 or proteinase 3 to generate a biologically active mature 18 kDa protein. Mature IL-18 binds to the IL-18Rα subunit resulting in the recruitment of IL-18Rβ on the cell surface. The interaction between IL-18 and the heterodimeric cell surface receptor induces signalling

pathways shared with other IL-1R family members such as Toll-like receptors and IL-1 receptors. IL-18 is expressed by macrophages, dendritic cells, osteoclasts, synovial fibroblasts, adipocytes, and epithelial cells. Whereas, the IL-18 receptor (IL-18R) is predominantly expressed on macrophages, lymphocytes, neutrophils, natural killer cells (NK), endothelial, epithelial and smooth muscle cells. In vivo, the binding of IL-18 to IL-18R complex is regulated by IL-18 binding protein (IL-18BP). IL-18BP is a naturally occurring protein which is constitutively expressed and secreted and binds with high-affinity to IL-18 (dissociation constant of 400 pM) neutralising it's biologic activity (Novick, Kim et al. 1999) (Kim, Eisenstein et al. 2000). IL-18BP is specific for mature IL-18 and does not bind the IL-18 precursor when assessed by Enzyme Linked Immunosorbent Assay (ELISA) (Novick, Schwartsburd et al. 2001) or BiaCore binding (Kim, Eisenstein et al. 2000). With the exception of IL-1F7 (Bufler, Azam et al. 2002), IL-18BP does not bind to other members of the IL-1 family or several cytokines tested.

One of the key biological functions of IL-18 is its role in host defence against microbial pathogens. IL-18 primes both innate and acquired immunity to viruses and other intracellular pathogens through activation and differentiation of Th1 and NK cells, the production of the pro-inflammatory cytokine IFN-γ, upregulation of Fas and Fas ligand, and also potentiation of other proinflammatory mediators. Studies in mice in response to challenge with the intracellular pathogen Mycobacterium avium have shown a strong requirement for a Th1 response and a role for IL-18 in the expulsion of the pathogen(Takeda, Tsutsui et al. 1998).

In addition to its role in the inflammatory response to microbes, recent studies have elucidated a broad spectrum of effector functions that implicate IL-18 as an important factor in human autoimmune diseases and metabolic diseases. Numerous studies in animals and humans implicate elevated levels of IL-18 as a contributing factor to the pathology of various diseases including inflammatory bowel disease (IBD), vasculitis, diabetes mellitus, adult-onset Still's disease, systemic lupus erythematosus, rheumatoid arthritis (RA), allograft rejection, atherosclerosis, atopy, and syndromes associated with acute tissue injury such as acute pancreatitis and fulminant hepatic failure. IL-18 has been shown to be a primary cytokine, driving the production of TNFα and IL1β in animal models and increasing the incidence of arthritis (Olee, Hashimoto et al. 1999) (Joosten, van De Loo et al. 2000) (Wei, Leung et al. 2001). Blockade of IL-18 by neutralising antibodies, or the use of the naturally occurring binding protein (IL-18bp) (Novick, Kim et al. 1999) in a murine model of collagen induced arthritis (CIA) (Banda, Vondracek et al. 2003), reduces joint inflammation and cartilage destruction (Plater-Zyberk, Joosten et al. 2001).

1.1.5 The Role of IL-18 in Crohn's Disease

The first evidence for the role of IL-18 in inflammatory bowel disease was provided by (Pizarro, Michie et al. 1999). This study revealed an upregulation of IL-18 in the intestine of patients with CD with a higher expression in active disease and a localization of IL-18 synthesis in intestinal epithelial cells (IECs) as well as macrophages and dendritic cells (DCs) in the lamina propria. Functional data followed this initial descriptive study indicating that mice were protected in various models of colitis, including dextran sulfate sodium (DSS)- and trinitrobenzene sulphonic acid (TNBS)-induced colitis, when either pro- IL-18 could not be activated or the active cytokine was neutralized via antibody (Kanai, Watanabe et al. 2001) (Siegmund, Rieder et al. 2001). In agreement with the human data, IL-18 production was localized to IECs and macrophages or DCs of the lamina propria. At that time, one could conclude that neutralisation of IL-18 should be beneficial for intestinal inflammation. Conflicting data were reported by other laboratories and IL-18 deficiency was shown to result in severe colitis (Takagi, Kanai et al. 2003). When experimental colitis was induced (by DSS) in Nlrp3-/- mice which are unable to produce mature IL-18, increased mortality and microscopic/macroscopic evidence of colitis was observed compared to WT mice. Disease deterioration could be reversed by the administration of IL-18 indicating a key role for IL-18 in disease prevention in this model.

The conflicting roles for anti-IL-18 reported in the literature may be due in part to the different susceptibilities in the mouse strains used or alternatively the mechanism of induction of colitis in the various models; TNBS induces a Th1 driven colitis in intestinal mucosa, whereas DSS is directly toxic to colonic epithelial cells of the basal crypts. Another hypothesis which has been proposed is that IL-18 exerts a dual role in intestinal homeostasis and colitis. Early in the mucosal immune response expression of IL-18 by IECs plays a role in maintenance of barrier immunity. However under chronic inflammation, and following breach of the intestinal mucosa by bacteria, the cytokine is expressed in the lamina propria; its excessive production results in deleterious effects and drives the expression of a pro-inflammatory cascade (Reuter and Pizarro 2004).

IL-18 is expressed by resident monocytes and macrophages in intestinal epithelial cells and functions as a pro-inflammatory cytokine, thus contributing to differentiation and activation of T cells. Furthermore, IL-18 upregulates the p38 and JNK MAP kinase's which are known to be important in the pathophysiology of CD. Accordingly, IL-18 offers an attractive target to interrupt inflammation in CD at several points.

Both rare and common human genetic evidence implicate the IL-18 pathway in the development of IBD and CD. Rare gain-of-function mutations in NLRC4, an upstream regulator of IL-18, are known to cause a syndrome of enterocolitis and auto-inflammation (Romberg, Al Moussawi et al. 2014) (Canna, de Jesus et al. 2014). A patient with severe enterocolitis caused by those mutations was successfully treated by inhibiting IL-18 using IL-18BP (Canna, Girard et al. 2017). This clinical study supports the role of IL-18 as a driver of the disease within those patients.

Common SNPs have also been linked to CD and IBD. In previous studies, common variants within the IL-18 promoter have been shown to directly impact its expression (Giedraitis, He et al. 2001) (Liang, Cheung et al. 2005) (Arimitsu, Hirano et al. 2006) (Zhou, Yamaguchi et al. 2005). Subsequent Mendelian randomisation analysis revealed that regulatory variants which increased IL-18 levels were also independently associated with increased risk of CD. This analysis established a causal genetic link between IL-18 levels and CD. In addition to genetic associations with IL-18 levels, genome-wide association studies have also mapped the IL-18RL1/IL-18RAP locus with CD risk (Franke, McGovern et al. 2010) (Jostins, Ripke et al. 2012). The associated SNPs are also correlated with changes in IL-18RL1/IL-18RAP expression levels. Recent unpublished data suggest that there may be additional signals in the receptor locus that require further interrogation. Together, the genetic data provides evidence for a causal link between activation of the IL-18 pathway and increased CD/IBD susceptibility in humans.

1.1.6 Anti-IL-18 monoclonal antibody (GSK1070806)

GSK1070806 is a specific humanised IgG1 antibody that binds to human IL- 18 with high affinity (KD = 30.3pM). GSK1070806 cross reacts with rhesus/cynomolgus IL IL-18 with high affinity (KD = 108 pM), but not mouse, rat, dog or pig IL-18. Biacore analysis and ELISA binding assays have shown that binding of GSK1070806 to IL-18 does not interfere with the binding of the natural endogenous inhibitor (IL-18BP) to IL-18.

1.1.7 Previous Human Experience with GSK1070806

Recognition that IL-18 may play an important role in various diseases has led to the development of investigational therapies targeting IL-18 or its signalling pathways, which have been well tolerated in healthy volunteers and patients with RA, Type 2 diabetes, and plaque psoriasis (Tak, Bacchi et al. 2006) (Mistry, Reid et al. 2014).

To date GSK1070806 has been administered to 89 participants.

In volunteers, single intravenous infusion doses of the anti-IL-18 monoclonal antibody, GSK1070806, were well tolerated in both healthy and obese participants (NCT01035645). No differences in infections, immune system disorders or haematological abnormalities were observed following single intravenous GSK1070806 infusions up to 10 mg/kg in 57 participants when compared with placebo. Four participants had serious adverse events (SAEs) (head injury, mild pericarditis (placebo group), kidney stones, and pneumothorax) that were all considered unrelated to study treatment by the Investigator (Mistry, Reid et al. 2014).

GSK1070806 was also evaluated in patients with type 2 diabetes (NCT01648153) (McKie, Reid et al. 2016), in which in two cohorts two repeat doses of GSK1070806 (0.25 and 5 mg/kg), administered 28 days apart, were well-tolerated in 25 patients when compared with placebo. The most frequently reported adverse event (AE) was nasopharyngitis which occurred in 11 participants. Headache, diarrhoea and hypertension were the second most frequently reported AEs, which occurred in 5 participants each. None of the reported AEs was considered related to GSK1070806. The most frequently reported MedDRA system organ class was 'Infections and Infestations'.

Single administration of 3mg/kg in 7 patients (followed by 10mg/kg after interim analysis) GSK1070806 is also being evaluated in an on-going Phase 2 single arm open label study for the prevention of Delayed Graft Function in Adult participants after renal transplantation(NCT02723786).

1.1.8 Patient Population Specific Information

Conflicting roles of IL-18 in gut mucosal protection have been reported in the literature (based on murine experiments). Patients will therefore undergo endoscopy prior to dosing and at 12 weeks. Endoscopy at screening will enable a visual assessment of the gut mucosa and any worsening of disease can be identified and treated accordingly using standard of care (SOC). The exclusion of patients with deep penetrating complications such as fistulae, plus the inclusion of a daily diary (diarrhoea and abdominal pain) in the trial should aid in the early identification of any worsening of symptoms.

For further information relating to GSK1070806 please refer to the current Investigator Brochure.

1.2 Trial Rationale

1.2.1 Justification for patient population

Despite the approval of a number of aTNFα therapies, vedolizumab and ustekinumab in CD, there is still a significant unmet need for effective therapies for the induction of clinical and endoscopic remission in moderate to severely active CD. The addition of a new biologic with a different mechanism of action will allow greater flexibility in treatment regimens and potentially combination therapy. An anti-IL-18 antibody is hypothesised to benefit patients with CD by a number of mechanisms including reduction of IL-18 drive to T cell differentiation and proliferation and inhibition of IFN-γ production.

The purpose of this trial is to investigate the safety and tolerability of GSK1070806 administered intravenously once on Day 1 for the treatment of patients with moderate to severely active CD as defined by CDAI and confirmed by endoscopy. Clinical activity will be measured using the CDAI, Patient Reported Outcome (PRO) of diarrhoea and abdominal pain, and by direct assessment of inflammation in the colon and terminal ileum using endoscopy and Simple Endoscopic Score for CD (SES-CD). Changes in faecal biomarkers of disease and biomarkers of systemic inflammatory status shall also be assessed.

One of the further key aims of this trial is to gain a better understanding of the molecular pathways through which GSK1070806 achieves a therapeutic benefit in CD. To enable this assessment, gut mucosal biopsies shall be taken pre-dose and at 12-weeks post-dose and will be evaluated/analysed by staff at the University of Birmingham (UoB) Institute of Translational Medicine (ITM) stratified medicine laboratory and GlaxoSmithKline(GSK).

1.2.2 Justification for design

The proposed trial will be a randomised, double-blind, placebo-controlled, trial to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and clinical activity of single intravenous infusion of GSK1070806 in patients with moderate-to-severe active CD.

A placebo controlled design is chosen as the most sensitive for determining effect size and benefit: risk profile of GSK1070806. Since subjects are allowed to continue with certain protocol-defined CD maintenance medications in stable doses, many will, in fact, be receiving some treatment over and above placebo making this more acceptable to both physicians and patients.

1.2.3 Choice of treatment

Single induction dosing of GSK1070806 given intravenously at a dose of 10 mg/kg is proposed for the trial.

A wide range of doses of GSK1070806 were investigated in the clinic so far;

- Single dose of GSK1070806 from 0.008 mg/kg up to 10 mg/kg in healthy volunteers and from 0.25 mg/kg to 3 mg/kg in obese participants;
- Two repeat doses of either 0.25 or 5 mg/kg 28 days apart in patients with type2 diabetes
- Single dose of 3 mg/kg in the renal transplant study.

These doses have been well tolerated with an acceptable safety profile.

As targeting IL-18 in CD patients is an unprecedented mechanism, a dose of 10 mg/kg has been selected to fully test the mechanism of action. This dose is predicted to maximise pharmacological and clinical effects, based on the ex-vivo pharmacodynamics effects that were observed in the whole blood stimulation assay during the first treatment in human (FTIH) trial in healthy and obese participants (NCT01035645), while also taking into account the change in the population studied. Maximum effect was observed up to day 56 in particular on IFN-γ with no clear differentiation between 1 and 3 mg/kg in healthy volunteers. Suppression of IL-18 in plasma was achieved at significantly lower doses, with 99.9% occupancy sustained for 90 days at a dose of 0.3mg/kg in the FTIH study.

Simulations using a physiologically based pharmacokinetic model based on the two pore hypothesis predict that a dose of 10 mg/kg is required to maintain >99% IL-18 suppression in the gut interstitium for 90 days, while >90% suppression can be achieved with a dose of 1 mg/kg.

2. OBJECTIVES AND OUTCOME MEASURES

2.1 Primary Objective

To evaluate the safety and tolerability of single dose intravenous (IV) administrations of GSK1070806 in patients with moderate to severe Crohn's disease.

2.2 Primary Outcome Measure

Safety and tolerability parameters include: adverse events, serious adverse, clinical laboratory tests, electrocardiograms, and vital signs. Frequency, type and severity of infections.

2.3 Secondary Objectives

1. To evaluate the clinical activity of single dose IV administrations of GSK1070806 in patients with moderate to severe CD.

2. To evaluate the serum pharmacokinetics (PK) following single dose IV administrations of GSK1070806 in patients with moderate to severe CD.

3. To evaluate the proportion of patients with moderate to severe Crohn's disease achieving clinical remission following single dose IV administrations of GSK1070806.

4. Time to clinical response following single dose IV administrations of GSK1070806 in patients with moderate to severe CD.

5. To evaluate the effect of GSK1070806 on established biomarkers of disease in patients with moderate to severe Crohn's disease.

6. To evaluate the potential of anti-GSK1070806 antibody formation following administration of GSK1070806 in patients with moderate to severe CD.

2.4 Key Secondary Outcome Measure

CDAI score over time (refer to Schedule of Events for assessment times).

2.5 Further Secondary Outcome Measures (Non-Hierarchical)

1. Serum concentrations of GSK1070806 over time and derived PK parameters if feasible AUC(0-τ), Cmax, Tmax and t½.

2. Abdominal pain (AP) over time (refer to Schedule of Events for assessment times).

3. Stool frequency (SF) over time (refer to Schedule of Events for assessment times).

4. Post-treatment (w12) SES-CD endoscopic score.

5. Proportion of patients in clinical remission defined as average daily Stool Frequency $\leq$ 2.8 and /or average daily Abdominal pain $\leq$ 1 and CDAI <150.

6. Kinetics of induction of clinical response defined as a ≥ 70 point decrease from baseline CDAI score (or score ≤ 150).

7. Serum C-reactive protein over time (refer to Schedule of Events for assessment times).

8. Faecal calprotectin over time (refer to Schedule of Events for assessment times).

9. Incidence and titers of serum of anti-GSK1070806 antibodies before and after GSK1070806 administration.

2.6 Exploratory Objectives (Non-Hierarchical)

1. To evaluate the pharmacodynamics (PD) effects of GSK1070806 in participants with Crohn's disease.

2. To evaluate the proportion of patients with Crohn's disease achieving endoscopic response following single dose IV administration of GSK1070806 at week 12.

3. To identify genetic variations associated with drug response and disease activity in Crohn's and related diseases.

2.7 Exploratory Outcome Measures

1. Gut biopsy tissue and/or systemic biomarkers, which may include but not limited to:
   - GSK1070806 and IL-18
   - Inflammatory biomarkers such as but not limited to, IP10, IFN-γ, CRP, IL-6
   - Composition of immune cell populations
   - Gene expression profiles by transcriptomic analysis

2. Proportion of patients in endoscopic response by SES-CD ≥ 50% reduction post baseline.

3. Genetic variations in host deoxyribonucleic acid (DNA) from blood will be analysed to determine their relationship with response to treatment with GSK1070806 and related diseases

3. TRIAL DESIGN

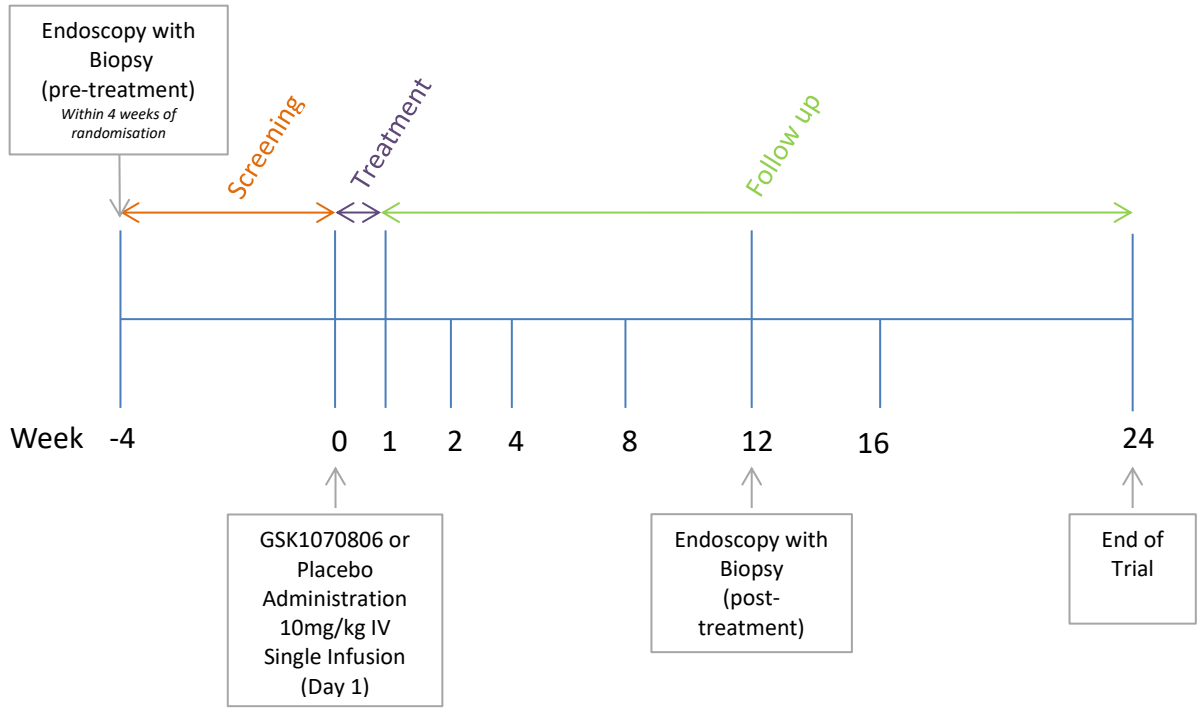

Figure 2 Trial Schema

3.1 Discussion of Design

The proposed study will be a randomised, double blind, placebo-controlled trial to investigate the safety, tolerability, clinical activity, pharmacokinetics and pharmacodynamics of single intravenous infusion (one dose on Day 1) of GSK1070806 or placebo, in patients with active, moderate to severe CD. The primary objective of the study is to assess the safety and tolerability of a single dose IV administration of GSK1070806. A secondary objective will be to evaluate the effect of GSK1070806 in change of CDAI over time. Further secondary endpoints will include assessment of endoscopic response in patients at week 12. (Other secondary endpoints are detailed in Section 2.3).

21 patients will be recruited with randomisation of 2:1 active drug to placebo in multiple centres in the UK.

An initial screening shall take place to identify patients diagnosed with CD for at least 3 months prior to screening and colonoscopic confirmation of active mucosal inflammation (SES-CD excluding narrowed component ≥6; or in patients with isolated ileal disease ≥4).

Patients who do not have colonoscopically demonstrated mucosal inflammation will be excluded even if they have MRI evidence of CD more proximally in the small intestine. Colonoscopic SES-CD criteria has to be fulfilled within 28 days prior to dosing.

The induction of clinical activity will be assessed at week 12 by CDAI score, average clinical SF and/or AP scores as well as by colonoscopic assessment of baseline photographic images and/or video recordings and week 12 photographic images and/or video recordings.

The first 5 patients randomised into the trial will be dosed at least 3 days apart. At the interim analysis time point, a safety decision will be taken on the subsequent recruitment and patient spacing out strategy.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the trial design requirements, including those specified in the Schedule of Events Table, are essential.

4. ELIGIBILITY

4.1 Inclusion Criteria

A patient will be eligible for inclusion in this study only if all of the following criteria apply:

1. Written informed consent prior to any of the screening procedures including discontinuation of prohibited medications. (see Section 7.11 for additional information)

2. Patients must have been diagnosed with Crohn's disease at least 3 months prior to Screening Visit 1

3. Patients are required to have endoscopic evidence of active Crohn's disease at Baseline defined by endoscopic appearance: SES-CD excluding the narrowed component of ≥ 6 (or ≥4 for patients with isolated ileal disease).

4. AST and ALT ≤ 2xULN; alkaline phosphatase and bilirubin ≤ 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

5. Male or female participants aged ≥16 years (up to 80 years)

Male participants:

6. A male participant must agree to use contraception as detailed in Appendix 5 of this protocol for at least 180 days post-dose of study medication and refrain from donating sperm during this period.

Female participants:

7. If the patient is breastfeeding, she must agree to stop breastfeeding once randomised into the trial. [1]
8. A patient is eligible to participate if she is not pregnant.
9. A woman of childbearing potential (WOCBP) is eligible only if she meets at least one of the following conditions:
   i. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrolment.
   ii. Agrees to follow the contraceptive guidance in Appendix 5 for at least 180 days post-dose of trial medication. If a hormonal method of birth control is selected from the list in Appendix 5 then patients must have been using these methods at least 1 month prior to GSK1070806 administration, or be abstinent, or utilise a condom as a method of contraception until the selected hormonal method has been in place for the 28 day period.
10. A woman who is not of childbearing potential is eligible only if she meets at least one of the following conditions:
    i. Premenopausal female with documented hysterectomy
    ii Premenopausal female with documented bilateral salpingectomy or oophorectomy
    iii. Postmenopausal female defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement

[1] A female patient who is breastfeeding may be screened. If randomised into the trial, this patient must agree to stop breastfeeding. Patients who are screened but ineligible can continue breastfeeding.

therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Note: Documentation can come from the site personnel's review of participant's medical records, medical examination, or medical history assessment.

The Investigator is responsible for ensuring that participants understand how to properly use the indicated methods of contraception by providing counsel directly or by referring participants to health care professionals with expertise in this area.

4.2 Exclusion Criteria

A participant will not be eligible for inclusion in this trial if any of the following criteria apply:

1. Diagnosis of ulcerative or indeterminate colitis

Crohn's Disease complications:

2. Evidence of an infected abscess by MRI or other examinations

3. Bowel surgery other than appendectomy within 12 weeks prior to screen and/or has planned surgery or deemed likely to need surgery for CD during the trial period

4. Participants with ileostomies, colostomies or rectal pouches

5. Participants with a bowel stricture that is fixed

6. Participants with evidence of short bowel syndrome

7. Participants requiring enteral or parenteral feeding

8. Deep penetrating ulcers at endoscopy thought to be at risk for perforation

Viral and bacterial infections:

9. Presence of Hepatitis B surface antigen (HBsAg*), (confirmed by Hepatitis B surface antigen test – within 12 months of randomisation)* core antigen (HBcAg) or surface antibody (HBsAb), positive Hepatitis C (qualitative enzyme immunoassay) test result

10. Known varicella, herpes zoster, or other severe viral infection within 6 weeks of randomisation

11. The participant has a history of tuberculosis (TB) disease or latent TB infection, in the absence of documented adequate therapy for same.

12. Positive screening test for TB (including T-SPOT.TB TB test), unless respiratory review confirms false positive test results

13. History of uncontrolled bacterial or fungal infection requiring intravenous antibiotics

14. Positive immunoassay for *Clostridium difficile* toxin and other enteric pathogens

Other exclusion criteria:

15. Cardiology assessment/co-morbidity defined as:

i. QTc >450 msec (480msec for those with Bundle Branch Block) and/or

ii. either QTcb or QTcf, machine or manual overread, males or females. The QT correction formula used to determine exclusion and discontinuation should be the same throughout the trial and/or

iii. based on single QTc value (average of triplicate readings) of ECG obtained over a brief recording period

16. The participant has congenital or acquired immunodeficiency, or a history of chronic or recurrent opportunistic infections

17. The participant has current evidence of, or has been treated for a malignancy within the past five years (other than localised basal cell, squamous cell skin cancer, cervical dysplasia, or cancer in situ that has been resected)

18. Use of any investigational drug within 30 days prior to screening, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer)

19. Participant has received live, attenuated or recombinant vaccine(s) within 2 months of randomisation or will require vaccination within 3 months of trial drug infusion

20. Any patients that are receiving medication(s) detailed in Section 7.11.2 of the trial protocol, will not be eligible for randomisation into the trial

5. SCREENING AND CONSENT

5.1 Informed Consent

It is the responsibility of the Principal Investigator (PI) or Co-investigators (detailed in the site delegation log) to obtain written informed consent for each patient prior to performing any trial related procedure. A Patient Information Sheet (PIS) is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time without any detrimental effect on their standard care. The patient should be given ample time (e.g. 24 hrs) to read the PIS and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient expresses an interest in participating in the trial they should be asked to sign and date the latest version of the Informed Consent Form (ICF). The PI or Co-investigator (detailed in the site delegation log) must then sign and date the form. A copy of the ICF should be given to the patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the patient is entered into the trial the patient's trial number should be entered on the ICF maintained in the ISF. In addition, if the patient has given explicit consent a copy of the signed Informed Consent Form must be sent in the post to the Trials Office for review.

Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the PIS and ICF. Throughout the trial the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to reconsent the patient in which case the process above should be followed and the patient's right to withdraw from the trial respected.

Electronic copies of the PIS and ICF are available from the CDAID Trials Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded on the Patient Screening/Enrolment Log and with the patient's prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

5.1.1 Pharmacogenomics collection consent

The trial includes the collection of a genetic blood sample as this sample will be used to analyse the patients DNA. This sample will be collected using a separate PIS (supplementary sheet) and ICF, in addition to the main PIS and ICF.

Patients can be provided with the information at any time after they have indicated that they would like to take part in the trial (ideally as part of the initial consent process). As this component of the trial is **OPTIONAL**, an individual patients decision on whether he/she would like to participate/provide an additional blood sample for pharmacogenomics analysis will not affect his/her ability to participate in the main trial.

Details of the initial and subsequent pharmacogenomics sample collection consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the pharmacogenomics PIS and ICF.

5.2 Screening – assessments and procedures

Prior to the formal screening process, patients will be required to provide written informed consent BEFORE any trial related procedure can be performed, as detailed in Section 5.1. It is anticipated that the majority of the screening process (except baseline colonoscopy procedure) will be completed at the same visit (i.e. all blood tests performed on the same day).
Each patient who has consented, and enters the screening process, will be allocated a screening number. Please use this number in any correspondence with the CDAID Trial Office. If the patient is eligible for the trial, the screening number should be completed on the Randomisation Form. A trial number will be allocated once the patient is randomised.

The screening process consists of two visits which are detailed below:

5.2.1 Screening Visit 1 (within 4 weeks of Randomisation)

- Informed Consent
- Demographic (age , gender, ethnicity)
- Medical and Crohn's history including any current symptoms any pre-existing conditions
- Evaluation of Inclusion / Exclusion Criteria
- Clinical assessment
- Vital signs (heart rate, blood pressure, body temperature (^{o}C), respiratory rate, (all taken in supine position) weight (kg), height (cm))
- Physical exam to be performed by clinician
- Serology screening
- *Clostridium Difficile* Testing
- Pregnancy test[1] (for female's patients of childbearing potential only)
- 12-lead electrocardiogram (ECG)
- TB screening - T-SPOT.TB test (see Appendix 4 – T-Spot.TB)
- Biochemistry bloods (see 7.8.1)
- Haematology bloods (see 7.8.1)
- Endoscopy with Biopsy[2, 3] with photographic images and/or video recordings
- Blood sample (serum) for additional research
- Adverse Event/SAE reporting
- Record of patient concomitant medication (only record con-meds that are currently being taken by the patient)
- CDAI assessment
- Patient Daily Diary

[1] To be performed within 28 days of expected day 1 of treatment (both urine or serum pregnancy tests are acceptable)
[2] To include biopsy collection (see Section 7.9)
[3] Can be performed at any time point within the screening period

5.2.2 Screening Visit 2 (within 1 week of Visit 3)

- Clinical assessment
- Vital signs (heart rate, blood pressure, temperature, respiratory rate)
- Physical exam to be performed by clinician
- Influenza Risk Screening (within 7 days of treatment)
- Biochemistry bloods (see 7.8.1)

- Haematology bloods (see 7.8.1)
- Endoscopy with Biopsy[1, 2] with photographic images and/or video recordings
- CDAI assessment
- Patient Daily Diary
- Adverse event data collection(including current symptom and any conditions since Visit 1
- Record of patient concomitant medication
- Evaluation of the inclusion/exclusion criteria
- Faecal calprotectin (patient stool sample)

N.B.: *After screening visit 2 randomisation can be undertaken – see Section 6.1)*

[1] To include biopsy collection (see Section 7.9)
[2] Can be performed at any time point within the screening period

6. TRIAL ENTRY

6.1 Randomisation

After the results of the screening process (Visit 2) are available, and the patient is eligible, they can be randomised with the CDAID Trials Office and given a unique trial number. The following will be verified by the local site PI and/or Co-Investigators before randomising the patient onto the trial:

- Confirmation of all the inclusion criteria – *at the time of Randomisation (Visit 2)*
- Review of all the exclusion criteria– *at the time of Randomisation (Visit 2)*
- Completion of Eligibility Form
- Completion of Randomisation Form

All the above must be completed before proceeding onto patient randomisation.

All patients must be randomised with the CRCTU at the University of Birmingham and their trial number will provided at the end of the Randomisation process.

Randomisation of patients can be achieved by logging on to:

https://www.cancertrials.bham.ac.uk

At this time point, patients will be allocated a unique trial number to preserve patient confidentiality. The schedule for investigations and follow up visits is summarised in Section 7.7 and 7.13

Emergency randomisation is not available in the CDAID trial.

6.1.1 Protocol waivers or exemptions

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the trial design requirements, including those specified in the schedule of events table, the trial protocol are essential and required for trial conduct. Any deviation from protocol procedures should be documented as a protocol deviation on the appropriate case report form (CRF).

7. TREATMENT DETAILS

7.1 Investigational Medicinal Product Preparation

7.1.1 Experimental group

Product name:	GSK1070806
Active Substance	GSK1070806 – Humanised IgG1 antibody
Dosage form:	100 mg/mL injectable solution
Unit dose strength(s)/Dosage level(s):	Single dose of 10 mg/kg
Route of Administration	IV infusion
Dosing instructions:	Dilute into 100 mL sterile IV infusion bag 0.9% Sodium Chloride (details see Pharmacy Manual)

7.1.2 Placebo Controlled group

Product name:	Sodium chloride (0.9%)
Active Substance	Not applicable
Dosage form:	injectable solution
Unit dose strength(s)/Dosage level(s):	100mls
Route of Administration	IV infusion
Dosing instructions:	100 mL sterile IV infusion bag 0.9% Sodium Chloride (details see Pharmacy Manual)

7.2 Dosage Form and Composition

The dosage form and composition of GSK 1070806 is detailed in the Pharmacy Manual.

7.3 Instructions for handling and preparation of Investigational Medicinal Product

A description of the methods and materials required for preparation of GSK1070806 is detailed in the Pharmacy Manual. Trial treatment must be dispensed or administered according to procedures described herein and in the Pharmacy Manual.

Only subjects enrolled in the trial may receive trial treatment. Only authorised site staff may supply or administer trial treatment. All trial treatment must be stored in a secure area with access limited to the Investigator and authorised site staff.

The Investigator is responsible for trial treatment, accountability, reconciliation, and record maintenance. The Investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain trial treatment accountability records throughout the course of the trial. The responsible person(s) will document the amount of trial treatment received from GSK (complete all appropriate procedures relating to the condition of the IMP/trial documentation; temperature logs etc.) and the amount administered to subjects. In addition to any excess stock disposed of in accordance with the local standard operating procedure for IMP disposal. The required accountability unit for this trial will be the vial. Discrepancies are to be reconciled or resolved. Procedures for final disposal of unused trial treatment are listed in the Pharmacy Manual.

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. However, precautions are to be taken to avoid direct skin contact, eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor and/or trial manager. A Material Safety Data Sheet describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from GSK/ Sponsor.

7.4 Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

7.5 Trial Treatment

This clinical trial is a randomised, double-blind, placebo- controlled trial therefore all patients randomised will receive one of the following groups (see Table 1)

Table 1: Treatment groups

Group 1	Control group: treatment with single infusion of inactive treatment (GSK1070806 Placebo)
Group 2	Experimental group: treatment with single infusion (10mg/kg) of active treatment (GSK1070806)

The infusion pump speed should be 80ml/per hour for all the patients with total infusion time of an hour.

7.6 Dose Modification

This clinical trial protocol includes a single infusion of GSK1070806 and therefore no patient dose modifications or dose reductions will be allowed during the trial.

7.7 Treatment Schedule

7.7.1 Treatment Visit 3 (Day 1 – Week 1)

- Clinical assessment
- Vital signs (heart rate, blood pressure, oral body temperature (^{o}C), respiratory rate) taken pre-dose, and at 30 minutes interval during infusion period and repeated at 30 minute intervals for a period of 3 hours post infusion (removal of needle). Weight (kg) to be measured pre-infusion only
- Physical exam to be performed by clinician
- Influenza risk screening (prior to treatment)
- Pregnancy test (for female's patients of childbearing potential only)
- 12-lead ECG pre-infusion and 60 mins post infusion
- Biochemistry bloods (see Section 7.8.8)
- Haematology bloods (see Section 7.8.8)
- Blood serum for PK (pre-infusion sample to be taken within 1 hour of start of infusion, end of infusion sample to be taken within 15 minutes of end of infusion, and one sample taken between 4 hours and 8 hours post infusion start, see Figure 3 Pharmacokinetics sample time points)
- Blood serum for PD (pre-infusion only)
- Bloods for FBC, INR, UE, LFT 2hrs post end of infusion period. See Table 3
- CDAI assessment
- Blood serum for Immunogenicity (pre dose*)* analysis*.*
- Patient Daily Diary
- GSK1070806 / or Matched Placebo infusion
- Faecal calprotectin (patient stool sample) (if available – post infusion – or within 24 hours post infusion)
- Adverse Event/SAE reporting
- Record of patient concomitant medication
- Genetics/pharmacogenomics sample for optional genetic research
- Blood sample (serum) for additional research

For infusion reaction management/concomitant medication associated with GSK1070806 see Section 8.1.1.3 and Section 7.11.

7.7.2 Treatment Visit 3a (Day 2-Week 1)

Treatment visit 3a visit may either be an clinic visit or a telephone visit. The two alternative visit schedules are described below;

7.7.2.1 In person visit – patient attends clinic

- Clinical assessment
- Vital signs (heart rate, blood pressure, oral body temperature (^{o}C), respiratory rate)
- Physical exam to be performed by clinician
- Biochemistry bloods (see Section 7.8.8)
- Haematology bloods (see Section 7.8.8)
- Blood serum for PK (some patients at the Birmingham site may have a 24 hr (post end of infusion) PK if they agree to this)
- Blood serum for PD (some patients at the Birmingham site may have a 24 hr (post end of infusion) PD if they agree to this)
- Patient Daily Diary
- Adverse Event/SAE reporting
- Record of patient concomitant medication

7.7.2.2 Telephone visit - virtual clinic

- Clinical assessment
- Adverse event/SAE reporting
- Record of patient concomitant medication

7.7.3 Treatment compliance

GSK1070806 or matched placebo will be prepared by site in accordance with the pharmacy manual. The allocated treatment will be prepared by suitably qualified pharmacy personnel (detailed one the site delegation log) and labelled with the trial specific label in order to maintain the trial blind. Only the site pharmacy personnel will be unblinded to the trial medication. All other trial personnel within the site will be blind to the allocated treatment for each individual patient. The allotted trial medication will subsequently be stored and be administered intravenously (within a given timeframe) to subject as an infusion at the trial site in accordance with the pharmacy manual and local procedures.

The full and accurate record of drug preparation (batch numbers, and time of preparation, dispensing and time of actual administration) will be maintained within the individual site pharmacy file and subsequent treatment compliance. This information will be provided to the Sponsor upon request and some information will be recorded within the case report form. Full drug accountability records and infusion start/stop times, flow rates, reasons for any interruptions in drug delivery will be maintained by the participating site and some of this information will also be recorded within the case report form.

Please refer to the current CDAID Pharmacy Manual for further information.

7.7.4 Treatment Discontinuation

This clinical trial protocol includes a single infusion of GSK1070806 and therefore the potential for treatment discontinuation only occurs within this single infusion. If an infusion is interrupted, suspended or stopped – a full record of the circumstances, outcomes will be maintained by the participating site within the patient medical records and recorded in the appropriate case report form.

7.7.5 Treatment of Trial Treatment Overdose

For this trial, any dose of GSK1070806 > 10 mg/kg will be considered an overdose.

There are no known antidotes and as such there are no recommend specific treatments for an overdose. In the event of an overdose the Investigator will use clinical judgement in treating the symptoms and should:

1. Contact the CDAID Trial Office and/or designated Clinical Coordinator/ medical advisor immediately

2. Closely monitor the subject for AEs /SAEs and laboratory abnormalities per the Investigator's discretion for at least 24 weeks or twice the length of the anticipated biologic effect of the dose received.

3. Obtain a plasma sample for pharmacokinetic (PK) analysis within 2 days from the date of the trial treatment overdose if requested by the Investigator (determined on a case-by-case basis).

4. Document the quantity of the excess dose in the CRF.

7.7.6 Treatment after the end of the Trial

Patients will not be able to receive any additional infusions of GSK1070806 outside the single infusion of GSK1070806 or matched placebo included in the clinical trial protocol and after completion of the trial. All enrolled patients will be receiving standard of care applicable at site. The individual local site Investigator is responsible for ensuring that considerations has been given to the post-trial care of the patients' medical condition being studied in this trial.

7.8 Assessments

7.8.1 Clinical Assessment

All clinical assessments will be performed by a suitability qualified medical practitioner. The Patient Daily Diary, CDAI score and adverse events will be assessed. When asking patients questions during the examination appropriate care will be taken not to induce bias into any potential response. This is very important when assessing potential adverse events or discussing the treatment. Open ended and non-leading verbal questions will be used where possible i.e.:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.8.2 Vital Signs

All vital signs will be performed by a suitability qualified medical practitioner/research nurse and shall include:

- Heart rate
- Blood Pressure
- Weight (kg)
- Body temperature
- Respiratory Rate

7.8.3 Physical Examination

The need for a physical examination will be determined by the local Investigator according to clinical need. The result of any additional examination will be recorded in the patients' medical notes and appropriate sections of the case report forms.

7.8.4 Serology Screening

The following blood test will be performed within 12 months of the Screening visits in local laboratories at investigative sites.

Table 2 Serology Blood Tests

	Blood test	Primary reason for assessment
Serology	Hepatitis B surface antigen (HBsAg), (confirmed within 12 months of randomisation) or, Core antigen (HBcAg) or, Surface antibody (HBsAb)	Eligibility assessment
	Hepatitis C (qualitative enzyme immunoassay) test result.	Eligibility assessment

7.8.5 Influenza Risk Screening

A review of patients recent medical history will be performed by a suitability qualified medical practitioner/research nurse – specifically related to any current evidence, or history within the last 14 days, of an influenza-like illness as defined by fever (>38°C) and two or more of the following symptoms; cough, sore throat, runny nose, sneezing, limb/joint pain, headache, vomiting/diarrhoea. The Investigator will confirm if the symptoms are related to CD.

7.8.6 Clostridium Difficile Testing

Clostridium Difficile testing will be carried out as per local practice to confirm eligibility.

7.8.7 Pregnancy Test

A pregnancy test should be performed for all women of child bearing potential within 14 days of expected day 1 of treatment (both urine or serum pregnancy tests are acceptable).

7.8.8 Biochemistry and Haematology

The following blood tests will be performed at each visit. Tests used for safety laboratory assessments will be done in local laboratories at investigative sites.

Table 3: Blood Tests

	Blood test	Primary reason for assessment
Biochemistry	Alkaline Phosphatase (ALP)	Safety
	Alanine Transaminase (ALT)	
	Aspartate Transaminase (AST)	
	Albumin	
	Bilirubin	
	Sodium	
	Potassium	
	Urea	
	Creatinine	

	Calcium	
	Total Protein	
	*Estimated Glomerular Filtration Rate (eGFR)	
	C-Reactive Protein	
Haematology	Haemoglobin	Safety
	Platelets	
	Red Blood Cells	
	White Blood Cells	
	Haematocrit	
	Mean Cell Volume	
	Mean Cell Haemoglobin	
	Neutrophils	
	Lymphocytes	
	Monocytes	
	Eosinophils	
	Basophils	
	INR	
	APTT Ratio	

*- calculated by Cockcroft-Gault equation or alternative as per institutional practice – Appendix 7

Only in the event of suspected Cytokine release syndrome adverse event: the following blood tests will need to be performed to confirm adverse event. These tests are considered as part of standard care when investigating this specific syndrome. Please see the Laboratory Manual for further details.

Table 4 Immunology blood tests

Immunology	TNF- α	Safety
	IFN-ϒ	
	IL-6	

7.8.9 Pharmacokinetics and Pharmacodynamics Sampling

Samples for PK and PD analysis will be taken at the following visits and time points outlined in Table 4, Table 5 and Figure 3 below.

Table 5 Pharmacokinetic sampling

Visit Number	Taken	Time point (if applicable)
3	**X**	Pre-dose End of infusion 4-8h post infusion start
3a	**X**	To be taken if patient attends
4	**X**	
5	**X**	
6	**X**	
7	**X**	
8	**X**	
9		
10	**X**	

Table 6 Pharmacodynamics sampling

Visit Number	Taken	Time point (if applicable)
3	**X**	Pre-dose
3a	**X**	To be taken if patient attends
4	**X**	
5	**X**	
6	**X**	
7	**X**	
8	**X**	
9	**X**	
10	**X**	

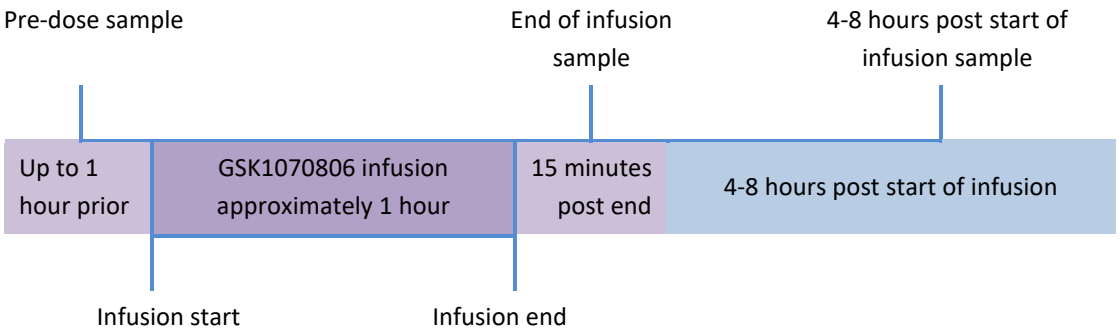

Figure 3 Pharmacokinetics sample time points

Concentrations of GSK1070806 will be determined in serum samples using the currently approved bioanalytical methodology at Covance Laboratories (Harrogate UK).

7.8.10 Endoscopy with Biopsy

Endoscopies will be performed during screening and at week 12 after dosing. This is standard of care procedure in CD. Colonoscopic assessment after drug administration to check endoscopic response is also often part of standard clinical practice. Up to 12 biopsies will be taken from the lesioned and non-lesioned region of the tissue at the pre-dose visit and at week 12 post treatment with GSK1070806. Endoscopies will include the capture of photographic images and/or video recordings. All endoscopies will be reviewed by a central reviewer who is blinded.

7.8.11 Crohn's Disease Activity Index

The following address was correct when the version of the protocol was approved:
http://www.igibdscores.it/en/score-cdai.html

7.8.12 Immunogenicity Blood Sample

For all patients, blood samples for the determination of Anti-drug Antibodies (ADA) will be collected as is scheduled in the Schedule of Events table. Please see the Laboratory Manual for further information.

7.8.13 Patient Daily Diary

The Patient Daily Diary will be given to the patient at every visit and reviewed by the Investigator.

7.8.14 Faecal Calprotectin Stool Samples

A faecal sample will be taken to measure faecal calprotectin at the time points indicated in Schedule of Events section. Information on sample processing will be provided in the Laboratory Manual.

7.8.15 Genetics/Pharmacogenomics Sample (for optional genetic research)

A 6ml blood sample for DNA isolation will be collected from patients who have consented to participate in the genetic analysis component of the trial. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the trial.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the patient. An additional signed ICF will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 8 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

7.8.16 Additional Research Samples (Biomarkers)

Biomarker(s)/Pharmacodynamics Biomarker

For all patients, blood serum samples will be collected as is scheduled in the Schedule of Events table. Please see the Laboratory Manual for further information.

Novel disease associated candidate biomarkers and those subsequently discovered as a response to the action of associated with action of GSK1070806 may be identified by application of

- gene expression analysis, which may be conducted on the blood and/or colon tissue biopsies RNA-sequencing and/or alternative equivalent technologies. This facilitates the measurement of relative abundances of RNA species resulting in a transcriptomic profile of each blood and/or tissue sample
- analysis of soluble inflammatory mediators in the blood including but not limited to, pro-inflammatory and anti-inflammatory cytokines and chemokines

Table 7 : Immunology Tests

Immunology	CXCL-10	Exploratory endpoints
	IFN-ϒ	
	CRP	
	IL-6	
	IL-18	

In relation to Immunology based testing, individual markers maybe evaluated using multiple sample types see Table **8** for summary.

Table 8 Immunology blood tests

Immunology	TNF- α	Safety
	IFN-ϒ	
	IL-6	

7.8.17 Liver Chemistry Management

Since participants will receive a single dose of trial medication, there are no liver-specific stopping criteria as such (although opportunities for an independent committee to review general safety data and, if necessary, advise the trial be stopped are detailed in Section 12.6). In the event of liver parameters deviating from the thresholds described in Appendix 6, follow instructions in that section.

Liver chemistry increased monitoring criteria have been designed to assure subject safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

7.9 Sample Collection (Tissue, Blood and Stool samples)

7.9.1 Tissue sample collection Formalin fixed and samples for gene expression analysis

Up to 12 biopsies will be taken from the lesioned and non-lesioned region of the tissue at the pre-dose visit and at Visit 8 (week 12) post treatment with GSK1070806. Tissue samples will be divided accordingly for histological assessment and gene expression analysis as feasibility dictates. A variety of techniques including immunohistochemistry and quantitative polymerase chain reaction may be used. Details of biopsy sample collection processing, storage and shipping procedures are provided in the Laboratory Manual.
Samples for paraffin embedding will be immediately placed in 10% neutral buffered formalin. Samples will then be shipped within 48 hours of collection to the Exploratory Biomarker Assay Laboratory at GSK (Collegeville, PA, USA) in accordance with the Laboratory Manual.

Samples for gene expression analysis will be immediately placed in 5ml tube containing RNA later. Specific sample collection kits, shipping containers, and airway bills and associated courier service will be provided specifically for this purpose by GSK.

7.9.2 Biopsy collection/colonoscopy known procedure related risks

Endoscopy will be performed during screening and at week 12 after dosing. This is standard of care procedure in CD. Colonoscopic assessment after drug administration to check endoscopic response is also often part of standard clinical practice. A colonoscopy is usually safe but in rare cases it can cause harm to the bowel. About 1 person in every 400 has bleeding after their colonoscopy but it is usually easy to stop. Bleeding is more common if a polyp is removed, but rare if biopsies are taken. Rarely, the bleeding is more difficult to stop and means that the person needs to be admitted to hospital. This happens to about 1 in every 2000 people having a colonoscopy. Even more rarely, colonoscopy can cause a small tear (perforation) in the bowel. This happens to about 1 in every 2500 people having a colonoscopy. If a patient received sedation for colonoscopy, hypoxia may occur rarely, but patients are constantly under monitoring.

7.9.3 Blood samples

7.9.3.1 Pharmacokinetic and pharmacodynamics samples

For all patients, blood samples for the determination of GSK1070806 serum levels will be collected as is scheduled in the Schedule of Events table / Section 7.8.9 of study protocol. Please see the latest version of the Laboratory Manual for further information.

7.9.3.2 Safety assessment samples

Samples will be taken for both Haematology and Biochemistry testing (see Section 7.8.8).
These samples will be processed in the local hospital laboratory as per standard practice. This information will be recorded in the appropriate sections of the case report form and individual patient's medical records.

All safety assessment results (including but not limited to blood tests) will be reviewed by the local medical team and acted on in accordance with the local standard practice. Any corrective / clinical action required in relation to any of these safety tests will be documented in the patients' medical records as well as the appropriate section of the case report form.

7.10 Supportive Treatment

The risk of infusion reactions to GSK1070806 is judged by both GSK and the study sponsor to be low based on previous clinical experience.

Due to the current relatively low numbers of patients exposed to the study drug, the theoretical risk of individual patient drug infusion reactions remains, it is for this reason that the following precautions will be undertaken;

1. Investigators/site personnel will be made aware of the risk of hypersensitivity reactions; which may present as an infusion reaction, and will monitor patient closely for a minimum of 3 hours post END of INFUSION

2. Investigational product will administered by the Investigator/site personnel prepared to manage infusion reactions and anaphylaxis, following their standard practice to manage any untoward infusion reactions noted during or after the infusion period.

3. For subjects with a history of allergies (allergic responses to food, drugs, insects, or a history of urticaria), chlorphenamine or equivalent (12.5-50 mg based on clinical judgement) or equivalent and paracetamol maybe administered prophylactically prior to dosing. Antihistamine H2-receptor antagonists (e.g. ranitidine) are also permitted.

7.11 Concomitant Medication

7.11.1 Permitted Concomitant Medications

The pharmaceutical/ trade name, dose, route of administration, indication and start/ stop date of each medication the patient takes during the trial will be recorded. New medications or changes to current medications during the trial will also be recorded. Permitted concomitant medications for participants are as follows:

1. Oral Corticosteroids: For participants receiving prednisone, or equivalent, the dose must be ≤20mg/day for ≥4 weeks prior to screening and planned to remain stable for the duration of the trial. For participants receiving budesonide the dose must be ≤6mg/day for ≥4 weeks prior to screening and planned to remain stable for the duration of the study

2. Immunosuppressant and other CD medications: For participants receiving azathioprine, methotrexate, or 6-mercaptopurine for CD, the dose must be stable for >8 weeks prior to screening and planned to remain stable for the duration of the study. For participants receiving methotrexate or 5-aminosalicyclic acid for CD, the dose must be stable for >4 weeks prior to screening and planned to remain stable for the duration of the study.

3. All other medications including over-the-counter medicines, supplements, vitamins and herbal remedies that each participant is taking at the time of consent will be permitted and recorded.

If there is adequate documentation of an undetectable drug level measured by a commercially available assay for any of the approved biologics (infliximab {Remicade}, adalimumab {Humira}, vedolizumab {Entyvio} ustekinumab {Stelara} , there is no minimum washout prior to Baseline. However in the absence of adequate documentation of undetectable drug levels, a washout period of 8 weeks will be necessary between the last dose of infliximab, adalimumab, vedolizumab and baseline. For ustekinumab the washout period will be 12 weeks.

7.11.2 Prohibited Medications and Non-drug Therapies

If any Subjects who start prohibited medications or therapies at any time during the trial, these individual patients circumstances should be discussed with the trial team (Sponsor- clinical coordinator). As the trial only includes a single dose of GSK1070806 is administered on Day 1, trial subjects should continue with the study assessments and be closely followed up for safety.

The following medications and therapies are prohibited at any time during the trial;

1. Use of other investigational agents (biologic or non-biologic, or non-drug therapy; investigational applies to any drug not approved/licensed for use in the country in which it is used).

2. Use of parenteral glucocorticoids within 4 weeks prior to randomisation.

3. Use of cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil within 4 weeks prior to start of therapy

4. Use of intravenous antibiotics within 2 weeks prior to start of therapy

5. Prior use/exposure to aTNF or vedolizumab is allowed but this therapy should have been discontinued a minimum of 8 weeks (last dose given) before randomisation. If there is adequate documentation of an undetectable drug level measured by a commercially available assay, there is no minimum washout prior to Baseline

6. Prior use/exposure to ustekinumab is allowed but this therapy should have been discontinued a minimum of 12 weeks (last dose given) before randomisation. If there is adequate documentation of an undetectable drug level measured by a commercially available assay, there is no minimum washout prior to Baseline

7.11.3 Vaccines

Live, attenuated or recombinant vaccines are not permitted 60 days prior to GSK1070806 administration or within 90 days of treatment with GSK1070806. Typical examples of excluded vaccinations include *(but not limited to)*:

- Nasal flu vaccines - Fluenz Tetra ™
- Yellow fever vaccine – commonly required for travel (https://www.cdc.gov/yellowfever/vaccine/index.html)

In the NHS -UK there is a well-defined vaccination program, further details can be found here:

http://www.nhs.uk/Conditions/vaccinations/Pages/vaccination-schedule-age-checklist.aspx

Please refer to the individual vaccination summary of product characteristics (SmPC) for additional information and/or contact the Trials Office clinical coordinator for additional advice.

7.12 Contraception and Pregnancy

All sexually active women of childbearing potential must agree to use a highly effective method of contraception from the Screening Visit (Visit 1) throughout the study period and for 180 days following the last dose of trial drug. If using hormonal agents the same method must have been used for at least 1 month before study dosing Lactating women must agree to discontinue breast feeding before trial treatment administration.

For the purposes of this trial, a female subject of childbearing potential is a woman who has not had a hysterectomy, bilateral oophorectomy, or medically-documented ovarian failure. Women ≤ 50 years of age with amenorrhea of any duration will be considered to be of childbearing potential.

Men, if not vasectomised, must agree to use barrier contraception (condom plus spermicide) during heterosexual intercourse from screening through to study completion and for 180 days from the last dose of study investigational medicinal product.

Refer to 8.1.1.6 of Study Protocol if a pregnancy is reported, either that of a female participant, or the partner of a male participant.

7.13 Patient Follow Up

7.13.1 Follow-up Visit 4 (Day 7 +/- 3 days. Week 1)

- Clinical assessment

- Vital signs (heart rate, blood pressure, oral body temperature (°C), respiratory rate, (all taken in supine position)
- Biochemistry bloods (see Section 7.8.8)
- Haematology bloods (see Section 7.8.8)
- Pharmacokinetics/Pharmacodynamics
- CDAI
- Patient Daily Diary
- Adverse Event/SAE reporting
- Record of patient concomitant medication
- Blood sample (serum) for additional research

7.13.2 Follow-up Visit 5 (Day 14 +/- 3 days. Week 2)

- Clinical assessment
- Vital signs (heart rate, blood pressure, oral body temperature (°C), respiratory rate, (all taken in supine position)
- 12 lead ECG
- Biochemistry bloods (see Section 7.8.8)
- Haematology bloods (see Section 7.8.8)
- Blood sample (serum) for additional research/Pharmacokinetics/Pharmacodynamics
- CDAI
- Patient Daily Diary
- Adverse Event/SAE reporting
- Record of patient concomitant medication

7.13.3 Follow-up Visit 6 (Day 28 +/- 3 days. Week 4)

- Clinical assessment
- Vital signs (heart rate, blood pressure, oral body temperature (°C), respiratory rate, (all taken in supine position)
- Physical examination
- Pregnancy test
- Biochemistry bloods (see Section 7.8.8)
- Haematology bloods (see Section 7.8.8)
- Pharmacokinetics/Pharmacodynamics
- CDAI
- Immunogenicity blood sample
- Patient Daily Diary
- Faecal calprotectin (patient stool sample)
- Adverse Event/SAE reporting
- Record of patient concomitant medication
- Blood sample (serum) for additional research

7.13.4 Follow-up Visit 7 (Day 56 +/- 3 days. Week 8)

- Clinical assessment to document clinical events and AEs
- Vital signs (heart rate, blood pressure, oral body temperature (°C), respiratory rate, (all taken in supine position)

- Physical examination
- Biochemistry bloods (see Section 7.8.8)
- Haematology bloods (see Section 7.8.8)
- Pharmacokinetics/Pharmacodynamics
- CDAI
- Immunogenicity blood sample
- Patient Daily Diary
- Adverse Event/SAE reporting
- Record of patient concomitant medication
- Blood sample (serum) for additional research

7.13.5 Follow-up Visit 8 (Day 84 +/- 3 days. Week 12)

- Clinical assessment to document clinical events and AEs
- Vital signs heart rate, blood pressure, oral body temperature (°C), respiratory rate, (all taken in supine position) and weight (kg)
- Physical examination
- Pregnancy test
- Biochemistry bloods (see Section 7.8.8)
- Haematology bloods (see Section 7.8.8)
- Pharmacokinetics/Pharmacodynamics
- Endoscopy with biopsy with photographic images and/or video recordings
- CDAI
- Immunogenicity blood sample
- Patient Daily Diary
- Faecal calprotectin (patient stool sample)
- Adverse Event/SAE reporting
- Record of patient concomitant medication
- Faecal calprotectin
- Blood sample (serum) for additional research

7.13.6 Follow-up Visit 9 (Day 112 +/- 7 days. Week 16)

- Clinical assessment
- Vital signs (heart rate, blood pressure, oral body temperature (°C), respiratory rate, (all taken in supine position)
- Physical examination
- Biochemistry bloods (see Section 7.8.8)
- Haematology bloods (see Section 7.8.8)
- Pharmacodynamics
- CDAI
- Immunogenicity blood sample
- Patient Daily Diary
- Adverse Event/SAE reporting
- Record of patient concomitant medication
- Blood sample (serum) for additional research

7.13.7 Follow-up / End of Study Visit 10 (Day 168 +/- 7 days. Week 24)

- Clinical assessment
- Vital signs (heart rate, blood pressure, oral body temperature (°C), respiratory rate, (all taken in supine position)
- Pregnancy test
- 12 lead ECG
- Biochemistry bloods (see Section 7.8.8)
- Haematology bloods (see Section 7.8.8)
- Pharmacokinetics/Pharmacodynamics
- CDAI
- Immunogenicity blood sample
- Patient Daily Diary
- Faecal calprotectin (patient stool sample)
- Adverse Event/SAE reporting
- Record of patient concomitant medication
- Blood sample (serum) for additional research

NB: All visit dates / times are related to Visit 3 (Day 1). If a visit is delayed for any reason the next visit date will be scheduled in relation to Visit 3. There are no planned treatment delays. If a drug infusion visit cannot be performed within the required timeframe, every attempt should be made to administer the infusion as close as possible to the permitted time window. In extreme situations, protocol-scheduled visits may be cancelled and declared as missed visits at the clinical discretion of the Investigator.

7.14 Patient Withdrawal

The Investigator will make every reasonable effort to keep each patient on treatment. However, if the Investigator removes a patient from the study treatment or if (s)he declines further participation final assessments will be performed, if possible. All the results of the evaluations and observations, together with a description of the reasons for study withdrawal, must be recorded in the CRF.

In the event of a patient's decision to withdraw from the trial, the Investigator must ascertain from which aspects of the trial the patient wishes to withdraw, and record the details on the appropriate CRF. All patients will continue to be followed-up (if they agree), and all information and tissue samples collected up until the point of retraction, will be retained and analysed.

Patients who are removed from treatment due to adverse events (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the CRF.
The following are justifiable reasons for the Investigator to withdraw a patient from study:

- Withdrawal of consent
- Serious violation of the trial protocol (including persistent patient attendance failure and persistent non-compliance)
- Withdrawal by the Investigator for clinical reasons not related to the study drug treatment

The maximum potential sample size, 36, has been calculated to cover patient withdrawals.

8. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 3. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the GSK1070806 Investigator Brochure prior to the transmission of the report to Sponsor.

8.1 Reporting Requirements

8.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 2 for definition) should be reported. Please note this includes abnormal laboratory findings.

8.1.1.1 Pre-existing conditions

Pre-existing conditions will be collected as part of the patients' medical history on the AE Form. However, a pre-existing condition will not be categorised as an AE unless the condition worsens by at least one CTC grade during the trial.

8.1.1.2 Hypersensitivity and Infusion Reactions

Hypersensitivity reactions are defined according to the NCI-CTCAE Version 4.0 definition of allergic reaction / hypersensitivity, as follows:

Grade 1: transient flushing or rash, drug fever <38°C

Grade 2: rash, flushing, urticaria, dyspnoea, drug fever ≥38°C

Grade 3: symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related oedema/angioedema, hypotension

Grade 4: anaphylaxis (a life-threatening event characterized by the rapid onset [often within minutes] of airway obstruction [bronchospasm, stridor, hoarseness], urticaria, and/or hypotension)

8.1.1.3 Infusion Related Reactions

Infusion-related reactions are defined according to the NCI-CTCAE Version 4.0 definition, as follows:

Grade 1: mild, transient reaction, infusion interruption not indicated; intervention not indicated

Grade 2: therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, non-steroidal anti-inflammatory drugs [NSAIDS], narcotics, I.V. fluids); prophylactic medications indicated for ≤24 hours

Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae

Grade 4: Life-threatening consequences; urgent intervention indicated consistent with usual medical practice, selected parenteral medications may be utilised as detailed below. Additional treatments, chosen according to clinical symptoms and local standards, may be utilised at investigator discretion.

8.1.1.4 Liver Related Toxicity : Biochemistry/LFTs

All liver related toxicity will be reported in accordance with Appendix 6 of the trial protocol using the Liver Toxicity Event Form and/or SAE form. Reporting of these events will need to be via the expedited procedure detailed in Section 8.2.1.2.

Medically significant events that need to be reported as an SAE include:

- ALT > 3xULN and total bilirubin[#] ≥ 2xULN (>35% direct),
- or ALT ≥ 3xULN and INR[##] > 1.5

[#] Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT > 3xULN and total bilirubin > 2xULN, then the event is still to be reported as an SAE.

[##] For patients receiving anticoagulants INR testing is not required and the threshold value stated above does not apply.

8.1.1.5 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 2 for definition).

8.1.1.6 Monitoring pregnancies for potential Serious Adverse Events

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. It is important to monitor the outcome of pregnancies (conception occurring within 6 months of study drug administration) of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the CDAID Trials Office as soon as possible. If it is the patient who is pregnant provide outcome data on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant consent must first be obtained and the patient should be given a Pregnancy Release of Information Form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the Pregnancy Release of Information Form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.

8.1.2 Reporting period

The reporting period for AEs will commence from the date of consent, (typically Visit 1: screening visit) and will continue until the follow-up visit (Visit 10: Day 168), The reporting period for SAE will commence from the date of consent, (typically Visit 1: screening visit) and will continue until the end of study (Visit 10: Day 168),

SAEs that are judged to be at least possibly related to the IMP must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

8.1.2.1 Reporting period : Liver related toxicity only

Due to the specifics associated with the expedited reporting requirements (SAE form) associated with liver related toxicity (8.1.1.4) the reporting time window will commence from the date of consent (typically Visit 1:

screening visit) and will continue until the follow-up visit (Visit 10: Day 168) only. Any SAE reports will be followed up until resolution irrespective of duration. All Liver related events will continue to be reported for the duration of the study – only the expedited reporting/use of SAE reporting procedures will be limited to this time window.

8.2 Reporting Procedure

8.2.1 Site

8.2.1.1 Adverse Events

AEs should be reported on an AE Form (and where applicable on an SAE form). An AE form should be completed at each visit and returned to the trials office.

AEs will be reviewed using the common terminology criteria for adverse events (CTCAE), version 4.0 (see appendix 4). Any AEs experienced by the patient but not included in the CTCAE should be graded by an investigator and recorded on the ae form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

8.2.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the relevant section of the ISF.

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet or emailed to the Trials Office using one of the numbers or the email address listed below as soon as possible and no later than 24 hrs after first becoming aware of the event:

To report an SAE by fax, fax the SAE Form with an SAE Fax Cover Sheet to:

0121 371 7246 (primary number)

0121 414 7989 (secondary number)

To report an SAE by email, email a scanned copy of the SAE Form to:

REG@trials.bham.ac.uk

On receipt the CDAID Trials Office will allocate each SAE a unique reference number. This number will either be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site or emailed back to the site as proof of receipt which should be filed with the SAE form in the ISF. If confirmation of receipt is not received within 1 working day please contact the Trials Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the CDAID Trials Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. This should

be done as soon as possible but can be done after returning to the Trial Office so as not to delay initial reporting. The form should then be kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

8.2.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

8.2.2 Trials Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Investigator Brochure) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

8.2.3 Reporting to the Competent Authority and Research Ethics Committee

8.2.3.1 Suspected Unexpected Serious Adverse Reactions

The CDAID Trials Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

Concurrently with the above, the trials office will report all such events to GSK's nominated safety representative (IMP provider).

8.2.3.2 Serious Adverse Reactions

The CDAID Trials Office will report details of all SARs (including SUSARs) to the MHRA and REC annually from the date of the Clinical Trial Authorisation, in the form of a Developmental Safety Update Report Adverse Events.

Details of all AEs will be reported to the MHRA on request.

8.2.3.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.

8.2.3.4 Other safety issues identified during the course of the trial

The MHRA and REC will be notified immediately if a significant safety issue is identified during the course of the trial.

8.2.4 Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

8.2.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

8.2.6 Provider of the medicinal product

All SAEs that have a direct causal relationship *(related to study medication)* to the IMP *(as determined by the clinical coordinator)* will be reported to the provider (GSK) of the Investigational Medicinal Product (GSK1070806) within 24 hrs of evaluation by email or fax.

Nb: For the purposes of clinical evaluation or initial reviews of any SAE events will be assessed as if the participant received active medication (GSK1070806). If after this initial review the events was determined to be related to AND unexpected to the study drug (SUSAR) the patients allocation will be unblinded before expedited reporting a potential SUSAR event to the regulatory authorities and drug manufacturer (GSK)

8.2.7 Code Breaks / Unblinding of trial medication

Code Breaks / Unblinding for Medical Reasons Only (Site staff or other medical personnel located within the Hospital of admission)

When a patient taking part in the CDAID clinical trial is admitted to a hospital for an adverse event, careful consideration should be taken before a code break request is made. The patient should only be unblinded if the identity of the study drug is necessary for patient care. When considering if the patient should be unblinded, reference should be made to the current Investigator Brochure / Reference safety Information for GSK1070806 for drug contra-indications and known adverse event management. Where possible, prior discussion and approval for unblinding of study medication should be sought from one of the CDAID clinical coordinator(s) before a formal request is made. Contact details of the CDAID clinical coordinator(s) can be found in the Trial Personnel section of the protocol.

An unblinding service will be provided by the University Hospitals Birmingham NHS foundation Trust (UHBFT) – pharmacy department.
Details of this service can be found in the ISF and the pharmacy folder or on the individual patient cards. This will allow the local site Investigator, or other medically qualified person, to identify the trial medication (GSK1070806 or matched placebo) for an individual patient in an emergency, 24 hours a day and 365 days of the year. For further information regarding code break procedures please refer to the pharmacy file and the local site investigator file, or contact the CDAID Trial Coordinator.

8.2.7.1 Code Breaks for serious adverse event clinical evaluation by CDAID clinical coordinators *(CDAID Trial office staff only)*

When a serious adverse event is received by the central CDAID trial office (Birmingham UK) is deemed unexpected and possibly, probably or definitely related to the IMP and classified as a Suspected Unexpected Serious Adverse Reaction at first clinical evaluation by one of the CDAID Clinical Coordinator(s), the treatment will be subsequently be unblinded by a member of the study team. The event will then be clinically re-evaluated taking the treatment medication (GSK1070806 or Placebo) information into consideration. The resultant classification of the individual event will be either Unrelated Serious Adverse Event (for patients who received placebo), or Suspected Unexpected Serious Adverse Reaction (SUSAR) and will be reported as per the national clinical trial regulations of in the UK. Neither the patient nor the treating physician will be informed of the results of the code break and the patient will remain on study as per the clinical trial protocol. A record of the unblinding

event will be stored along with the SAE and clinical evaluation in the main study Trial Master File. If it is subsequently deemed necessary to inform the treating clinician, trial site staff or patient of the treatment allocation (for patient safety reasons only), then the patient will come off study treatment and be followed up as per protocol. All code break requests for this study will be made via the University Hospitals Birmingham NHS foundation Trust (UHBFT) – pharmacy department.

9. DATA HANDLING AND RECORD KEEPING

9.1 Data Collection

Data will be collected during this clinical trial. Data will be captured on case report forms (CRF), initially this will be on paper forms. Once the electronic remote data capture (eRDC) systems is implemented sites will be informed and further details provided. The Case Report Form (paper CRF/eRDC) is listed in Table 6 below.

Table 9 : Description of Case Report Forms

Form	Summary of data recorded	Schedule for submission
Eligibility Checklist	Confirmation of eligibility	Faxed at point of randomisation .
Randomisation	Patient details and trial Number	At point of randomisation
Dosing Forms		
GSK1070806 / Placebo Dosing	Dose level, visit, date, dosing details	Within 2 weeks of dosing
Sample Analysis Forms		
Pharmacokinetics	Date, visit, sample collection, time taken	Within 2 weeks of visit
Pharmacodynamics	Date, visit, sample collection, time taken	Within 2 weeks of visit
Pharmacogenomics	Date, visit, sample collection, time taken	Within 2 weeks of visit
Additional Research	Date, visit, sample collection, time taken	Within 2 weeks of visit
Faecal Calprotectin	Date, visit, sample collection, time taken	Within 2 weeks of visit
Assessment Forms		
CDAI	Date, details of CDAI scoring	Within 2 weeks of visit
Endoscopy with Biopsy	Date, details of endoscopy and biopsies	Within 2 weeks of visit
Endoscopic Score for CD Form	Date, visit, details of SES-CD scoring and Rutgeerts Score if applicable	Within 2 weeks of visit
Laboratory	Date, visit, results, clinical significance	Within 2 weeks of visit
ECG	Date, visit, results, interpretation	Within 2 weeks of visit
Demographics	Date, visit, age, gender, ethnicity	Within 2 weeks of visit
Physical Examination	Date, visit, investigations, result	Within 2 weeks of visit
Vital Signs	Date, visit, time, results	Within 2 weeks of visit
Pregnancy Test	Date, visit, result	Within 2 weeks of visit
Clostridium Difficile Testing	Date, visit, results	Within 2 weeks of visit

Form	Summary of data recorded	Schedule for submission
Influenza Risk Screening	Date, visit, assessment, outcome	Within 2 weeks of visit
Serology Screening	Date, visit, results	Within 2 weeks of visit
T-SPOT TB Test	Date, visit, results	Within 2 weeks of visit
Adverse Event	Start and stop dates, grade according to CTCAE version 4.0, causality	Within 2 weeks of each visit
Concomitant Medication	List of concomitant medication	Within 2 weeks of each visit
Ad Hoc Forms		
Treatment Discontinuation	Date, reasons	Immediately after discontinuation of treatment
Serious Adverse Event	Date, details of the SAE	Within 24 hrs of being made aware of the SAE
Liver Toxicity	Date, details of liver toxicity	Within 24 hours of liver toxicity event
Pregnancy Notification	Date, patient details and details of pregnancy	Within 24 hrs of being made aware of the pregnancy
Death	Date, cause of death	Immediately upon notification of death
Deviation	Date, details of deviation l	Immediately upon discovering deviation.
Withdrawal	Date, details of withdrawal	Immediately upon patient withdrawal

The CRF must be completed, signed/dated (for paper CRFs only) and returned to the CDAID Trials Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

Data provided on the Quality of Life Forms will not be captured on source data. This data will be written directly onto the CRF's.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The completed originals should be sent to the CDAID Trials Office and a copy filed in the ISF.

Trial forms may be amended by the CDAID Trials Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

9.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed ICFs, ISFs, Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years after the end of the trial or following the processing of all biological material collected for research, whichever is the later. Do not destroy any documents without prior approval from the CRCTU Archivist.

10. QUALITY MANAGEMENT

The CDAID clinical trial in patients with CD is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU) according to the current guidelines for Good Clinical Practice (GCP). Participating sites will be monitored by CRCTU staff to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki: October 1996 (Appendix 1).

10.1 Site Set-up and Initiation

All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements, Investigator Registration Forms and supply a current CV and GCP to the CDAID Trials Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the CDAID Trials Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The CDAID Trials Office must be informed immediately of any change in the site research team

10.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the CDAID Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the CDAID trial staff access to source documents as requested.

10.3 Central Monitoring

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms (DCFs) requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group and the Trial Steering Committee and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the Research Ethics Committee (REC) and the Medicines for Healthcare products Regulatory Agency (MHRA).

10.4 Recruitment Period

Recruitment in the CDAID trial is estimated to take place over an approximate 12-18 month period. Due to the total number of included patients being set at 21 in total, the maximum recruitment rate required per site will be approximately one /two patients per month. With an estimated 5 new referrals per week at each site, the perception is that this target will be met without difficulty.

10.5 Study Timelines (estimates)

First Patient First Visit (FPFV)	=	November 2018
First Patient First Treatment (FPFT)	=	December 2018
Last Patient Last Treatment (LPLT)	=	December 2019
Last Patient Last Visit (LPLV)	=	May 2020

10.6 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the CDAID Trials Office of any MHRA inspections.

10.7 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the Trials Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

11. END OF TRIAL DEFINITION

The end of trial will be the date of Last Patient Last Visit (LPLV). The CDAID Trials Office will notify the MHRA and REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial. Within the same timeframe a summary clinical trial report will also be provided to the funders of the project (GSK)

After closure of the trial with the MHRA, the Sponsor is no longer required to notify the MHRA and REC of changes of Principal Investigator. However, sites should continue to notify the CDAID Trials Office of changes in Principal Investigator by completing and returning (where required) an Investigator Registration Form together with a current signed and dated CV.

12. STATISTICAL CONSIDERATIONS

The proposed analysis methods are described in Section 12.2. Success of the trial with respect to CDAI score will be defined as concluding that the mean response profile under GSK1070806 is superior (i.e. takes lower values) to that under placebo. This repeated measures analysis will be performed using a regression model. The determination of success is not attached to any particular time-point, but considers outcomes at all times. Secondary outcome measures will provide supportive evidence for the effect of GSK1070806 in patients with active CD.

Up to 21 patients will be randomised to GSK1070806 or placebo in a 2:1 ratio. The sample size has been chosen based on feasibility and practical constraints. This trial was initially conceived using a sample size of at least 30 patients. An indication of the statistical performance of the trial with n=30 using the proposed analysis method is given in Section 12.3.

12.1 Definition of Outcome Measures

Outcome measures are defined in Section 2.

12.2 Analysis of Outcome Measures

12.2.1 Outcomes with Repeated Measures

Outcomes with repeated measures (i.e. those with at least two post-baseline measurements, such as CDAI) will be analysed by hierarchical models. Terms will be included to reflect the effects of assessment time, the interaction of treatment arm with assessment time, and baseline heterogeneity in patients. Inference on the effect of GSK1070806 with respect to an outcome measure will be made by assessing the necessity of the treatment arm variables in modelling the mean outcome paths by trial arm, i.e. investigating if the mean outcome paths diverge. Smooth functions of time will be used in the modelling where they can be justified by the data, but a fully-specified model with estimates of treatment effects in each arm at each time-point will be used if smooth functions are not appropriate. Further model features, such as specialised covariance structures will be considered as necessitated by the data. The estimated mean difference between treatment arms through time will be reported with appropriate estimates of variability. Demonstrations of the proposed analysis method with respect to CDAI are given in Section 12.3.1.

It is our intention to use a Bayesian implementation of the above method to compare CDAI outcomes (and other clinical efficacy outcomes) under GSK1070806 and placebo. We propose to use moderately informative priors on the expected outcomes of patients allocated to placebo. These will be justified using published studies where placebo was used and CDAI was assessed in patients with CD. Priors with mean zero will be used for the mean response to experimental drug in excess of placebo effect. This will allow us to preferentially randomise to the experimental therapy, whilst maintaining statistical performance in a manner consistent with published data.

12.2.2 Other Outcome Types

Outcomes with a baseline measurement and only a single post-baseline measurement can be analysed by ANCOVA, with treatment arm as the explanatory variable, and baseline value as an adjusting covariate if the above model approach is unsuitable.

Dichotomous outcomes (e.g. incidence of adverse events, or response) will be analysed by Fisher's exact test, with treatment arm as the explanatory variable.

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to appropriate standards.

Key pharmacodynamics/biomarker outcome measures (expression of blood or serum and faecal biomarkers, e.g. IFN-γ, CRP, IL6, Calprotectin) and serum level of IP10, total and free IL-18 will be descriptively and/or graphically summarized as appropriate.

The presence or absence of antibodies to GSK1070806 will be descriptively and/or graphically summarised as appropriate to the data.

Full details will be included in the Statistical Analysis Plan.

Analysis of SES-CD will be adjusted to take account of baseline value.

12.3 Justification of Sample Size

The sample size is justified here with respect to the key secondary outcome measure, CDAI score. In a repeated measures study, efficacy may manifest at a variety of assessment times. In the early phase setting, we do not know when efficacy will manifest. Thus, we seek an analysis method that will be flexible enough to detect efficacy, regardless of the time horizon. As such, we demonstrate statistical performance using simulation in a small number of indicative scenarios with differing response profiles. The scenarios are detailed in sections below, and summarised in Table 10. The method of simulating patient CDAI paths is described in Section 12.3.1 and reaching a trial decision in Section 12.3.2.

12.3.1 Simulating CDAI paths for patients in a scenario

1) Baseline values of CDAI score for patients allocated to placebo and GSK1070806 are randomly sampled from a Normal (285, 80^2) distribution. Thus, baseline CDAI scores are centred at 285 and 95% of values are in the approximate interval (125, 445).
2) Vectors of treatment-effects at weeks (0, 2, 4, 8, 12, 16, 24) are selected for placebo, $\lambda_P(t)$, and GSK1070806, $\lambda_E(t)$. These reflect the value of the mean CDAI path through time as a multiple of the baseline value. Values less then 1 show improvement, i.e. falling CDAI scores. The chosen subscripts are *P* for placebo and *E* for experimental treatment.
3) The value at time *t* of the CDAI path for a patient with baseline score y_0 allocated to treatment *A* is

   $$y_0 * \lambda_A(t) + \varepsilon$$

   where ε is a noise term, distributed N(0, 30^2). For instance, if a patient has $y_0 = 300$, is allocated to GSK1070806 with $\lambda_E(t) = 0.9$, and happens to take $\varepsilon = 12$ at time *t*, then for that patient:

   $$y_t = 300 * 0.9 + 12 = 282$$

The mean baseline value and variability of baseline scores were selected to mimic those reported in a recently-published randomised controlled trial (RCT) of CD: (Zhang, Lv et al. 2018). Under the described method, the variability of CDAI scores are driven by the variability of the baseline scores and the noise terms. The variance of the noise, 302, was chosen by trial-and-error so that the overall variability of the CDAI scores approximately matched those at the time horizons reported in [Zhang et al. 2017].

12.3.2 Reaching a trial decision in simulations

In simulations, we analyse outcomes using the model

$$y_{ij} = \alpha + a_i + \beta_j + \gamma_j z_i + \epsilon_{ij}$$

where:

- y_{ij} is the CDAI value of patient *i* at time t_j;
- α is the mean baseline CDAI value across both arms;
- a_i is the random effect for the baseline CDAI score for patient *i*;
- β_j is the fixed placebo effect at time t_j;
- γ_j is the fixed effect of the experimental drug over placebo at time t_j;
- z_i takes the value 1 for patients allocated to GSK1070806, else 0;
- ϵ_{ij} is the noise time for patient *i* at time t_j;
- $a_i \sim N(0, \sigma_a^2)$
- $\epsilon_{ij} \sim N(0, \sigma^2)$

The presence of a treatment effect is formally tested by the hypothesis:

$$\gamma_1 = \gamma_2 = \cdots = \gamma_j = 0$$

The presence of aggregate treatment benefit is tested via the supplemental requirement that:

$$\sum_j \gamma_j < 0$$

We present in the following sections the performance of these combined criteria, fitting mixed effects models by REML using the nlme package in R, interpreting p-values less than 0.05 as being significant.

It should be noted that the analysis method in this section does not reflect exactly our proposal for the trial. As noted above, we propose to use the Bayesian analogue to this method with informative priors on the placebo effects. This extra information should increase the ability of the model to distinguish between the paths by arm, without unduly increasing the false positive rate. Furthermore, we would hope to model the CDAI paths using smooth functions of time (for instance, polynomials). These would require fewer parameters than the saturated model above. This would hopefully improve statistical performance as well.

12.3.3 Scenario 1

In this null scenario, we assume that the placebo effect is positive but very small, and that GSK1070806 is assumed to have no effect on CDAI beyond placebo effect. The values of λP(t) and λE(t) are identical, given in column A of Table 10. The expected change from baseline is shown in column G. A single trial simulation using n1 = 10 placebo paths and n2 = 20 experimental paths is shown in Figure 4. We see that the mean lines are co-located and the confidence intervals largely overlap. This is the null scenario. The probability of approving GSK1070806 in this scenario is approximately 3.1%.

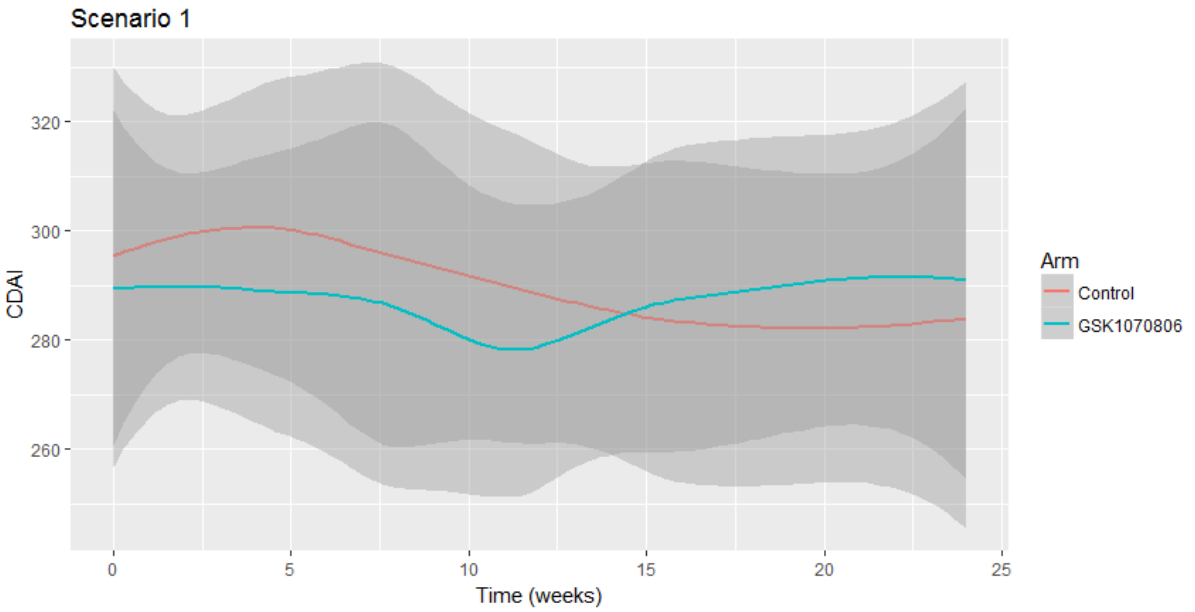

Figure 4 - n_1 = 10 placebo paths and n_2 = 20 experimental paths summarised by loess smoothers, plus bootstrapped 95% confidence intervals of the mean process value.

12.3.4 Scenario 2

In this active scenario, GSK1070806 is assumed to have a large and progressive effect on CDAI until week 12, where the experimental response curve plateaus. Patients allocated to placebo are assumed to respond as described in Scenario 1, i.e. with a positive but very small effect. The values of λP(t) are given in column A and λE(t) in column B of Table 10. The expected changes from baseline are shown in columns G and H. A single trial simulation using n1 = 10 placebo paths and n2 = 20 experimental paths is shown in Figure 5. We see that the mean lines are quite distinct, although the confidence intervals do not truly separate. Despite this, the power garnered from analysing the outcomes over all time-horizons simultaneously means that the probability of approving GSK1070806 in this scenario is approximately 92.8%.

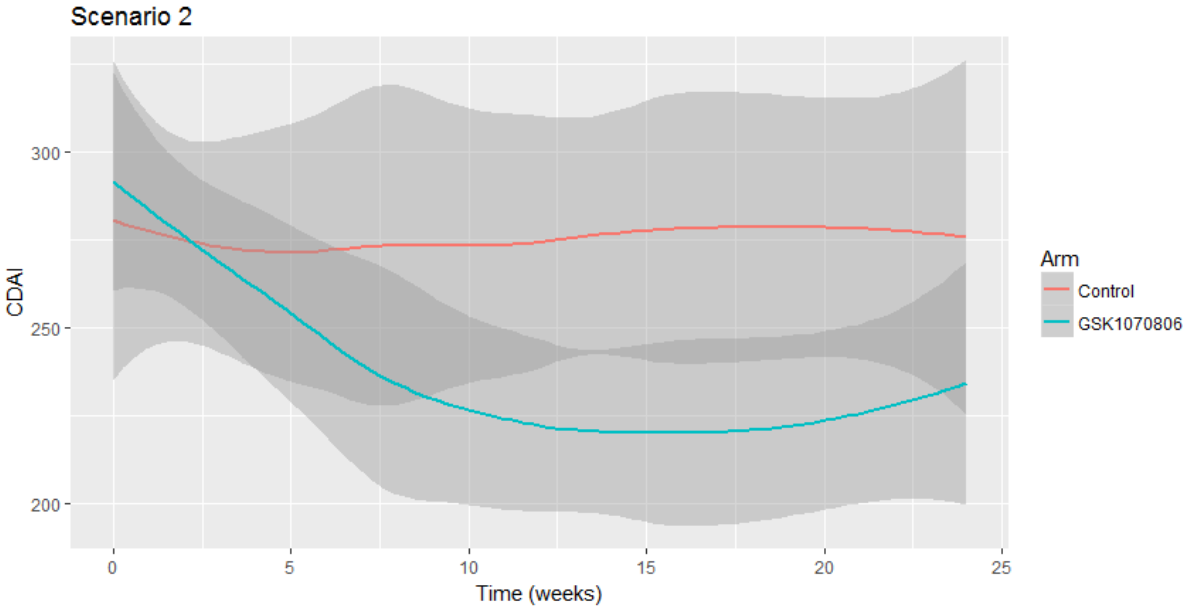

Figure 5 - n_1 = 10 placebo paths and n_2 = 20 experimental paths summarised by loess smoothers, plus bootstrapped 95% confidence intervals of the mean process value.

12.3.5 Scenario 3

In this active scenario, GSK1070806 is assumed to have a strong (albeit weaker than scenario 2) and progressive effect on CDAI until week 16, where the expected response curve plateaus. Patients allocated to placebo are assumed to respond as described in Scenario 1. The values of λP(t) are given in column A and λE(t) in column C of Table 10. The expected changes from baseline are shown in columns G and I. A single trial simulation using n1 = 10 placebo paths and n2 = 20 experimental paths is shown in Figure 6. We see that the mean lines are quite distinct, and that the confidence intervals scarcely separate. Again, despite this, the power garnered from analysing the outcomes over all time-horizons simultaneously means that the probability of approving GSK1070806 in this scenario is approximately 86.0%. The weight of evidence supporting a difference in response curves could be loosely interpreted as correlating with the area between the two curves. The probability of approval is lower here than in scenario 2 because that area is smaller.

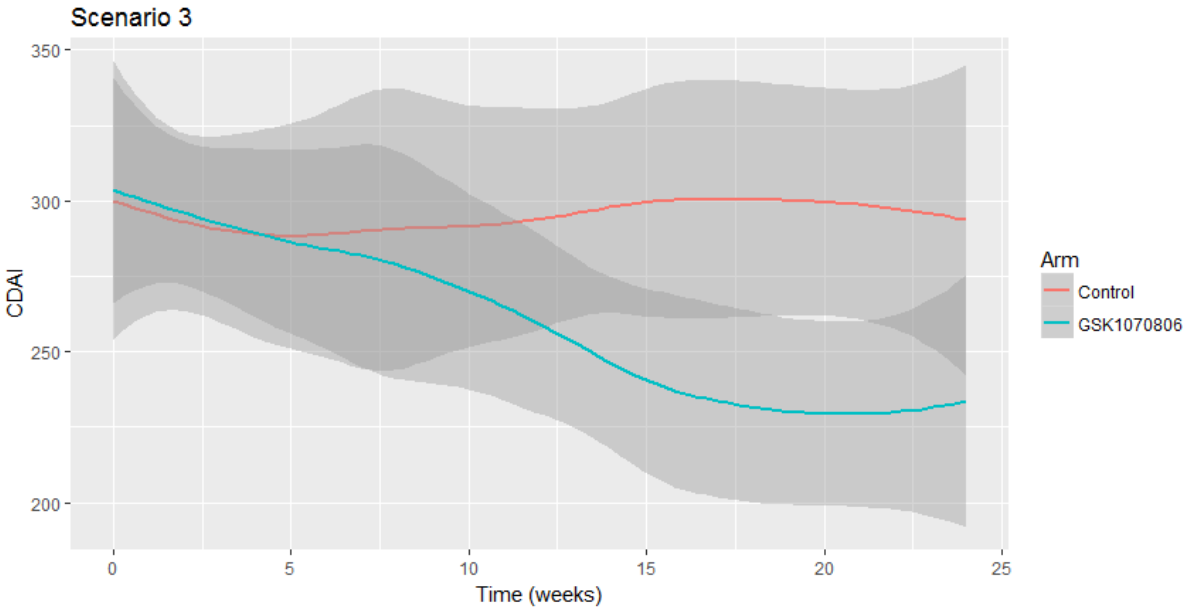

Figure 6 - n_1 = 10 placebo paths and n_2 = 20 experimental paths summarised by loess smoothers, plus bootstrapped 95% confidence intervals of the mean process value.

12.3.6 Scenario 4

In this active scenario, GSK1070806 is assumed to have a strong (albeit weaker than scenario 2) and progressive effect on CDAI until week 12, where the expected response curve plateaus. Patients allocated to placebo are assumed to respond as described in Scenario 1. The values of λP(t) are given in column A and λE(t) in column D of Table 10. The expected changes from baseline are shown in columns G and J. A single trial simulation using n1 = 10 placebo paths and n2 = 20 experimental paths is shown in Figure 7. We see that the mean lines are quite distinct, and that the confidence intervals never separate. The probability of approving GSK1070806 in this scenario is approximately 85.1%.

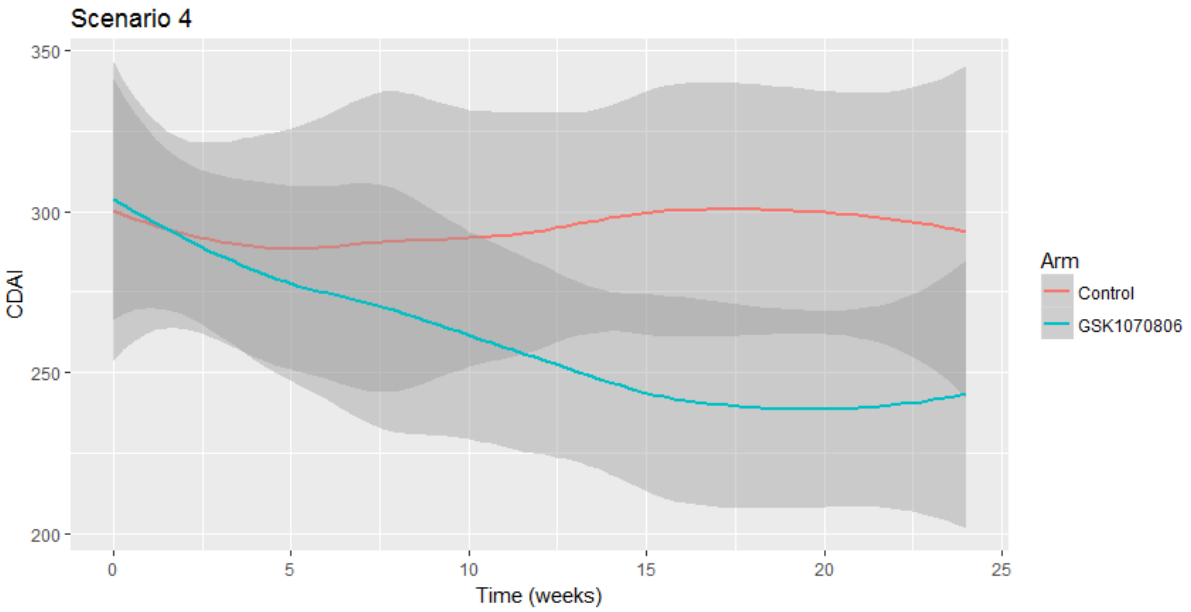

Figure 7 - n_1 = 10 placebo paths and n_2 = 20 experimental paths summarised by loess smoothers, plus bootstrapped 95% confidence intervals of the mean process value.

12.3.7 Scenario 5

Hitherto, we have used weak placebo effects. In a recent placebo-controlled RCT in CD (Sandborn, Lee et al. 2017)], large falls in CDAI and a high response rate were observed in patients on placebo and experimental drug alike. More generally, a meta-analysis of placebo response rates showed that responses to placebo are common and often large (Su, Lichtenstein et al. 2004). In this scenario, we assume that placebo are strong, and that responses to GSK1070806 are stronger still. The values of λP(t) are given in column E and λE(t) in column F of Table 10. The expected changes from baseline are shown in columns K and L. A single trial simulation using n1 = 10 placebo paths and n2 = 20 experimental paths is shown in Figure. The probability of approving GSK1070806 in this scenario is approximately 88.0%.

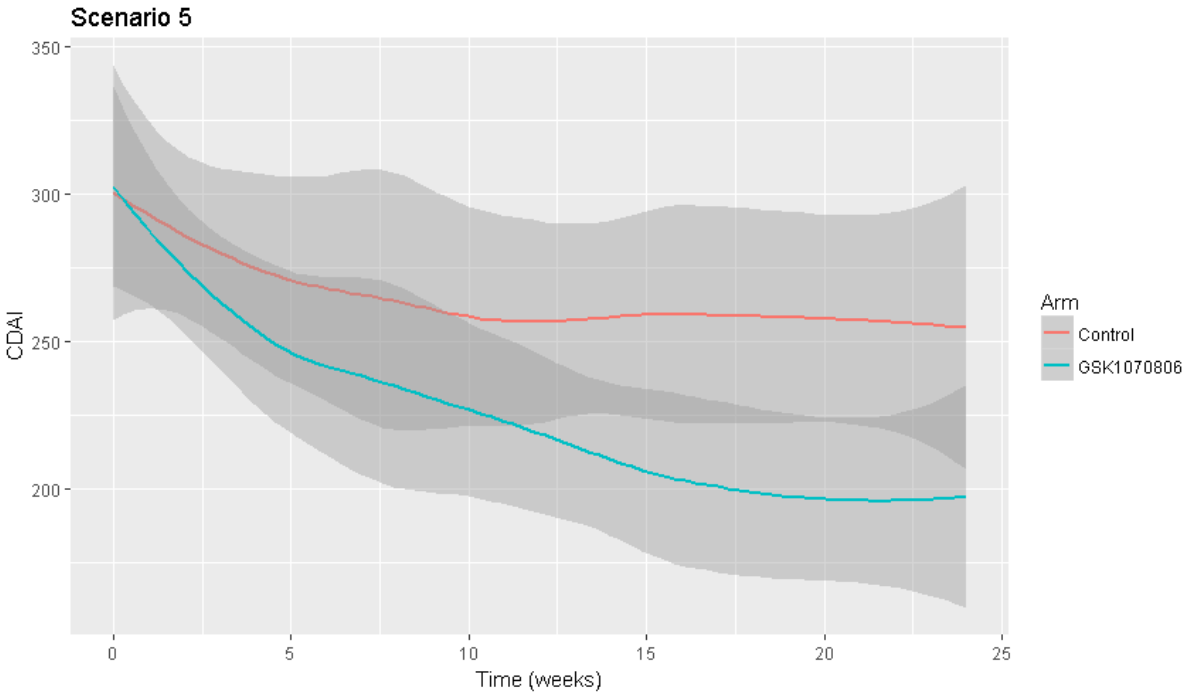

Figure 8 - n1 = 10 placebo paths and n2 = 20 experimental paths summarised by loess smoothers, plus bootstrapped 95% confidence intervals of the mean process value

12.3.8 Summary

This section summarises the simulated information presented in the preceding sections.

Table 10 Columns A-D show the scalars, λ(t), applied to baseline CDAI values to generate post-baseline values.

The mean CDAI score at baseline for patients allocated to placebo and GSK1070806 alike is 285. Change in mean CDAI path is calculated by scaling this baseline mean by the relevant scalar, e.g. 285 * 0.99 – 285 = -3 and 285 * 0.95 – 285 = -14 (0 d.p.).

Column	A	B	C	D	E	F	G	H	I	J	K	L
	Scalar of mean CDAI path						Change in mean CDAI path vs baseline					
Time (weeks)	Placebo in Scen 1-4; & GSK1070806 in Scen 1	GSK1070806 in Scen 2	GSK1070806 in Scen 3	GSK1070806 in Scen 4	Placebo in Scen 5	GSK1070806 in Scen 5	Placebo in Scen 1-4; & GSK1070806 in Scen 1	GSK1070806 in Scen 2	GSK1070806 in Scen 3	GSK1070806 in Scen 4	Placebo in Scen 5	GSK1070806 in Scen 5
0	1.00	1.00	1.00	1.00	1.00	1.00	0	0	0	0	0	0
2	0.99	0.95	0.97	0.96	0.97	0.90	-3	-14	-9	-11	-9	-28
4	0.99	0.90	0.95	0.92	0.94	0.82	-3	-28	-14	-23	-17	-51
8	0.98	0.80	0.89	0.86	0.89	0.75	-6	-57	-31	-40	-31	-71
12	0.98	0.78	0.83	0.81	0.85	0.70	-6	-63	-48	-54	-43	-86
16	0.98	0.78	0.78	0.81	0.85	0.68	-6	-63	-63	-54	-43	-91
24	0.98	0.78	0.78	0.81	0.85	0.66	-6	-63	-63	-54	-43	-97
Prob (Approve)	0.031	0.928	0.860	0.851		0.880						

12.4 Evaluability

Patients are evaluable when they receive IMP. Inevaluable patients may be replaced.

12.5 Planned Sub Group Analyses

No subgroup analyses are planned.

12.6 Planned Interim Analysis

The independent data monitoring committee (DMC, see Section 13.5) will review an interim analysis of all study outcomes after **6 patients** have received trial treatment and at least 28 days of follow-up has been completed for each. There will not be a pause in recruitment at this time point. The primary objective of the meeting will be to identify any early signs of excess toxicity. If the rate / severity of AEs / SAEs materially exceeds that in the control arm, or what may be expected in this patient population, then the DMC may advise that recruitment be paused pending further investigation, or suspended altogether. The expected background rate of infection will be determined based on data from publications, registries, trial site databases, and ongoing studies in similar patient populations.

12.7 Planned Final Analyses

The final analysis will be conducted and distributed for publication within six months of the final assessment for the final patient.

13. TRIAL ORGANISATIONAL STRUCTURE

13.1 Sponsor

The trial sponsor is the University of Birmingham.

13.2 Coordinating Centre

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham according to their local procedures.

13.3 Trial Management Group

The Trial Management Group (TMG) is comprised of the Chief Investigator and other collaborators as detailed elsewhere in this document. The TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference or in person as required. Members of the TMG include the CI, CRCTU Trial Management Team Leader, Senior Trial Coordinator, Trial Coordinator, Lead Trial Statistician, Trial Statistician, Medical/IMP consultant (GSK representative) and a Pharmacy Representative. The TMG will meet or hold a teleconference every 2 months during recruitment, or as required.

13.4 Trial Steering Committee

The clinical trial is a small phase Ib/IIa study and will not involve more than 3 separate study sites and therefore a formal trial steering committee will not be required to provide independent oversight of patients recruitment, project timelines etc.

13.5 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent data monitoring committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will comprise at least an independent Crohn's/inflammatory bowel disease specialist, and independent statistician.
Interim safety reports results will be provided to the DMC and discussed via teleconference at a minimum. Section 12.6 details interim analyses for the DMC to review outcomes after 6 patients have received study treatment.
Additional meetings may be called if recruitment is much slower/ faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Management Group (TMG) who will convey the findings of the DMC to both the funders GSK and study sponsor. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety.
The DMC will report directly to the CDAID Trial Management Group (TMG) who will convey (when applicable) the findings of the DMC to the sponsors, GSK, MHRA and the Ethics Committee. The DMC have the right to recommend closure of the trial if any issues are identified which may compromise patient safety.

13.6 Finance

This is a clinician-initiated and clinician-led trial funded by an academic investigator-led education/research grant provided by GSK. GSK will be supplying GSK 1070806, the investigational medicinal product (IMP), free of charge to all individual NHS trusts that will be directly treating patients as part of this clinical trial.

13.6.1 Payments to individual NHS trusts (Per-patient payment)

Refer to the Clinical Study Site Agreement for details.

14. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998 and Human Tissue Act 2008) and the Principles of Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the Research Ethics Committee (REC) prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trials Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

15. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and Data Protection Act 2018 for health and care research. The University of Birmingham, as the Sponsor for the CDAID study, will be using information from patient medical records in order to undertake this trial and will act as the data controller for the study. This means that the University of Birmingham are responsible for looking after the information and using it properly. University of Birmingham and the NHS will keep identifiable information about the patients for at least 25 years after the study has finished, to allow the results of the study to be verified if needed.

All information collected by the Sponsor will be securely stored at the Trials Office at the University of Birmingham on paper and electronically and will only be accessible by authorised personnel. The only people in the University of Birmingham who will have access to information that identifies a patient will be people who manage the study or audit the data collection process.

The NHS will use the patient`s name and contact details to contact patients about the research study, and make sure that relevant information about the study is recorded for their care, and to oversee the quality of the trial. With the patient`s permission, the research team (at site) will notify the patient`s GP that they intend to participate in the study.

With the patient's consent, their full name (on consent form only), initials and date of birth will be collected at trial entry. The research team (at site) will send a copy of the signed consent form in the post to the Trials Office. This will be used to perform in-house monitoring of the consent process.

In routine communication between the hospital and the Trials Office, the patient will only be identified by study number and initials. Data may be provided to the Trials Office on paper or electronically.

By taking part in the study, the patient will be agreeing to allow research staff from the Trials Office at the University of Birmingham to look at the study records, including their medical records. It may be necessary to allow authorised personnel from government regulatory agencies (e.g. Medicines and Healthcare products Regulatory Agency (MHRA), the Sponsor and/or NHS bodies to have access to patient medical and research records. This is to ensure that the study is being conducted to the highest possible standards. Anonymised data from the study may also be provided to other third parties (e.g. the manufacturer of the trial treatment) for research, safety monitoring or licensing purposes.

The Investigator must maintain documents not for submission to the Trials Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

16. INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry guideline's for patient compensation.

17. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

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APPENDIX 1 - WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964and amended by the29th World Medical Assembly, Tokyo, Japan, October 1975, 35th World Medical Assembly, Venice, Italy, October 1983, 41st World Medical Assembly, Hong Kong, September 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. 4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject

in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN

SUBJECTS (Non-Clinical Biomedical Research)

7. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

8. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

9. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

10. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

APPENDIX 2 - DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event

Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***
    - Other Medically significant events that need to be reported as an SAE include

    - Any suspected or definite diagnosis of cytokine release syndrome grade 3 – 5. *In order to confirm the case of cytokine release syndrome, an additional blood sample will need to be taken for cytokine assay (e.g. TNF-α, IFNγ, IL-6). This information is to be provided as part of the SAE form.*

    - Is associated with liver injury and impaired liver function defined as:

    - ALT $\geq$ 3xULN and total bilirubin[#] $\geq$ 2xULN (>35% direct), **or** ALT $\geq$ 3xULN and INR[##] > 1.5.

[#] Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT $\geq$ 3xULN and total bilirubin $\geq$ 2xULN, then the event is still to be reported as an SAE. [##] INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE 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 that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

APPENDIX 3 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX 4 – T-SPOT.TB

Oxford Diagnostics Laboratories

SERVICE DESCRIPTION

Oxford Diagnostic Laboratories (ODL®) offers a national TB testing service to laboratories and clinicians using the T-SPOT®.*TB* test.

Further information on the T-SPOT.*TB* test, including its limitations, is set out in our published documentation.

Specimen Acceptance Criteria

We require 6ml of blood collected in one standard heparin (green-topped) vacutainer tube. Paediatric samples require less blood (please call the laboratory to seek advice, as blood volumes depend on age). Samples must be accompanied with a completed ODL test Request Form and must reach ODL within 32 hrs of venepuncture. Blood samples should be stored at 18-25°C; do not refrigerate samples. Please ensure that you include your Customer Account Number and Quote/Agreement Number on all test requests. Specimens must arrive by 2.00pm Monday to Saturday. ODL is closed on public holidays and over the Christmas and New Year period each year (please call us, or consult our website, to find out the exact dates for this year).

We place no restriction on the numbers of samples that can be sent at one time, however, if sending large numbers of samples we would appreciate advance notification to help us better plan our workflow. We endeavour to provide results two working days after the

sample is received by ODL.

What will Oxford Diagnostic Laboratories do?

1. We will carry out the Service, as described here and in the Terms and Conditions of Service, and following the instructions given on the test Request Form.

2. The service results will be sent by email (and fax or post if requested) to the requesting laboratory within 2 working days of receipt of sample. For incidents, results are reported within three working days.

3. The invoice for the Service will be sent by post within 3 further working days, unless otherwise agreed.

4. ODL will be responsible for disposal of any samples provided.

Results Interpretation and Quality Control

A typical result would be expected to have few or no spots in the Nil Control and _20 spots in the Positive Control. Each spot represents the footprint of an individual cytokine-secreting T cell, and evaluating the number of spots obtained provides a measurement of the abundance of *M. tuberculosis* complex sensitive effector T cells in the peripheral blood.

A Nil Control spot count in excess of 10 spots should be considered as 'Indeterminate'. Refer to the T-SPOT.*TB* Technical Handbook for possible causes (download from www.oxfordimmunotec.com). If this occurs, another sample should be collected from the individual and sent to ODL for testing.

Typically, the cell functionality Positive Control spot count should be _ 20 or show saturation (where spots are too numerous to count).

A small proportion of patients may have T cells which show only a limited response to PHA. Where the Positive Control spot count is< 20 spots, it should be considered as 'Indeterminate', unless either Panel A or Panel B is 'Positive' as described below, in which case the result is valid.

The T-SPOT.*TB* test results are interpreted by subtracting the spot count in the Nil Control well from the spot count in each of the Panel wells, according to the following algorithm:

- The test result is 'Positive' if (Panel A minus Nil Control) and / or (Panel B minus Nil Control) _ 6 spots.

- The test result is 'Negative' if both (Panel A minus Nil Control) and (Panel B minus Nil Control) _ 5 spots. This includes values less than zero.

Due to potential biological and systematic variations, where the higher of (Panel A minus Nil Control) and (Panel B minus Nil Control) is5, 6 or 7 spots, the result may be considered as Borderline (equivocal). Borderline (equivocal) results, although valid, are less reliable than results where the spot count is further from the cut-off. Retesting of the patient, using a new sample, is therefore recommended.

A 'Positive' result indicates that Tuberculosis infection is likely.

A 'Negative' result indicates that Tuberculosis infection is unlikely.

The results should be used and interpreted only in the context of the overall clinical picture. A negative test result does not exclude the possibility of exposure to or infection with *M. tuberculosis.*

APPENDIX 5 – MODIFIED LIST OF HIGHLY EFFECTIVE METHODS OF AVOIDING PREGNANCY IN WOMEN OF CHILDBEARING POTENTIAL

This list does not apply to WOCBP with same sex partners, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyles. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive (Hatcher RA 2011)
4. Injectable progestogen (Hatcher RA 2011)
5. Contraceptive vaginal ring (Hatcher RA 2011)
6. Percutaneous contraceptive patches (Hatcher RA 2011)
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject (Hatcher RA 2011). The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination of the subject and/or semen analysis, or medical history interview provided by her or her partner.

This is an all-inclusive list of those methods that meet the sponsor definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label.

For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The sponsor definition is based on the definition provided by the ICH (ICH 2009).

The Investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception by providing counsel directly or by referring subjects to health care professionals with expertise in this area.

APPENDIX 6 - LIVER SAFETY REQUIRED ACTIONS AND FOLLOW-UP ASSESSMENTS

Phase II liver chemistry increased monitoring criteria have been designed to assure subject safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry increased monitoring criteria and required follow up assessments Liver Chemistry Increased Monitoring Criteria	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin1, 2	ALT > 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR2	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic3	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Event	
Actions	**Follow Up Assessments**
• Report the event to Trials Office **within 24 hours** • Complete the liver event CRF and complete an SAE - if the event also meets the criteria for an SAE**2** • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below). "Baseline" refers to the laboratory assessments performed closest and prior to dosing of study treatment. **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained within 72 hrs after an identified liver event if within 6 months post dose.5 • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin 2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form

• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended For All other criteria: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form For bilirubin or INR criteria: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ? 3xULN and bilirubin ? 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT > 3xULN and bilirubin > 2xULN (>35% direct bilirubin) or ALT > 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample.

APPENDIX 7 – EQUATION FOR ESTIMATED GLOMERULAR FILTRATION RATE

COCKCROFT-GAULT

$$\text{Creatinine clearance (estimated GFR)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 1.23}{\text{serum creatinine in micromol/l}}$$

For women multiply the result of calculation by 0.85.

APPENDIX 8– GENETICS

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a [blood/saliva] sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK1070806 and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK1070806 and other potential inflammatory indications such as irritable bowel disease and celiac disease. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples will be analysed if it is hypothesized that this may help further understand the clinical data.
- DNA samples will be analysed for [describe planned analyses]. [Additional] analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK1070806 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- GSK will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK1070806 other potential inflammatory indications such as irritable bowel disease and celiac disease continues but no longer than 15 years after the last subject last visit or other period as per local requirements.