Clinical Study Protocol

Protocol Title:	**A Phase 2 study to investigate the efficacy, safety, and tolerability of six weeks treatment with V565 in subjects with active Crohn's disease**
Protocol Number:	**V56502**
Date of Protocol:	**24 August 2016**
Date of Protocol Amendment:	**02 December 2016**
Version:	**Version 1.3**
Product:	**V565**
IND No.:	**130643**
EudraCT No.:	**2016-002939-15**
Study Phase:	**Phase 2**
Sponsor:	**VHsquared Ltd.**

Confidentiality Statement

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Signatures

PROTOCOL TITLE: A Phase 2 study to investigate the efficacy, safety, and tolerability of six weeks treatment with V565 in subjects with active Crohn's disease

PROTOCOL NO: V56502

Version 1.3 02 December 2016

Date

Date

SYNOPSIS

Name of Sponsor/Company:	VHsquared Ltd.
Name of Finished Product:	V565
Name of Active Ingredient:	V565
Title of Study:	A Phase 2 study to investigate the efficacy, safety, and tolerability of six weeks treatment with V565 in subjects with active Crohn's disease
Primary Investigator:	Multiple sites
Protocol No:	V56502
Study site(s):	Proposed sites: Approximately 76 Proposed territories: North America, European Union (EU) (including West, Central and East EU countries).
Study duration: The study consists of six site visits over approximately 12 weeks. The duration of treatment is 42 days (six weeks repeat dose administration).	**Phase:** 2

Objectives:

Primary Objective:

To evaluate the efficacy of V565 555 mg three times a day (TID) in subjects with active Crohn's disease (CD) measured by the proportion of subjects achieving response to therapy. Response is defined as reduction in the Crohn's Disease Activity Index (CDAI) scores and in inflammatory markers (C-reactive protein [CRP] or faecal calprotectin [FCP] at Day 42.

Secondary Objectives:

- To further characterise the efficacy of V565 in subjects with active CD assessed by changes in CDAI scores and/or inflammatory markers
- To assess the effects of V565 based on changes in Abdominal Pain and Stool Frequency instrument (PRO-2) scores
- To assess safety and tolerability of V565

Pharmacokinetic Objectives:

- To determine the concentration of V565 in serum and urine

Exploratory Objectives:

- To assess the proportion of subjects achieving CRP or FCP levels within normal limits
- To assess changes in CDAI scores and CRP or FCP levels over time
- To determine changes in anti-V565 antibody titre
- To evaluate the frequency of loose or watery stools, assessed using the Bristol Stool Form Scale (BSFS)
- To evaluate changes in abdominal pain using the Numeric Pain Scale (NPS)
- To evaluate changes in faecal urgency

Exploratory Endoscopy Substudy Objectives:

- To investigate the effect of V565 on changes in endoscopic mucosal appearance, evaluated with an overall assessment and the Simple Endoscopic Score for Crohn's Disease (SES-CD), as determined by a central reader

Methodology: This study will be a multiple-site, double-blind, placebo-controlled, parallel-group proof-of-concept study in approximately 126 subjects with active CD. This study will include subjects who have a confirmed diagnosis of CD for at least three months and have CD involving the ileum and/or colon. Inclusion and exclusion criteria are described in detail in subsequent sections. The duration of treatment will be 42 days (six weeks); each subject's participation in the study will be approximately 12 weeks. This includes a screening period of up to 28 days, a treatment period of 42 days and a follow-up period of 14 days after the last dose of study drug. Subjects will be randomised into two treatment arms: either V565 or placebo using a 2:1 active: placebo ratio. Randomisation will be stratified to ensure treatment groups have similar rates of prior anti-tumour necrosis factor alpha (TNFα) therapy. Subjects will receive three V565 185 mg capsules three times daily or matching placebo, for 42 days. The total daily V565 dose is 1665 mg. Subjects will be treated with study drug as an add-on to any permitted stable medications already being taken for CD. No alteration of background CD medication will be permitted for the duration of the study. There are six study visits. Two screening visits to assess eligibility will occur during Days -28 to Day -1; these are Visit 1 (start of screening), and Visit 2 (eligibility ileocolonoscopy). Additional study visits will occur on Day 1 (randomisation and initiation of treatment), Day 14 (Interim Visit), Day 42 (End of Treatment Visit), and Day 56 (Follow up Visit). Collection of subject-reported variables of the CDAI will be via diaries given to the subject at Visit 1. Prior to Visit 2, the subject-reported variables will be combined with the variables collected at the site on Visit 1 and the CDAI score will be calculated. In order to have an ileocolonoscopy, eligible subjects must have sufficient diary entries to calculate a CDAI score, a CDAI score ≥220 to ≤450 and a CRP ≥5 mg/L (or if CRP is normal, FCP ≥250 μg/g) prior to Visit 2. A previous ileocolonoscopy conducted within 12 weeks before Visit 1 may be substituted for the Visit 2 ileocolonoscopy provided it is forwarded to the central reader and was performed in such a way as to enable evaluation by the central reader. The Visit 2 ileocolonoscopy will be evaluated by a central reader for to assess the overall appearance of the mucosa for the presence of active disease and scored using the SES-CD. Active disease must be confirmed by the central reader for the subject to proceed to Visit 3 and to be randomised on Day 1. The efficacy of V565 will be evaluated by assessing CDAI scores, biomarkers (CRP or FCP), and the PRO-2. Exploratory efficacy measures include changes in CDAI scores, changes in CRP (or FCP) values over time, [redacted] This study will also evaluate the immunogenicity of V565. In an exploratory endoscopy substudy, subjects with more severe disease at the Visit 2 ileocolonoscopy (a SES-CD ≥7, if ileum and colon are involved or ≥4 if only the ileum is involved) will undergo a second ileocolonoscopy at the end of treatment (Day 42) to evaluate changes in the mucosa. Pharmacokinetic (PK) evaluations will be based on concentrations of V565 measured in serum and urine. Safety will be assessed through evaluations of adverse events (AEs), clinical laboratory results, vital signs, physical examinations, electrocardiograms (ECGs) and concomitant medications.	
Planned number of subjects:	Approximately 126 randomised to receive study drug in a 2:1 active:placebo ratio (84:42) Approximately 114 to complete (76:38) based on an estimated dropout rate of 10% during treatment

Diagnosis and main criteria for inclusion:	This study will enrol adult subjects with active CD. The main criteria for inclusion are: 1. History of CD (confirmed by ileocolonoscopy) of at least three months duration prior to Visit 1 2. CDAI score of ≥220 to ≤450 during Screening 3. CRP ≥5 mg/L (or, if CRP is normal, FCP ≥250 µg/g) at Screening 4. Active CD of ileum and/or colon as determined by the baseline ileocolonoscopy 5. Female subjects must not be pregnant and male and female subjects must agree to use effective contraception throughout the study and for 90 days after the last dose of study drug. 6. Subject must have failed or experienced intolerance to at least one of the following: aminosalicylates, corticosteroids; immunosuppressants (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]). The main criteria for exclusion are: 1. CD of mouth, stomach, oesophagus or duodenum which, in the opinion of the Investigator, is likely to be causing symptoms 2. Known history of or suspicion of ulcerative colitis, indeterminate colitis, microscopic colitis, ischaemic colitis or radiation-induced colitis, based on medical history, endoscopy and/or histological findings. 3. Any gastrointestinal (GI) manifestations of CD that might affect the evaluation of efficacy 4. Prior primary efficacy failure of or secondary loss of response to anti-TNFα therapy, or any contraindication to anti-TNFα therapy 5. The use of medications prior to the study or during the study with the potential to affect the evaluation of efficacy 6. Recent changes in background CD medications. 7. History or recurrent infections, a current infection with a GI pathogen or an increased risk of infection
Test product, dose and mode of administration:	V565 Oral capsule Dose: 185 mg/capsule Regimen: Three capsules, three times daily, for 42 days
Reference therapy, dose, and mode of administration:	Matching placebo capsules administered in the same manner as test product.

Criteria for evaluation:

Primary Efficacy Endpoint:

- Proportion of responders at Day 42, defined as subjects achieving both CDAI ≥70-point reduction from Baseline ***OR*** CDAI score <150, ***AND*** a reduction of ≥40% from the baseline value of CRP or FCP

Secondary Efficacy Endpoints:

- Proportion of subjects achieving a ≥100-point reduction in CDAI score and a concomitant reduction of 50% in CRP or FCP at Day 42
- Proportion of subjects achieving a ≥70-point reduction in CDAI score at Day 42
- Proportion of subjects achieving a ≥100-point reduction in CDAI score at Day 42
- Proportion of subjects achieving a CDAI score of <150 CDAI at Day 42
- Changes from Baseline in scores for PRO-2 at Day 14 and Day 42

Safety Endpoints:

- Evaluations of AEs, clinical laboratory results, physical examination findings, ECGs and vital signs throughout the study

Pharmacokinetic Endpoint:

- Serum and urine concentration of V565 prior to first administration of study drug and at Day 14, Day 42, and Day 56. In addition, On Day 1, a post-dose urine sample will be obtained at the site 4 to 8 hours after the first dose of study drug.

[redacted]

Statistical methods:

Determination of sample size**:**

The sample size is based on being able to claim superiority of V565 over placebo; the primary endpoint is defined as a response rate, based on CDAI reduction/remission and CRP or FCP results.

[redacted]

Statistical Analysis:

As appropriate, variables will be summarised descriptively (frequency and percentage will be summarised for categorical variables; mean, standard deviation [SD], median, minimum, and maximum will be presented for continuous variables) by study visit and by treatment group. All study data will be listed by subject.

A detailed Statistical Analysis Plan (SAP) including dictionaries used for coding and software used will be finalised prior to the initial unblinding of the study.

Efficacy

The primary endpoint will be analysed using a logistic regression model with treatment as the fixed effect and prior anti-TNFα therapy, baseline CDAI score, baseline CRP and baseline FCP values as covariates. For the active treatment versus placebo comparison, the results will be presented in terms of an odds ratio together with its associated 95% confidence interval (CI) and 2-sided p-value. Two-sided 95% CIs for the odds ratio will be provided.

Unless otherwise specified, the proportions of subjects fulfilling the relevant requirements will be presented with 95% CIs for all the primary and secondary endpoints.

Safety

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be tabulated in incidence tables by System Organ Class (SOC) and Preferred Term.

AEs will be summarised by SOC, Preferred Term, and treatment group. AEs will be further summarised by maximum severity and relationship to study medication. Prior and concomitant medications will be summarised by treatment. Other routine safety assessments such as vital signs, ECG and safety laboratory tests will be summarised by treatment group using statistics for continuous or categorical data, as appropriate.

Pharmacokinetics

The drug concentration results in serum and urine will be summarised by planned sampling time and treatment group.

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-HBc, Total	Hepatitis B core total antibody
Anti-HBs	Hepatitis B surface antibody
Anti-HCV	Hepatitis C antibody
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AZA	Azathioprine
BMI	Body mass index
β-hCG	Beta human chorionic gonadotropin
BP	Blood pressure
BSFS	Bristol Stool Form Scale
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	Confidence Interval
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CRP	C-reactive protein
CTFG	Clinical Trial Facilitation Group
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	End of treatment
EU	European Union
FCP	Faecal calprotectin
FDA	Food and Drug Administration
GCP	Good Clinical Practice

GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCT	Haematocrit
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HPMC	Hydroxypropyl methylcellulose
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive Web Activated Response System
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
6-MP	6-Mercaptopurine
MTX	Methotrexate
NPS	Numeric Pain Scale
NSAID	Non-steroidal anti-inflammatory drug
PK	Pharmacokinetics
PP	Per Protocol
PRO-2	Abdominal Pain and Stool Frequency Instrument
QTcF	QTc using the Fridericia correction
SAE	Serious adverse event
SAF	Safety (Population)
SAP	Statistical Analysis Plan
SD	Standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SOC	System Organ Class
SOP	Standard operating procedure

SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TID	Three times a day (ter in die)
TNFα	Tumour necrosis factor alpha
ULN	Upper limit of normal
U.S.	United States of America
VHH	Variable heavy chain antibody

2.0 INTRODUCTION

2.1 Background Information

Inflammatory bowel disease (IBD) includes both Crohn's disease (CD) and ulcerative colitis as well as other less prevalent, destructive diseases of the gastrointestinal (GI) tract. Crohn's disease is characterised by a chronic, relapsing, progressive course of intestinal inflammation and damage and generally begins in young adulthood. The incidence and prevalence of CD is increasing worldwide with current incidence of 6 to 15/100,000 and prevalence estimated at 50 to 200/100,000 [1]. The highest incidences of CD have been reported in northern Europe, the UK and North America suggesting common etiological factors, but the rate of growth is increasing rapidly in other parts of the world [2].

The aetio-pathogenesis of CD is not fully understood but genetic and environmental factors interact to promote an excessive and poorly controlled mucosal inflammatory response against components of gut micro-flora. The excessive production of proinflammatory cytokines within mucosal and sub-mucosal tissues drives chronic inflammatory processes within the gut wall that are responsible for development of the disease immunopathology. Evidence from clinical studies with systemically delivered anti-tumour necrosis factor alpha (TNFα) antibodies has clearly established that blocking the biological effects of TNFα is beneficial in the treatment of CD and has confirmed the central importance of this master proinflammatory cytokine as a mediator of disease pathogenesis.

If disease control is inadequate, the chronic inflammation leads to significant inflammatory, infectious and structural complications. The complications result in an increased need for hospitalisation and surgery, impaired quality of life, and disease-related mortality. For example, in CD approximately half of all patients will experience an intestinal complication within 20 years, often leading to the need for surgical intervention [3]. Moreover, persistent and extensive intestinal inflammation increases the risk of developing small bowel and colorectal carcinoma [4].

The traditional goal of treatment in IBD is to first induce, and then to maintain, clinical remission. Therapeutic decisions tend to be driven by the absence of clinical symptoms but accumulating data show that achieving this goal does not necessarily determine the subsequent clinical course of the disease or prevent the damaging long-term sequelae [5, 6]. The goal for therapy has thus shifted to include achieving healing of the gut mucosa with a view to reducing disability and bowel damage. The conventional strategy adopted for treatment (stepwise, sequential introduction of therapies starting with the least expensive and least systemically active medications and then gradually intensifying therapy) is being challenged because it is associated with lower efficacy, disease progression, a potentially higher risk of infections and, in moderate to severe disease, increased mortality. The use of

this conventional treatment strategy increases the likelihood that structural complications will develop before therapies proven to prevent such complications are introduced.

Parenterally administered TNFα monoclonal antibodies such as infliximab, adalimumab and certolizumab pegol have been validated as transformative CD therapies that can affect disease progression and improve long-term outcomes. They are utilised for induction of a clinical response, remission, prevention of relapse, corticosteroid sparing and mucosal healing in patients with moderate to severely active CD. Data have accumulated to support the case for earlier intervention with these systemic TNFα biologics. Observational, subgroup analyses and randomised control trial data, both in adults and in paediatric populations, indicate that TNFα antagonists are much more effective when given to patients within 1 to 2 years of initial diagnosis and that early intervention prior to prolonged steroid administration improves clinical outcomes [6, 7, 8].

Therefore, the goal of therapy has expanded from just the control of symptoms to include the prevention of disease. Further, the indications are that the earlier a potent, safe, disease modifying TNFα antagonist therapy can be provided to patients, the better the outcomes. However, the only biological agents to date that have been shown to be capable of achieving this goal are severely restricted to patients who have either failed or not responded to conventional therapy. Only a minority of patients with CD currently receive systemic anti-TNFα therapy and they are generally used as second or third line agents. Two major barriers to expanded use across a wider spectrum of patients with CD are cost and safety concerns. In addition, immunogenicity is a major issue that affects the durability of response seen with systemic anti-TNFα biologics. This may result in both primary and secondary loss of response and lead to cycling between different products.

VHsquared Ltd. (hereinafter, the “Sponsor”) is developing an orally active, protease stabilised, engineered domain antibody against TNFα that may deliver significant advantages over current systemically administered anti-TNFα agents. The enhanced safety profile provided by local targeting and minimal systemic exposure and the expected low immunogenicity has the potential to provide the proven efficacy benefits of anti-TNFα therapy to a wider spectrum of patients. It may allow earlier intervention in the disease course, thus potentially maximising the clinical benefit of TNFα inhibition. The minimal systemic exposure would promote use in paediatrics and pregnancy, areas where parenteral administration and lack of a safe potent oral formulation are currently problematic.

The multi-particulate V565 oral formulation planned for further clinical use has been evaluated in a toxicology programme with dosing up to six weeks, and a Phase 1 clinical study including 49 healthy volunteers and subjects with dosing up to 14 days. Results from these studies support further investigation of V565 as a potential therapy for CD.

In Part 1 (n=29) 19 healthy volunteers received a single dose of V565 at a dose of either 62 mg (n=4), 185 mg (n=4), 555 mg (n=3), 1665 mg (n=4), 4995 mg (n=4), or placebo (n=10) in a conventional single ascending dose design.

In Part 2 (n=10) eight healthy volunteers received multiple doses of V565 (1665 mg three times a day [TID]) and two received placebo TID for 14 days. The objectives were to assess safety and tolerability of multiple doses of V565, and to investigate potential immunogenicity following multiple dosing.

In Part 3 (n=4) otherwise healthy subjects with a terminal ileostomy received a single dose of V565 1665 mg to evaluate V565 luminal concentrations at the terminal ileum.

Part 4 (n=6) was a single ascending dose study that investigated systemic exposure in subjects with mild to moderate CD. Two subjects received a single 555 mg dose and, following review by the Safety Review Committee, a further four subjects received a single 1665 mg dose. This was considered important as patients with CD have increased intestinal permeability compared to healthy volunteers, which could potentially lead to increased systemic exposure. In addition, in this part of the study, urine collections were scheduled as an indirect method of assessing systemic exposure in case V565 was not detectable in serum samples.

The results of the Phase 1 study are summarised below:

- V565 has been administered to 37 human subjects in single doses up to 4995 mg and in multiple doses up to 1665 mg TID for 14 days. V565 was safe and well tolerated. There were no deaths, no serious adverse events (SAEs) and no adverse events (AEs) leading to withdrawal or change of dose. Almost all AEs were mild, with the only severe AE being a report of tonsillitis with initial symptoms starting approximately three hours after a 62 mg dose.
- V565 was not detectable in any serum sample in any part of the study.
- V565 was detected in the urine collection taken four to eight hours after dosing of one subject with CD in Part 4, confirming that active V565 passes across the lamina propria.
- No neutralising anti-drug antibodies were detected in any subject.
- High concentrations of active V565 were detected in ileal fluid and faeces.

Additional non-clinical information is provided in the current version of the V565 Investigator's Brochure (IB).

2.2 Rationale

There is a medical need for a targeted anti-TNFα therapy that would minimise systemic exposure (and the side effects associated with systemic exposure), while providing effective treatment to the affected portions of the GI tract. Data from the Phase 1 study suggest that, relative to other anti-TNFα products (which are given parenterally and result in systemic

exposure), orally administered V565 results in a very low level of systemic exposure. Therefore, V565 may be expected to have a better safety profile than other anti-TNFα products. In addition, orally administered V565 provides a more convenient route of administration than the parenteral route used for other anti-TNFα products. This proof-of-concept Phase 2 study will evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity in subjects who receive V565 in combination with any ongoing, permitted background treatment for CD. Permitted background treatments (those that will not interfere with the evaluation of the efficacy of V565) are described in Section 5.10.2.

2.3 Hypothesis

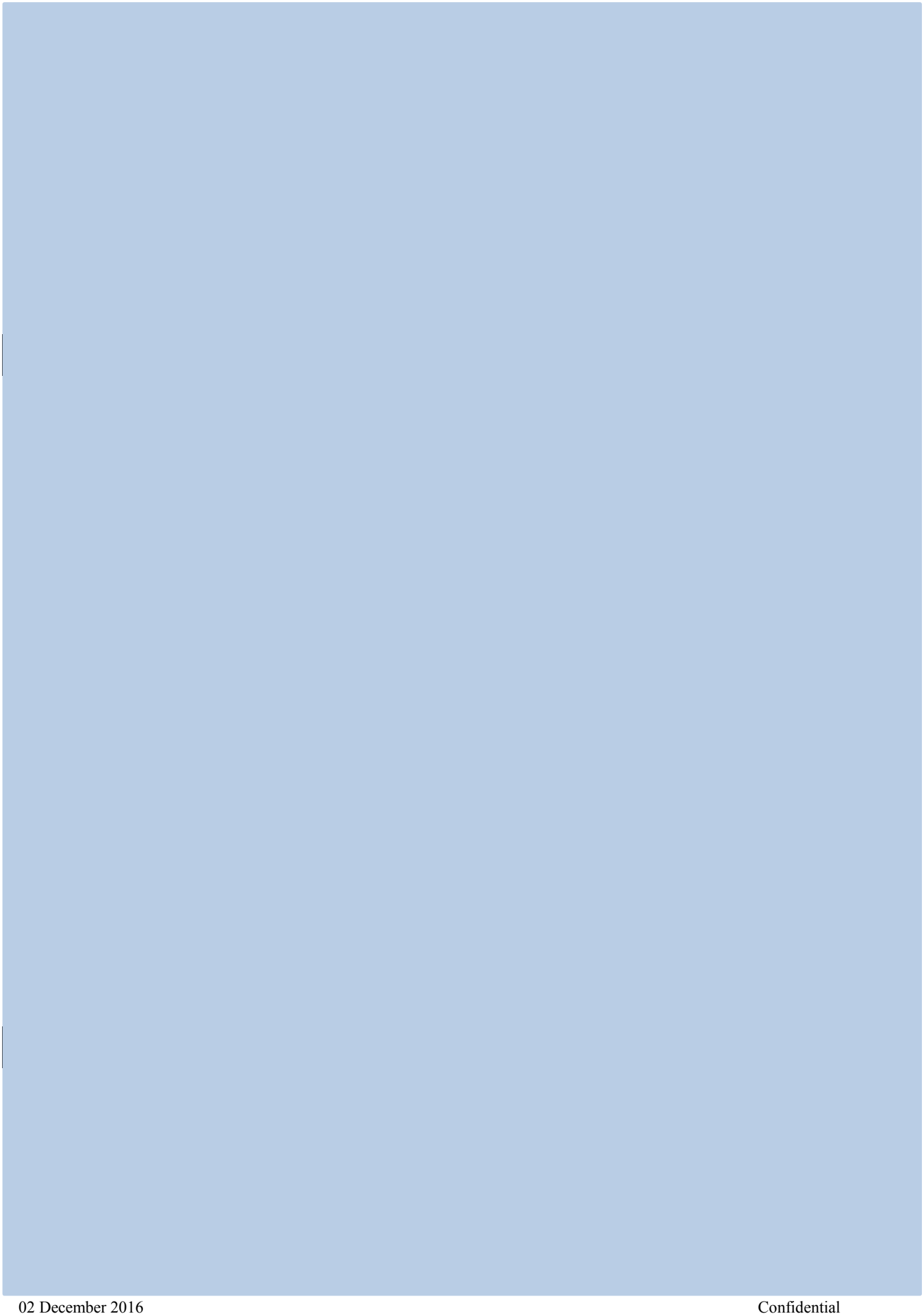
The hypothesis of this study is that the proportion of subjects at Day 42 achieving both

- Crohn's Disease Activity Index [CDAI] ≥70-point reduction from Baseline OR a CDAI score <150

AND

- A reduction of ≥40% from baseline value of C-reactive protein [CRP] or faecal calprotectin [FCP])

will be higher in subjects who receive V565 than in subjects who receive placebo when used in combination with their permitted background CD medications.



3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective is to evaluate the efficacy of V565 555 mg TID in subjects with active CD measured by the proportion of subjects achieving response to therapy. Response is defined as reduction in the Crohn's Disease Activity Index (CDAI) scores and in inflammatory markers CRP or FCP at Day 42.

3.1.2 Secondary Objectives

Secondary objectives are:

- To further characterise the efficacy of V565 in subjects with active CD assessed by changes in CDAI scores and/or inflammatory markers
- To assess the effects of V565 based on changes in Abdominal Pain and Stool Frequency Instrument (PRO-2) scores
- To assess safety and tolerability of V565

3.1.3 Pharmacokinetic Objectives

The PK objectives are to determine the concentration of V565 in serum and urine.

3.1.4 Exploratory Objectives

The exploratory objectives are to:

- To assess the proportion of subjects achieving CRP or FCP levels within normal limits
- To assess changes in CDAI scores and CRP or FCP levels over time
- To determine changes in anti-V565 antibody titre

3.1.5 Exploratory Endoscopy Substudy Objectives

- To investigate the effect of V565 on changes in endoscopic mucosal appearance, evaluated with an overall assessment and the Simple Endoscopic Score for Crohn's Disease (SES-CD), as determined by a central reader

4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This study will be a multiple-site, double-blind, placebo-controlled, parallel-group proof-of-concept study in approximately 126 subjects with active CD. This study will include subjects who have a confirmed diagnosis of CD for at least three months and have CD involving the ileum and/or colon. Inclusion and exclusion criteria are described in detail in Section 4.4.

The duration of treatment will be 42 days (six weeks); each subject's participation in the study will be approximately 12 weeks. This includes a screening period of up to 28 days, a treatment period of 42 days and a follow-up period of 14 days after the last dose of study drug.

Subjects will be randomised into two treatment arms: either V565 or placebo using a 2:1 active:placebo ratio. Randomisation will be stratified to ensure treatment groups have similar rates of prior anti-TNFα therapy.

Subjects will receive three V565 185 mg capsules three times daily or matching placebo, for 42 days (six weeks). The total daily V565 dose is 1665 mg.

Subjects will be treated with study drug as an add-on to any permitted stable medications already being taken for CD. Permitted CD medications are described in Section 5.10.2. No alteration of background CD medication will be permitted for the duration of the study.

There are six study visits. Two screening visits to assess eligibility will occur during Days -28 to Day -1; these are Visit 1 (start of screening), and Visit 2 (eligibility ileocolonoscopy). Additional study visits will occur on Day 1 (randomisation and initiation of treatment), Day 14 (Interim Visit), Day 42 (End of Treatment Visit), and Day 56 (Follow up Visit).

Collection of subject-reported variables of the CDAI will be via the diaries given to subjects at Visit 1. Prior to Visit 2, the subject-reported variables will be combined with the variables collected at the site on Visit 1 and the CDAI score will be calculated. In order to have an ileocolonoscopy, eligible subjects must have sufficient diary entries to calculate a CDAI score, a CDAI score ≥220 to ≤450 and a CRP ≥5 mg/L (or if CRP is normal, FCP ≥250 µg/g) prior to Visit 2.

A previous ileocolonoscopy conducted within 12 weeks before Visit 1 may be substituted for the Visit 2 ileocolonoscopy provided it is forwarded to the central reader and was performed in such a way as to enable evaluation by the central reader.

The Visit 2 ileocolonoscopy will be evaluated by a central reader for to assess the overall appearance of the mucosa for the presence of active disease and scored using the SES-CD.

Active disease must be confirmed by the central reader for the subject to proceed to Visit 3 and to be randomised on Day 1.

The efficacy of V565 will be evaluated throughout the study by assessing changes in CDAI scores and changes in inflammatory markers (CRP or FCP). Efficacy will also be evaluated with the PRO-2.

Exploratory efficacy measures include changes in CDAI scores, changes in CRP (or FCP) values over time, [redacted] This study will also assess the immunogenicity of V565.

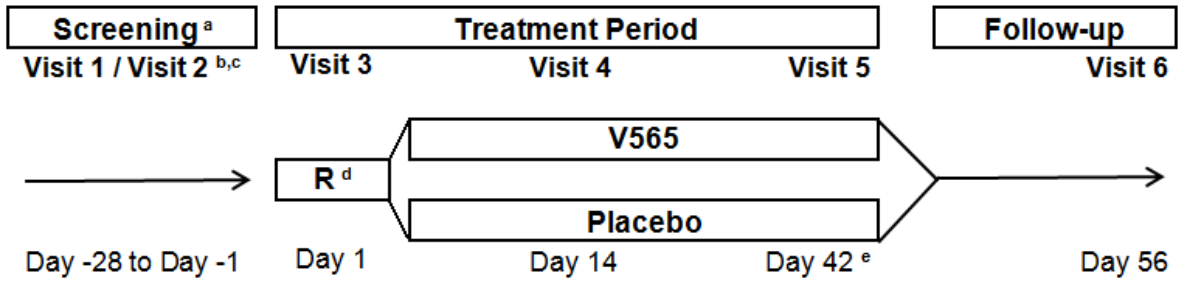
In an exploratory endoscopy substudy, subjects with more severe disease at the Visit 2 ileocolonoscopy (a SES-CD ≥7, if ileum and colon are involved or ≥4 if only the ileum is involved) will undergo a second ileocolonoscopy at the end of treatment (Day 42) to evaluate changes in mucosal appearance.

The PK evaluations will be based on V565 concentrations measured in serum and urine to evaluate systemic exposure (serum) and determine the levels of active V565 in urine samples.

Safety will be assessed through evaluations of AEs, clinical laboratory results, vital signs, physical examinations, ECGs and concomitant medications.

A study diagram in presented in Figure 1. The Schedule of Events is presented in .

Figure 1: Study Diagram



a. Screening may be a maximum of 28 days but may be shorter depending on the amount of time required to determine that a subject is eligible for the study based on all inclusion/exclusion criteria, including laboratory values, CDAI score, CRP (or FCP) level and results of the ileocolonoscopy.
b. All eligible subjects will have an ileocolonoscopy at Visit 2. The timing of Visit 2 is flexible, but must not occur until the subject has been declared eligible with regard to CDAI scores and CRP (or FCP) levels. The ileocolonoscopy must occur prior to Day 1.
c. Subjects will enter an exploratory endoscopy substudy if the subject's baseline SES-CD score is ≥7 (if ileum and colon involved) or ≥4 (if the lesions are confined to the ileum).
d. Subjects may not be randomised unless the ileocolonoscopy at Visit 2 indicates the presence of active disease.
e. Subjects in the exploratory endoscopy substudy will have a post-treatment ileocolonoscopy scheduled for Day 42.

CDAI: Crohn's Disease Activity Index; CRP: C-reactive protein; FCP: Faecal calprotectin; R: Randomisation; SES-CD: Simple Endoscopic Score for Crohn's Disease

[redacted]

4.2 Description of Study Periods

4.2.1 Screening: Visit 1 and Visit 2 (Ileocolonoscopy) (Day -28 to Day -1)

The subjects will be screened during the 28-day period prior to randomisation using the procedures outlined in to ensure that all eligibility criteria are fulfilled. Screening may be a maximum of 28 days but may be shorter depending on the amount of time required to determine that the subject is eligible for the study.

In order to have an ileocolonoscopy, eligible subjects must have sufficient diary entries to calculate a CDAI score, a CDAI score ≥220 to ≤450 and a CRP ≥5 mg/L (or if CRP is normal, FCP ≥250 µg/g) prior to Visit 2.

When it is determined that the subject is eligible for the Visit 2 ileocolonoscopy, the site will contact the subject, confirm the date and instruct the subject in the use of the preparation for the ileocolonoscopy according to local practice. All assessments scheduled for Visit 2 should be done prior to the ileocolonoscopy.

A previous ileocolonoscopy conducted within 12 weeks before Visit 1 may be substituted for the Visit 2 ileocolonoscopy provided it is forwarded to the central reader and was performed in such a way as to enable evaluation by the central reader.

Active disease must be confirmed by the central reader in order for the subject to proceed to Visit 3 and to be randomised on Day 1.

Assessments conducted at Visits 1 and 2 may be repeated once if they are out of range or unacceptable, providing that they are completed and that the results known within the screening period. The re-test value(s) will supersede the original values for the evaluation of the subject's eligibility.

If a subject cannot be declared eligible within the 28-day screening period and the Investigator wishes to re-screen the subject, the Investigator must contact the [redacted] Medical Advisor for permission to re-screen. Requests for re-screening will be handled on a case-by-case basis. A re-screening can be allowed once only for an individual subject, regardless of the reason. The subject will be allocated a new screening number.

4.2.2 Treatment Period

During the treatment period, the subject will attend three site visits (Day 1, Day 14 and Day 42). If possible, site visits will be scheduled for the morning. The window for the Day 14 and Day 42 visits is -3 days to +1 day.

On Day 1, subject compliance with diary completion will be reviewed to confirm that diary compliance is still acceptable. If all eligibility requirements have been met (including those based on the results of the ileocolonoscopy), the subject will be randomised. If not, the subject will be considered a screen failure and the reason for the screen fail will be recorded.

Eligible subjects will be randomly assigned to receive one of two oral regimens: V565 555 mg TID or placebo.

The Day 1 assessments and procedures presented in will be completed prior to starting treatment with study drug. Treatment will begin on Day 1 at the site and continue to Day 42. Additional information on dosing is available in Section 5.8.

Subjects will continue to fill out their diaries daily throughout the treatment period. At each visit, site personnel will review the diaries and assess compliance with study drug administration and with the use of the diary.

Pharmacokinetic samples (blood and urine) will be collected at each study visit. On Day 1, subjects will be asked to provide a pre-treatment sample and an additional sample 4 to 8 hours after the first dose of study drug.

The subjects take their last dose of study drug on Day 42. The subjects will return to the site on Day 42 for the assessments and procedures indicated in . The subject diaries will be collected at this time. Subjects participating in the endoscopy substudy will have their second ileocolonoscopy performed on Day 42.

4.2.3 Follow-up: Day 56

The subject will return to the site for a follow-up visit at Day 56, approximately two weeks after the last dose of study drug. The procedures performed during the follow-up visit are presented in .

4.2.4 30-day Post-treatment

Serious adverse events reported spontaneously will be collected for 30 days after the last dose of study drug.

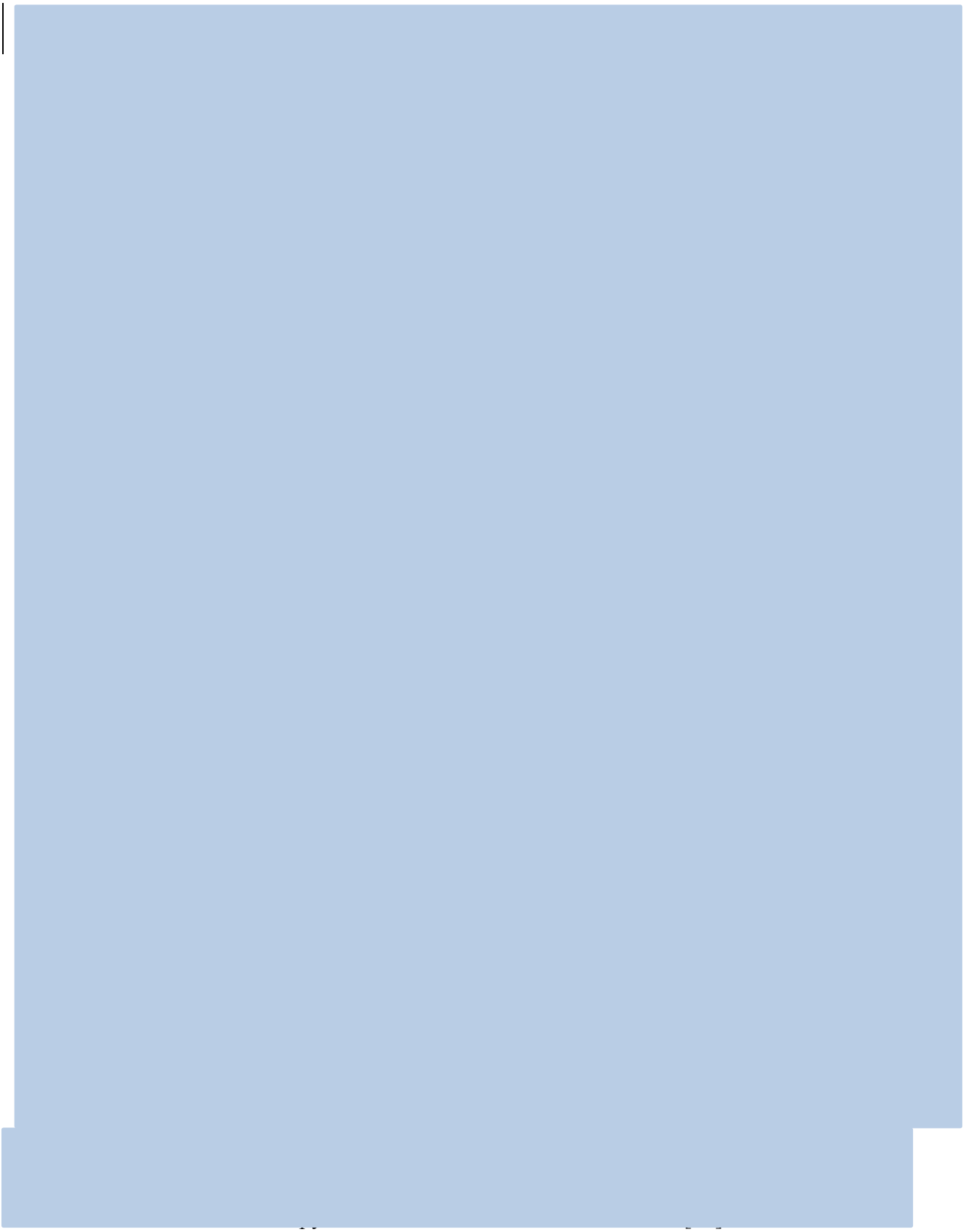
4.2.5 Early Termination Visit

A subject will have an Early Termination Visit if they discontinue treatment with study drug or withdraw from the study. If a subject withdraws from the study, or is discontinued from treatment with study drug, every effort should be made to complete an Early Termination Visit with the same assessments as scheduled for Day 42. The Early Termination Visit should be scheduled as soon as possible after it has been decided that the subject will be permanently discontinued from treatment with study drug. In addition to the Early Termination Visit, the Follow-up Visit should be performed on Day 56 if possible. Details describing subject withdrawal are presented in Section 4.5.

4.2.6 Unscheduled Visits

Unscheduled visits, if needed, may occur at any time as deemed necessary by the Investigator or site staff. If a subject returns to the site for an unscheduled visit due to a safety reason, assessments indicated in should be performed. In addition, the Investigator may do other

safety assessments as deemed necessary. These assessments are not required for subjects who return to the site for administrative reasons (e.g., to pick up additional study drug).



4.4 Selection of Study Population

4.4.1 Inclusion Criteria

Subjects who meet these inclusion criteria will be eligible to enrol in the study:

1. Male or female subjects aged 18 to 80 years, inclusive at Visit 1
2. Willing and able to provide written informed consent
3. Willing and able to attend study visits and follow study procedures
4. History of Crohn's disease (confirmed by ileocolonoscopy) of at least three months duration prior to Visit 1
5. CDAI score of ≥220 to ≤450 during Screening
6. CRP ≥5 mg/L (or, if CRP is normal, FCP ≥250 µg/g) at Screening
7. Active CD of ileum and/or colon as determined by the baseline ileocolonoscopy
8. Subjects for the exploratory endoscopy substudy must have a SES-CD ≥7 (if ileum and colon are involved) or ≥4 (if only the ileum is involved) at the baseline ileocolonoscopy.
9. Subject must have failed or experienced intolerance to at least one of the following: aminosalicylates, corticosteroids; immunosuppressants (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]).
10. Permitted CD medication regimen expected to remain stable during the period of the study
11. Females of childbearing potential must have a negative serum pregnancy test at Visit 1 and agree to use effective contraception from signing informed consent and for at least 90 days after the last dose of study drug. Males who are sexually active with a female partner of childbearing potential must be willing to use effective contraception from signing informed consent and for 90 days after the study.
    a. Females of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation, salpingectomy, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as no menses for ≥12 months without an alternative medical cause. Females with questionable menopausal history (e.g., irregular menstrual periods and age >40 years) are considered to be of childbearing potential.
    b. Females of childbearing potential: Females of childbearing potential must use acceptable highly effective (according to Clinical Trial Facilitation Group [CTFG] recommendations) methods of birth control in this study. These include:
        i. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
        ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
        iii. Intrauterine device
        iv. Intrauterine hormone-releasing system
        v. Bilateral tubal occlusion
        vi. Vasectomised partner
        vii. Sexual abstinence (see definition in Section 6.2.2)

12. Fertile males who are sexually active with a female partner of childbearing potential must agree to use contraception (condom plus spermicide or partner using acceptable highly effective method) from signing informed consent and for 90 days after last dose.
13. Fertile males should be instructed that they are not to donate sperm during the study or up to 90 days the last dose of study drug.
14. In regards to contraception, subjects must follow the strictest applicable local requirement as specified by the Regulatory Agency or Ethics Committee approving the trial.

4.4.2 Exclusion Criteria

Subjects who meet any of these criteria are not eligible to enrol in this study.

1. Crohn's disease of mouth, oesophagus, stomach or duodenum which, in the opinion of the Investigator, is likely to be causing symptoms
2. Known history of or suspicion of ulcerative colitis, indeterminate colitis, microscopic colitis, ischaemic colitis or radiation-induced colitis, based on medical history, endoscopy and/or histological findings
3. Any GI manifestations of CD that might affect the evaluation of efficacy:
    a. Prior significant GI resection
    b. Current abscess or symptomatic stricture
    c. Abdominal, enterocutaneous or pelvic active fistulas or fistula likely to require surgery during the study. Non active/non draining fistulas (including seton drained fistulas) are allowed.
    d. History of short bowel syndrome
    e. Presence of ileostomy or colostomy
4. Isolated disease confined to the recto-sigmoid colon (approximately the last 25 cm)
5. Any abdominal surgery within the six months before Visit 1 that required entering peritoneal cavity
6. Planned surgery or likely need for surgery during the study period
7. Any history of GI tract dysplasia or neoplasia
8. Any history of lymphoproliferative disease
9. Required enteral or parenteral feeding within 6 months before Visit 1 (oral supplements are acceptable)

Exclusion Criteria Related to Medications

10. Prior primary efficacy failure of or secondary loss of response to anti-TNFα therapy, or any contraindication to anti-TNFα therapy
11. History of sensitivity to any of the study drug, components, or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates participation in the study
12. Prior use of any other biological therapy other than anti-TNFα therapy for IBD
13. Any live, attenuated, recombinant vaccine vaccination during the study, or inoculation with such vaccines within four weeks prior to Visit 1.
14. Use of any investigational product within 30 days prior to Visit 1, or five half-lives or twice the duration of the biological effect of the product (whichever is longer)
15. **Chronic use** of non-steroidal anti-inflammatory drugs (NSAIDs) is prohibited within four weeks of Visit 1 (except low dose aspirin [<325 mg/day] for cardioprotection which must have been used at stable dose for at least 4 weeks prior to Visit 1

16. Use of the following medications as shown below:
    a. Corticosteroids administered IV, intramuscularly (IM), subcutaneously (SC) or rectally within 2 weeks prior to Visit 1 (Topical use [e.g., inhaled, nasal, aural or ocular] of corticosteroids is allowed)
    b. Oral corticosteroids at the following doses: prednisone >20 mg/day or equivalent, or budesonide >6 mg/day – 4 weeks prior to Visit 1
    c. Parenteral antibiotics – 2 weeks prior to Visit 1
    d. Local use (enema or suppository) of 5-aminosalicylic acid (5-ASA) within 4 weeks prior to Visit 1
    e. Chronic opioid use – 4 weeks prior to Visit 1
    f. Immunosuppressant use (other than those permitted as per Section 5.10.2) including, but not limited to, cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil and/or apheresis) – 8 weeks prior to Visit 1
    g. Anti-TNFα therapy – 12 weeks prior to Visit 1
17. Changes in dose of the following medications during the time periods shown below:
    a. Oral corticosteroids (change in dose) – 4 weeks prior to Visit 1
    b. Oral corticosteroids (discontinuation) – 2 weeks prior to Visit 1
    c. Oral aminosalicylates (change in dose or discontinuation) – 2 weeks prior to Visit 1
    d. Probiotic therapy (change in dose or discontinuation) – 4 weeks prior to Visit 1
    e. Methotrexate (change in dose or discontinuation) – 8 weeks prior to Visit 1
    f. Azathioprine/6-MP (change in dose or discontinuation) – 12 weeks prior to Visit 1

Exclusion Criteria Related to Medical Conditions and Laboratory Results

18. History of a clinically significant infection within two weeks prior to Visit 1 or during the screening period which may, in the opinion of the Investigator or Medical Monitor, compromise the subject's safety, interfere with the evaluation of study drug or reduce the subject's ability to participate in the study. A clinically significant infection is one requiring treatment with parenteral (IV or IM) antibiotic, antiviral, or antifungal medication or any major infection requiring hospitalisation.
19. History of recurrent, clinically significant bacterial, viral, fungal, mycobacterial or other infections or any major episode of infection requiring hospitalisation or treatment with parenteral medication
20. Known varicella, herpes zoster, or other severe viral infection within six weeks prior to Visit 1
21. A history of TB or latent TB infection, in the absence of documented adequate therapy for the disease.
22. Positive result of TB surveillance as determined (at a minimum) by the QuantiFERON-TB Gold Test (performed at the central lab). The subject may also be evaluated for the presence of TB with any additional test required by local practice.
23. Unable to refrain from travelling to countries with a high prevalence of infectious disease until the end of the study.
24. Congenital or acquired immunodeficiency (including known human immunodeficiency virus [HIV]) or a history of chronic or recurrent opportunistic infections

25. Current evidence of, or recent (within the past five years) treatment for a malignancy other than localised basal cell, squamous cell skin cancer, cervical dysplasia, or cancer in situ that has been resected
26. Evidence of previous or present Hepatitis B or C infection by testing Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (Anti-HBs), Hepatitis B core total antibody (Anti-HBc, Total) and Hepatitis C antibody (Anti-HCV)
27. Stool positive for *C. difficile* or positive for any other enteric pathogen (e.g., *Shigella, Salmonella, Yersinia, Campylobacter*, parasites or parasitic ova)
28. Evidence of hepatic dysfunction, or elevations in serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >2 times the upper limit of normal (ULN), or a total bilirubin value >1.5 times ULN; alkaline phosphatase (ALP) >2 times ULN; current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
29. White blood cell count $\leq 3.0\times10^9$/L or $>18.0\times10^9$/L, serum creatinine >1.5 mg/dL, haemoglobin <9 g/dL, activated partial thromboplastin time (APTT) ≥1.5 times ULN
30. QTc using the Fridericia correction (QTcF) ≥450 msec for males or ≥470 msec for females
31. Concurrent illness or disability that, in the opinion of the Investigator or Sponsor/designee, may affect the interpretation of clinical data, or otherwise contraindicates participation in this clinical study (e.g., an unstable cardiovascular, autoimmune, renal, hepatic, pulmonary, endocrine, metabolic, GI, haematological, or neurological condition or mental study impairment)

Other Exclusion Criteria

32. History of alcohol or drug abuse within the last two years
33. Lactating women
34. If male, planning to donate sperm during or up to 90 days after study

4.5 Subject Withdrawal

All subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. In addition, subjects will be withdrawn from study drug and from the study in the following circumstances:

- The Investigator decides that the subject should be withdrawn. If this decision is made because of an intolerable AE or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. The Medical Monitor is to be notified immediately.
- The subject is unwilling to continue in the study.
- Noncompliance or protocol violations that in the opinion of the Investigator or Sponsor/designee necessitates the subject being removed. The decision to withdraw the subject should be taken in consultation with the Medical Monitor.
- Pregnancy
- Events that require emergency unblinding
- Has infectious complications that require stopping or reduction of immunosuppressive therapy

- Requires any abdominal surgery or surgery for fistula or abscesses; the decision to withdraw the subject should be taken in consultation with the Medical Monitor.
- The Investigator or the Sponsor, for any reason, stops the study.

In general, before the decision is made to withdraw the subject, consultation with the Medical Monitor is recommended.

If a subject chooses to withdraw from the study (permanently stop taking the study drug), they will be encouraged to return to the site for safety reasons to complete the assessments planned for Visit 5 (Day 42) during an Early Termination Visit and for the Follow-up Visit (Day 56).

The Investigator should ensure that all reasonable attempts (telephone calls, contact with primary care physician, certified letter) are made to obtain follow-up safety information on subjects who do not return to the site for study visits or are lost to follow-up.

Subjects who are withdrawn from the study after randomisation and who receive at least one dose of study drug will not be replaced. These subjects cannot be rescreened.

Subjects who withdraw from the study after dosing should be advised by the Investigator to continue contraception restrictions for 90 days after the last administration of study drug.

The Investigator will ensure that the reasons for withdrawal are documented on the subject's medical records (source documents) and in the electronic Case Report Form (eCRF). If the subject withdraws due to an AE, the details of the AE must be entered on the AE section of the eCRF. If the reason for subject withdrawal is not known, every effort must be made to contact the subject to establish the reason for withdrawal.

4.6 Lost to Follow-up

Subjects will be considered lost to follow-up when they fail to attend study visits without stating an intention to withdraw from the study. The Investigator should show due diligence by documenting in the source documents the steps taken to contact the subject through at least three telephone calls and/or emails and one registered letter. The subject should be recorded as "lost to follow-up" in the eCRF if all reasonable attempts made to contact the subject have failed.

5.0 STUDY TREATMENTS

5.1 Treatments Administered

The subjects in this study will receive either V565 (three 185-mg capsules for a dose of 555 mg TID, for a total daily dose of 1665 mg) or an equal number of matching placebo capsules (TID) for 42 days (six weeks).

5.2 Identity of Investigational Product(s)

V565 is a 115 amino acid 12.6 kDa single domain variable heavy chain antibody (VHH), active against human TNFα. The antibody is manufactured in *Saccharomyces cerevisiae*.

The drug substance is formulated into 3 mm round mini-tablets. The mini-tablets are coated with a polymer sub-coat and a Eudragit® enteric coat is applied to engender release in the required area of the GI tract. Once coated, the mini-tablets are encapsulated in hydroxypropyl methylcellulose (HPMC) capsules.

The formulation is engineered to release the mini-tablets from the capsules in the stomach. The size of the mini-tablets enables them to escape through the pylorus and migrate through the GI tract. The mini-tablet coating releases active molecule at a pH designed to ensure delivery of high concentrations of V565 to the ileum and distal parts of the GI tract.

The components of the V565 drug product are presented in Table 1.

There is one dose strength for V565 active capsules. The V565 dose per capsule is 185 mg. Each 185 mg Size 00 pink opaque HPMC capsule contains 15 mini-tablets. Placebo HPMC capsules are identical to capsules containing V565 and contain an equivalent number of mini-tablets of identical size, shape, and colour. The placebo mini-tablets are made of the same components as in Table 1 but contain no active V565.

Table 1: Components of V565 Drug Product

Component	Purpose
Mini-tablet Cores	
V565	Active ingredient
Mannitol	Compression aid
Microcrystalline cellulose	Compression aid
Croscarmellose sodium	Super disintegrant
Magnesium stearate	Lubricant
Sub-coat	
Hydroxypropylmethyl cellulose	Polymer coat
Enteric Coat	
Eudragit®	Enteric polymer coat
Triethyl citrate	Plasticiser
Talc	Anti-tacking agent
Sodium lauryl sulphate	Surfactant

5.3 Storage

All study drug will be stored below 25°C in an adequate storage area, which is a secure, temperature controlled, locked environment with restricted access. Study drug must not be refrigerated or frozen.

No special procedures for the safe handling of V565/placebo are required.

The Sponsor and their authorised representatives such as study monitors or auditors as well as regulatory inspectors will be permitted, upon request, to audit the supplies, storage and dispensing procedures and records in accordance with applicable regulatory requirements, provided that the blind of the study is not compromised.

Once study drug has been dispensed to study subjects, it should be stored in accordance with the instructions on the label.

5.4 Supply, Packaging and Labelling

Bulk V565/placebo will be manufactured and supplied by

Capsules will be packed into Duma special high-density polyethylene (HDPE) containers fitted with a low-density polyethylene tamper evident cap in compliance with EU Good Manufacturing Practice (GMP) conditions and labelled in accordance with local regulations (Duma Handycap manufactured by Gerresheimer Pharmasystems). Matching placebo will also be supplied.

Study drug will be labelled with multi-language booklets in accordance with GMP and country-specific regulations as required by the regulatory bodies in the countries where the study is conducted.

5.5 Accountability

In accordance with GCP, the Investigational Site will account for all supplies of V565/placebo. Details of receipt, storage, assembly, and return will be recorded.

All unused supplies of V565/placebo will be returned to the Sponsor at the end of the study in accordance with instruction by the Sponsor. The study drug may be destroyed at the site with the consent of the Sponsor.

5.6 Method of Assigning Subjects to Treatment Group

Once the subject provides an informed consent and meets inclusion and exclusion criteria, the study site will request the study drug assignment using the Interactive Web Activated Response System (IWRS). Approximately 126 subjects will be randomised in a 2:1 ratio (84 subjects in the V565 arm and 42 subjects in the placebo arm). Randomisation will be stratified to ensure treatment groups have similar rates of prior anti-TNFα therapy.

5.8 Selection and Timing of Dose for Each Subject

Each dose will consist of three capsules of V565 (three 185-mg capsules, total dose 555 mg) or placebo. Study drug will be administered orally TID. The subjects will be instructed to take the capsules with sufficient fluid one hour before meals and at least two hours after the previous meal.

No dose adjustments are permitted.

5.9 Blinding

This is a randomised, double-blind, placebo-controlled study with limited access to the randomisation code. Study drug and placebo capsules will be identical in physical appearance. The treatment each subject will receive will not be disclosed to the Investigator, study site staff, subject, Sponsor, designee or contracting clinical safety laboratories.

Investigators are strongly discouraged from requesting the blind be broken for an individual subject, unless there is a subject safety issue that requires unblinding and would change subject management.

The decision to break the blind in an emergency situation remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented. Emergency unblinding should only be performed by the Investigator through the IWRS. In case of unblinding, the subject should be withdrawn from the study (permanently stops the study drug, but attends the Early Termination Visit and Follow-up Visit if possible).

5.10 Prior and Concomitant Treatments

All medications (prescription and non-prescription), treatments, and therapies taken by the subject from the time consent is signed throughout their entire participation in the study, including those initiated prior to the start of the study, must be recorded on the subject's source document and on the appropriate page of the eCRF. The dose, unit, frequency, route, indication, date the medication was started, and date the medication was stopped (if not ongoing) must be recorded.

5.10.1 Prior and Concomitant Medications

The use of medications in the 12 weeks prior to Visit 1 should be reported in the eCRF, indicating the dose, frequency, indication and start and stop dates. The use of some prior medication or therapy more than 12 weeks prior to Visit 1 may affect a subject's eligibility

for enrolment. These medications are listed in the exclusion criteria (see Section 4.4). Details about medications prohibited during the study are presented in Section 5.10.3.

5.10.2 Permitted Medications

Medications considered necessary for the safety and well-being of the subject may be permitted during the study at the discretion of the Investigator provided they are not listed as a prohibited medication in Section 5.10.3.

- Background CD Therapy: Subjects will remain on their background CD therapy throughout the study. It should be noted that the doses of background concomitant medications given for the treatment of CD may not be changed during the study. No new background CD therapy may be added to the subject's treatment regimen after Visit 1.
- Oral Corticosteroids:
- Oral Aminosalicylates:
- Methotrexate:
- Azathioprine/6-MP:
- Oral Antibiotics:
- NSAIDs such as low dose aspirin [<325 mg/day] may be continued at an unchanged dose.
- Probiotics may be continued at an unchanged dose.

5.10.3 Prohibited Medications

The use of the following medications either alone or in combination for the treatment of CD is prohibited **during the study.**

- Local use (enema or suppository) of 5-ASA
- Corticosteroid administered IV, IM, SC or rectally. (Note: topical use [e.g., inhaled, nasal, aural or ocular] of corticosteroid is allowed during the study.)
- Use of other immunosuppressant agents (other than those permitted as per Section 5.10.2) or therapy (e.g., apheresis) including, but not limited to, cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil
- Anti-TNFα therapy other than the study drug.
- Any other biological therapy for IBD.

- Parenteral or enteral nutrition therapy.
- Chronic use of NSAIDs other than for cardioprotection (as detailed in Section 5.10.2).
- Chronic use of opioids (e.g., codeine, fentanyl, tramadol, etc.).
- Vaccination with live, attenuated, or recombinant vaccines.

Note: Subjects should not discontinue prohibited pre-existing background CD medications prior to Visit 1 in order to qualify for the study.

The use of any prohibited medication is considered a protocol deviation and the details including the starting date and its dosage should be recorded in the eCRF. Subjects should be withdrawn from the study if any prohibited medications are taken or if background CD therapy is changed during the study.

5.11 Medical Care of Subjects after End of Study

The Sponsor will not provide any additional care to subjects after they leave the study. Subjects will return to the care of their personal physician.

5.12 Treatment Compliance

It is the Investigator's responsibility to ensure that subjects are instructed in the proper use of study drug and that the subjects are fully compliant with their assigned dosage regimen, as well as the timing for taking the study drug relative to meals (see Section 5.8).

The prescribed dosage, timing, and mode of study drug administration may not be changed. Any departures from the intended regimen must be recorded in the eCRF.

At Day 14 and Day 42, previously dispensed study drug will be retrieved by the Investigator and compliance assessed. Subjects will be asked to return all unused medication at each visit.

Adequate compliance is defined as taking between 80% and 120% of dispensed study drug. Compliance problems (e.g., missing 2 or more consecutive full days [at least 6 doses] or taking less than 80% or more than 120% of the doses between study visits) should be discussed with the Medical Monitor to determine if the subject may continue in the study.

5.13 Study Drug Accountability

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study drug using the Drug Accountability Form. These forms must be available for inspection at any time.

All study drug supplies should be accounted for at the termination of the study and a written explanation provided for discrepancies. All unused study drug supplies and packaging materials are to be inventoried and returned by the Investigator as instructed by the Sponsor. The study drug may be destroyed at the site with the consent of the Sponsor.

6.0 EFFICACY, PHARMACOKINETIC, SAFETY, HEALTH OUTCOME, AND PHARMACOGENOMIC ASSESSMENTS

6.1 Efficacy Assessment

6.1.1 Subject Diary

During Visit 1, a diary will be given to each subject. Subjects will be trained how to complete the diary and instructed in the use of the diary. The importance of completing the diary daily throughout the study will be stressed. The subject will complete the diary daily throughout the study until Day 42 (the End of Treatment Visit). The diary will be used to record the subject-reported variables of the CDAI,

Site personnel will assess the subject's compliance with the use of the diary throughout the study.

During the screening period, subjects must have entered sufficient diary data to allow calculation of the CDAI score (see Section 6.1.2). Subjects with poor compliance completing the diary during screening will be considered screen failures. Subjects with poor compliance completing the diary during the treatment period may be withdrawn from the study.

The data obtained from the subject diary will be used for calculation of the subject-reported variables of the CDAI and other efficacy outcomes measures such as the PRO-2,

The subject will record the following information in the subject diary to assess CD activity:

1. Number of liquid or very soft stools
2. Abdominal pain/cramps
3. General well-being
4. Fever over 100°F (37.8°C)
5. Use of anti-diarrheal drugs (e.g., loperamide, diphenoxylate, or opiates)

6.1.2 Crohn's Disease Activity Index

Crohn's Disease Activity Index (CDAI) is the most commonly used measure of clinical activity in patients with CD [12, 13, 14]. Some of the data used to calculate the CDAI is obtained from the subject diary (see Section 6.1.1) and some is obtained at site visits. The CDAI will be calculated at the time points identified in .

The CDAI consists of eight variables:

1. Total number of liquid or very soft stools (total for previous 7 days)
2. Abdominal pain/cramps rating (total for previous 7 days)

3. Subjective general well-being rating (total for previous 7 days)
4. Total number of listed categories the subject has experienced during the last 7 days (Note: all of these are assessed by the Investigator with the exception of fever, which is obtained from the subject diary.)
    a. Arthritis or arthralgias
    b. Iritis/uveitis, erythema nodosum, or pyoderma gangrenosum
    c. Aphthous ulcers
    d. Anal fissures, fistulae, or abscess
    e. Other fistula (specified by site personnel)
    f. Fever higher than 100°F or 37.8°C during previous week
5. Use of anti-diarrheal drugs (e.g., loperamide, diphenoxylate, or opiates)
6. Presence of abdominal mass
7. Anaemia based on haematocrit (HCT) value entered into formula:
    a. For men = 47 – HCT value
    b. For women = 42 – HCT value
8. Body weight in kilograms (kg) entered into formula:
    a. ([standard weight in kg – actual weight kg] / [standard weight in kg]) x 100%

The responses are scored numerically and weighted. Total CDAI scores range from 0 to approximately 600 points; a higher score indicates a more active disease. A CDAI score of <150 points denotes remission, a score between 150 to 219 points denotes mildly active disease, a score of ≥220 to ≤450 points denotes moderately active disease, and a score of >450 points denotes severe disease.

During the study, the CDAI will be calculated from the scores obtained from the subject-reported variables of the CDAI and the results recorded at the site. Haematocrit values will be extracted from the central laboratory results and used for the calculation of the CDAI score.

Subjects who prematurely discontinue treatment prior to Day 42 will be asked to continue to record CDAI data until the Early Termination Visit.

Instructions for recording the CDAI score will be given at Visit 1 (see Section 6.1.1). Data should be reviewed at each study visit, including unscheduled visits.

A sample of a CDAI score worksheet is provided in the Appendix (Section 12.1)

6.1.3 Biomarkers of Inflammation

The collection of CRP and/or FCP will occur at the time points indicated in .

C-reactive protein is an acute-phase reactant produced in the liver and is an easily measured non-specific marker of inflammation. It is a widely used marker of inflammation in CD and elevations in CRP have been associated with endoscopic inflammation in CD [15, 16].

C-reactive protein will be analysed in blood samples. If CRP values are normal, FCP will be assessed in the faecal samples. FCP will be used as the eligibility test if CRP results are <5 mg/L. During the treatment and follow up phase of the study, FCP will only be evaluated in subjects whose screening CRP was <5 mg/L, and who qualified for the study based on their screening FCP value.

Calprotectin is abundant in the cytosol of activated neutrophils. The amount of FCP is directly proportional to neutrophil influx into the intestinal tract and is a reliable non-specific marker of intestinal inflammation [17, 18, 19]. While currently endoscopy with biopsy is considered the gold standard for evaluating the extent and location of inflammatory mucosal lesions, studies have shown that FCP may also be a useful marker of intestinal inflammation.

On Day 1, the faecal sample for FCP should be collected prior to administration of the first dose of study drug. The subject may also provide a sample from faeces passed one day prior to the scheduled visits. These samples will be collected in sterile containers (to be provided to the subjects) and refrigerated at home. At each sampling time point, approximately 2 g to 5 g of faeces will be collected.

6.1.4 Abdominal Pain and Stool Frequency Instrument (PRO-2)

PRO-2 will be calculated at the time points indicated in .

The PRO-2 is a composite score that measures abdominal pain and soft stool frequency averaged over seven days [20]. The data for the total PRO-2 score is extracted from selected subject-reported variables of the CDAI included in the subject diary. These data are the entries for the number of liquid or soft stools/day and abdominal pain (rated on a scale of 0-3) assessed over the course of seven days.

6.1.5 Ileocolonoscopy

It is important to confirm that subjects are eligible for the ileocolonoscopy prior to Visit 2. During the screening period, subjects must have entered sufficient diary data to allow calculation of the CDAI score, have CDAI scores ≥220 to ≤450 and CRP level ≥5 mg/L [or if CRP is normal, FCP level ≥250 µg/g]). The timing of the Visit 2 is flexible but the ileocolonoscopy must not be done until it has been documented that the subject is eligible for the ileocolonoscopy.

It should be noted that subjects who have had an ileocolonoscopy within 12 weeks of Visit 1 do not require an ileocolonoscopy at Visit 2 ***provided it is forwarded to the central reader and was performed in such a way as to enable evaluation by the central reader.***

Video images of all endoscopic procedures will be captured and sent to a qualified central reader.

The images will be examined to determine the central reader's overall impression of the state of mucosa to assess eligibility for randomisation and to calculate the SES-CD (see

Section 6.1.6). Active disease must be confirmed by the central reader in order for the subject to proceed to Visit 3 and randomisation on Day 1.

6.1.6 SES-CD

The SES-CD assesses the mucosal appearance of the intestine in subjects with CD [21]. It includes four variables: ulcer size, the extent of ulcerated surface, extent of affected surface, and stenosis.

Each of these four components are assessed in the five segments of the ileum and colon: ileum, right colon, transverse colon, left colon (descending and sigmoid), and rectum. The SES-CD is the sum of the individual scores of each of the components across the five segments. For the SES-CD, a higher score indicates more severe disease.

In addition to obtaining baseline information on the condition of the mucosa, changes in overall mucosal appearance and changes in the SES-CD in response to treatment will be evaluated in an exploratory endoscopy substudy. This substudy will include subjects with a baseline SES-CD ≥7 (if ileum and colon are involved) or ≥4 (if the lesions are confined to the ileum). These subjects will have an additional ileocolonoscopy at Day 42.

6.1.7 Exploratory Efficacy Measures

6.2 Safety Assessments

Safety will be monitored during the study as detailed in . Safety variables include evaluations of AEs, laboratory evaluations, vital signs, physical examinations, ECGs and concomitant medications.

6.2.1 Adverse Events

Definition of AE: An AE is any untoward medical occurrence in a subject enrolled in this study (i.e., that occurs after the informed consent form [ICF] is signed), regardless of its causal relationship to study drug.

An AE can therefore be any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease.

An AE includes a/an:

- Exacerbation of a pre-existing condition or disease.
- Increase in frequency or intensity of a pre-existing condition.
- Continuous persistent pre-existing disease or symptoms that worsen after the subject provides informed consent.

If a clinically significant abnormal laboratory finding or other abnormal test result meets the definition of an AE or SAE, then the AE eCRF page or SAE eCRF page must be completed, as appropriate. Clinically significant laboratory results include those that:

- Result in discontinuation from the study.

- Require treatment or any other therapeutic intervention.
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality).
- Are associated with clinical signs or symptoms judged by the Investigator to have a clinically significant impact.

A diagnosis (if known), or clinical signs and symptoms (if diagnosis is unknown), rather than the clinically significant abnormal laboratory finding or test result, should be entered on the AE or SAE eCRF page. If no diagnosis is known and clinical signs and symptoms are not present, then the clinically significant abnormal finding should be recorded as an AE.

An AE does not include a/an:

- Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE. Any complication of the procedure is also considered to be an AE.
- Pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and/or convenience admissions).
- The disease or disorder being studied or sign or symptom associated with the disease or disorder, unless more severe or frequent than expected for the subject's condition.

Any medical condition that is present prior to informed consent should be recorded as medical history and not be reported as an AE.

Treatment-emergent Adverse Event: A TEAE is defined as

1. A new event that occurs during or after treatment with study drug or
2. Any event present at Baseline that worsens in either intensity or frequency after exposure to study drug.

Definition of Serious Adverse Event:

An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to study drug or not), that, at any dose:

- Results in death – the death was an outcome of an AE.
- Is life-threatening (the subject is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalisation or prolongation of existing hospitalisation: Hospital admissions and/or surgical operations planned before or during a study

are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

- Results in persistent or significant disability/incapacity, i.e., the AE resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the AE resulted in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life
- Is a congenital abnormality/birth defect in the offspring of a subject who received drug – it is suspected that exposure to study drug prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
- Other: Medically significant events, which do not meet any of the criteria above, but may jeopardise the subject and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation.

Other Adverse Event Definitions:

An Adverse Drug Reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose.

An Unexpected ADR is defined as any adverse reaction, the nature of which is not consistent with the applicable product information and is unexpected. An adverse reaction is 'unexpected' if its nature and severity are not consistent with the information about the medicinal product in question set out in Section 7 of the IB.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., for applicable product information, include the IB for an unapproved investigational product or the package insert/summary of product characteristics for an approved product). Therefore, if a treatment-related SAE occurs and it was not mentioned in the applicable product information, then it will be reported as a SUSAR.

Definitions of Severity

The severity of the AE will be characterised as "mild, moderate or severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject's usual daily activity.

Definitions of Relationship

Causal relationship must be assessed by the Investigator answering the following question:

'Is there a reasonable possibility that the drug caused the event?'

Yes There is a reasonable or strong temporal relationship, and the events are unlikely attributed to other drugs, underlying diseases or other factors.

No There is no strong temporal relationship, and/or use of other drugs, underlying diseases, or other factors provide plausible explanations for the occurrence of the event.

6.2.1.1 Monitoring of Adverse Events

The Investigator is responsible for recording all AEs observed during the study (screening, treatment, and follow-up periods). At each visit, the subject will be asked if they have experienced any untoward occurrence since the last trial visit. In addition, subjects will be instructed to contact the study site at any time after the ICF is signed if any symptoms develop.

All AEs/SAEs should be recorded individually in the study subject's own words (verbatim) unless, in the opinion of the Investigator, the AEs/SAEs constitute components of a recognised condition, disease, or symptom. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE rather than the individual signs/symptoms.

All AEs will be recorded on the eCRFs and include a description of the event, severity, time of occurrence, and duration. In addition, any action (e.g., treatment and follow-up tests) and the outcome should be provided along with the Investigator's assessment of the relationship to the investigational drug.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In cases in which the subject dies, the cause of death should be recorded as an SAE; death is considered the outcome of the SAE.

Adverse events should be followed until recovery to the normal state has been achieved. In the event of a subject not returning to the study site, the outcome of this event will be recorded as unknown.

6.2.1.2 Recording of Adverse Events

All AEs that occur after the subject has signed consent (regardless of severity and/or perceived relationship to study drug) are to be recorded on the appropriate AE sections (either

'serious' or 'non-serious') in the eCRF. Spontaneously reported SAEs that occur for up to 30 days after the last dose of study drug will also be recorded. The Investigator should complete all the details requested including dates of onset, severity, action taken, outcome, relationship to study drug. Each event should be recorded separately.

6.2.1.3 Reporting of Serious Adverse Events

In the case of an SAE (including SUSARs), the Investigator must complete, sign and date the SAE pages from the eCRF, and check that the data are consistent.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the study drug, must be reported immediately (within 24 hours of the study site's knowledge of the event) by sending a completed, separate SAE Report Form by fax or email to as displayed below::

Contact Method	
Fax	
Email	

The report will contain all available information concerning the SAE to enable the Sponsor (or an authorised representative) to file a report, which satisfies regulatory reporting requirements. These timelines apply to initial reports of SAEs and to all follow-up reports.

All SAEs will be recorded on the SAE Report Form, the Adverse Events Form in the eCRF, and source documents. Criteria for documenting the relationship to study drug as well as severity and outcome will be the same as those previously described.

SAEs considered causally related to study treatment that are spontaneously reported to the Investigator more than 30 days after a subject's last dose of study drug should also be collected and reported as described previously, regardless of the time after the trial.

The information must include at least the following:

- Name, address, and telephone number of the reporting Investigator
- Investigational product and study code.
- Subject identification number, sex, and date of birth (recorded as permitted by local authorities).
- Description of the AE, measures taken and outcome.
- Preliminary classification of causal relationship by the Investigator

Additional follow-up information should be completed on an SAE Form with a copy sent to and the original included in the SAE section of the eCRF.

6.2.1.4 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

Investigators will be notified of all SAEs that require prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor or [redacted] will ensure that all applicable SAEs are reported to the appropriate regulatory authorities on behalf of the Sponsor. In countries where the sponsor is responsible for IEC submissions of applicable SAEs, this will be performed by [redacted]

6.2.1.5 Follow-Up of Adverse Events

Any AEs observed from Screening/randomisation up to the final study visit will be followed up to resolution. Resolution means that the subject has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE.

6.2.1.6 Pregnancy

Females of childbearing potential will have a serum pregnancy test performed at Screening and a urine pregnancy test at Day 1 to ensure the exclusion of pregnant women from the study. Female subjects will be instructed to inform the site if they become pregnant during the study. Male subjects will be instructed to inform the site if their partner becomes pregnant during the study.

Female subjects of childbearing potential will have an additional test for pregnancy at Day 42 (the end of the study) and at Day 56 (the Follow-up Visit). In addition, a pregnancy test will be performed at the Early Termination Visit, if a female of childbearing potential discontinues the study prior to Day 42.

Any known or suspected pregnancy that occurs during the study (either in female subjects or female partners of male subjects) must be reported to [redacted] within 24 hours of the time the Investigator becomes aware of the event, using the Pregnancy Report Form. Suspected pregnancies in subjects will be confirmed with a pregnancy test. Pregnant females will be discontinued from the study.

The Sponsor/designee has a responsibility to monitor the outcome of all pregnancies reported during the study. The Investigator must follow up and document the course and the outcome of all pregnancies even if the subject withdraws consent or the study has finished.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of contraceptive medications or a suspected AE is associated with pregnancy.

Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalisation for normal delivery of a healthy new-born should not be considered an SAE.

All outcomes of pregnancy must be reported by the Investigator to [redacted] on the Pregnancy Outcome Report Form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion. The Investigator must follow up and document the course and the outcome of all pregnancies even if the subject was withdrawn from the study or if the study has finished. The pregnancy will be followed up to delivery; the Investigator must report any complications that occur even though the study has finished.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (see Section 6.2.1.3).

6.2.2 Contraception

The need to avoid pregnancy and acceptable methods of contraception should be discussed with male subjects and female subjects of childbearing potential prior to the administration of study drug.

Females of childbearing potential must have a negative serum pregnancy test at Visit 1, a negative urine test at Day 1, and agree to use effective contraception from signing informed consent and for at least 90 days after the last dose of study drug. Males who are sexually active with a female partner of childbearing potential must be willing to use effective contraception from signing informed consent and for 90 days after the study.

1. Females of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation, salpingectomy, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as no menses for ≥12 months without an alternative medical cause. Females with questionable menopausal history (e.g., irregular menstrual periods and age >40 years) are considered to be of childbearing potential.

2. Females of childbearing potential must use acceptable highly effective (according to Clinical Trial Facilitation Group [CTFG] recommendations) methods of birth control in this study. These include:

    - Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
        - oral
        - intravaginal
        - transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation
        - oral
        - injectable

- implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner (provided that partner is the sole sexual partner of the female of childbearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success.)
- Sexual abstinence must be true sexual abstinence defined as refraining from heterosexual intercourse as part of the preferred and usual lifestyle of the subject. This behavior must cover the entire period of risk associated with the study treatment, which includes at least the time of screening up to at least 90 days after the end of treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study. Periodic abstinence (e.g., calendar ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

3. Fertile males who are sexually active with a female partner of childbearing potential must agree to use contraception (condom plus spermicide or partner using acceptable highly effective method) from signing informed consent and for 90 days after last dose.

4. Fertile males should be instructed that they are not to donate sperm during the study or up to 90 days the last dose of study drug.

5. Subjects must follow the strictest applicable local requirement in regards to contraception as specified by the Regulatory Agency or Ethics Committee approving the trial.

6.2.3 Clinical Laboratory Evaluations

Blood will be drawn and urine samples will be collected from each subject at each study visit. The clinical laboratory parameters used as screening tests, efficacy outcomes or for safety monitoring are presented in Table 2.

Clinical laboratory tests will be reviewed for results of potential clinical significance throughout the study (see Section 6.2.1 for definition of clinically significant laboratory results). If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE. However, if possible, the underlying condition causing the laboratory abnormality, rather than the abnormality itself, should be reported as the AE. Clinically significant laboratory results will be followed to resolution or until the Investigator considers the abnormality chronic and/or the subject to be stable.

A central laboratory designated by the Sponsor will be used for all laboratory assessments during the trial. Urine pregnancy testing will be done by dipsticks (supplied by the central laboratory).

If an immediate result is required, a sample should be sent to both the local and central laboratory.

Table 2: Clinical Laboratory Testing

Haematology: White blood cell count (differential, percentages and absolute count) Haemoglobin Haematocrit Red blood cell count Mean corpuscular volume Mean corpuscular haemoglobin Mean corpuscular haemoglobin concentration Red cell distribution width Platelet count Urinalysis: Colour Clarity/Appearance Specific gravity pH Protein Blood Glucose Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase Microscopy Additional Tests (Screening only): Activated partial thromboplastin time Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core total antibody Hepatitis C antibody *C. difficile* toxin and presence of other enteric pathogens QuantiFERON-TB Gold Test	Serum Chemistry: Sodium Potassium Blood urea nitrogen/Urea Creatinine Glucose Calcium Phosphorus Total protein Albumin Aspartate aminotransferase Alanine aminotransferase Total bilirubin Alkaline phosphatase Additional Tests (Females of childbearing potential): Serum pregnancy test (at Visit 1) Urine pregnancy at Day 1, Day 42 and Day 56 If the urine pregnancy test gives equivocal results at these visits, or is positive, a serum pregnancy test will be performed to determine if the subject is pregnant. Biomarkers C-reactive protein Faecal calprotectin

6.3 Vital Signs, Physical Examination and Other Safety Assessments

6.3.1 Vital Signs

Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and body temperature. These data will be collected at the visits indicated in .

Blood pressure (measured after at least five minutes in the sitting position) and HR (measured after at least five minutes in the sitting position) will be recorded at every study visit. Automatic or manual devices may be used, but the same device should be used for any given subject throughout the study wherever possible. The same arm should be used for all measurements, if possible. Blood pressure and HR should be measured after the subject has rested (sitting quietly) for at least five minutes, and more than 10 minutes after any blood draw.

Temperature will be measured as per local standard of care.

6.3.2 Physical Examination, Height and Weight

A full physical examination will be performed at the time points indicated in . Physical examinations will be performed by a physician. The complete physical examination performed at Visit 1 and Day 42 will include the examination of the following:

- General appearance
- Eyes
- Ears, nose, throat
- Chest/respiratory
- Heart/cardiovascular
- Gastrointestinal/liver musculoskeletal/extremities
- Dermatological/skin
- Thyroid/neck
- Lymph nodes
- Neurological/psychiatric

At other time points (Day 1, Day 14 and Day 56), a brief physical examinations will include assessments of the skin, lungs, cardiovascular system, abdomen (liver and spleen) and other symptom-directed assessments as appropriate.

Weight (without shoes and in normal street clothes) will be measured at each study visit.

Height (without shoes) and body mass index (BMI) will be measured at Baseline.

6.3.3 Electrocardiogram

Electrocardiograms will be evaluated at the time points indicated in . Electrocardiogram recordings will be obtained after the subject has been supine and at rest for at least five minutes. ECG results will be evaluated at the investigational site to monitor safety during the trial. The Investigator or designee will review, sign, and date each ECG reading. The Investigator or designee will determine if any abnormal results are of clinical significance. The ECG will be repeated if any results are considered by to be clinically significant.

6.3.4 Medical History

Medical history (including CD history) will be collected at Visit 1.

A complete medical history will include evaluation (past or present) of the following:

- General
- Head and neck
- Eyes, ears, nose, throat
- Chest/respiratory
- Heart/cardiovascular
- Gastrointestinal/liver
- Gynaecological/urogenital
- Musculoskeletal/extremities
- Skin
- Neurological/psychiatric
- Endocrine/metabolic
- Haematologic/lymphatic
- Allergies/drug sensitivities
- Past surgeries
- Substance abuse
- Any other diseases or disorders

A detailed history of CD, including date of diagnosis, disease severity, disease duration, disease location, associated complications, hospitalisations and extra-intestinal manifestations will be collected during Screening. The subject's CD drug history will also be recorded.

6.4 Immunogenicity

Blood samples will be evaluated for the presence of anti-V565 antibody at the time points indicated in . Samples will be collected, labelled, stored, and shipped as detailed in the Central Laboratory Manual. Samples will be processed by LG

6.5 Pharmacokinetics

The concentration of V565 will be determined in serum, and urine at the time points indicated in . Samples will be collected, labelled, stored, and shipped as detailed in the Central Laboratory Manual. Samples will be processed by

6.5.1 Blood

Samples will be obtained for the determination of V565 in serum. The following information will be captured for blood sample collection in each subject's eCRF:

1. Subject's study number and initials
2. Time and date of first V565 dose administration on Day 1 and time and date of the most recent V565 dose prior to PK sampling on Day 14 and 42.
3. Time and date of each blood sample collected for PK analysis
4. Time and date of subject's most recent ingestion of food prior to dose administration Samples will be collected, processed, labelled, stored, and shipped as detailed in the Central Laboratory Manual.

6.5.2 Urine

Urine samples for analysis of V565 in urine will be collected as follows:

1. Prior to administration of the first dose of V565 on Day 1. Date/time of urine collections will be captured in each subject's eCRF.
2. Post-dose on Day 1, 4 to 8 hours after the first dose of study drug, prior to leaving the clinic
3. During the Day 14 and Day 42 visits, complete urine voids will be collected prior to the subject leaving the clinic. The weight (g) or volume (mL) and pH of the urine void along with the date/time of urine collections will be captured in each subject's eCRF. Date and time of the last dose prior to urine collection will also be captured in the eCRF.

Aliquots of the respective urine sample will be frozen and stored until determination of V565 concentration as outlined in the Central Laboratory Manual.

6.6 Pharmacogenetics

A blood sample for exploratory genetic research will be obtained from consenting subjects pre-dose, at Visit 3 (Day 1). Although genotype is a stable parameter, sample collection prior to the first dose on Day 1 is preferred to avoid introducing bias through excluding subjects who may withdraw due to an AE; it is important to include such subjects in any genetic analysis. If the sample is not drawn at Visit 3 (Day 1), it may be taken at any visit until the last study visit. Only one sample should be collected per subject for possible genetic analysis. Samples will be collected, labelled, stored, and shipped as detailed in the Central Laboratory Manual.

Participation in this optional genetic research is voluntary. A separate ICF will be used for subjects who elect to contribute samples for pharmacogenetic analyses. This sample may be

analysed only for genes involved in the drug metabolism, safety, and clinical efficacy of V565. These samples may provide information on how individuals metabolise and react to the study drug.

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years from the date of the last subject's last visit, after which they will be destroyed. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. No personal details identifying the individual will be available to any person.

6.7 Appropriateness of Measurements

All efficacy, safety, and tolerability assessments used in this study are standard and generally accepted as appropriate for this type of study.

7.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the Sponsor is responsible for study drug documentation and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Central laboratories for clinical laboratory parameters
- Site Initiation visit
- Early site visits post-enrolment
- Routine site monitoring
- Ongoing site communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report

In addition, the Sponsor and/or Quintiles Clinical Quality Assurance Department may conduct periodic audits of the study processes, including, but not limited to study site, site visits, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorised for all study related documents including medical history and concomitant medication documentation to authorised Sponsor's representatives and regulatory authorities.

7.1 Monitoring

The Sponsor has engaged the services of a contract research organisation (CRO), to perform all monitoring functions within this clinical study. monitors will work in accordance with SOPs. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study site, informing the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, monitors will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study site.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each site while subjects are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification).

7.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of C

Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study site. Data collection will be completed by authorised study site staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorised study site staff prior to the study being initiated and prior to any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to sign off electronically on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, and the time and date of the change will be logged. Roles and rights of the site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study site staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application, meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents

and sources of information used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study drug, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

eCRF records will be automatically appended with the identification of the creator by means of their unique UserID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and Anatomical Therapeutic Chemical (ATC) system. Concomitant diseases/medical history will be coded using MedDRA.

7.3 Quality Assurance Audit

Study sites, the study database and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or [redacted] on behalf of the Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

8.0 STATISTICS

8.1 Determination of Sample Size

The sample size is based on being able to claim superiority of V565 over placebo; the primary endpoint is defined as a response rate, based on CDAI reduction/remission and CRP or FCP results.

A subgroup of subjects will be assessed by endoscopy for changes in overall mucosal appearance and changes in SES-CD. However, the study is not powered to show a difference in these endpoint.

8.2 Statistical Methods

The default summary statistics for continuous variables include number of contributing observations [n], mean, standard deviation (SD), median, minimum, and maximum.

For categorical variables, the number and percentage (the percentage of subjects in each category relative to the total number of subjects in the relevant analysis population or relative to the total number of subjects in the relevant analysis population, with assessments available [where appropriate]) in each category will be the default summary presentation.

Unless otherwise specified, “Baseline” is defined as the last observed value of the parameter of interest prior to the first intake of study medication (this includes unscheduled visits). For numerical variables, change from Baseline will be calculated as the difference between the value of interest and the corresponding baseline value.

Unless otherwise specified, all formal statistical tests will be two-sided at the 5% significance level. Point estimates of treatment differences will be accompanied with two-sided 95% confidence intervals (CIs) where applicable.

In the case of normality assumption violations, appropriate non-parametric methods will be used for analysis.

All data will be presented in by-subject listings.

The statistical analysis will be performed using SAS® Version 9.2 or higher.

8.2.1 Primary Efficacy Analysis

The primary clinical efficacy endpoint of the study is the proportion of subjects at Day 42 that have both CDAI ≥70-point reduction from Baseline or CDAI <150, ***and*** a reduction of ≥40% from the baseline value of CRP or FCP.

8.2.2 Secondary Efficacy Analyses

The secondary endpoints below will be analysed using the same model as used in the primary endpoint analysis.

- Proportion of subjects achieving a ≥100-point reduction in CDAI score and a concomitant reduction of 50% in CRP or FCP at Day 42
- Proportion of subjects achieving a ≥70-point reduction in CDAI score at Day 42
- Proportion of subjects achieving a ≥100-point reduction in CDAI score at Day 42
- Proportion of subjects achieving a CDAI score of <150 CDAI at Day 42

For the PRO-2 score assessments, the changes in total scores from Baseline to Day 14 and Day 42 will be analysed using a Mixed Model for Repeated Measures (MMRM) with treatment as the fixed effect, prior anti-TNFα and baseline scores as covariates.

8.2.3 Exploratory Analyses

The exploratory endpoint evaluating the proportion of subjects achieving CRP (or FCP) levels within normal limits at Day 14 and Day 42 will be summarised using frequency and percentage.

The endpoints evaluating changes in CDAI score over time and changes in CRP (or FCP) results over time will be summarised using descriptive statistics.

The anti-V565 antibody responses will be summarised and listed for the safety (SAF) population.

In the exploratory endoscopy substudy, changes in the central reader's overall assessment and changes in SES-CD from Baseline to Day 42 will be summarised using descriptive statistics. Summary statistics presentation will be separated for subjects with ileum and colon involvement and for subjects with only ileal mucosal lesions.

Any additional analyses or data presentation details will be described in the SAP.

8.2.4 Pharmacokinetic Analysis

Samples for analysis of concentrations of study drug will be collected as specified on the Schedule of Events (). Individual PK blood sample collection dates/times, urine sample collection dates/times/sample volume and the associated V565 concentrations will be listed.

Serum V565 concentrations will be summarised using descriptive statistics by planned sampling time.

The amount of V565 excreted in each urine collection will be determined as V565 concentration × urine volume of the urine sample and listed for each subject by visit.

8.2.5 Safety Analyses

All safety data will be provided in by-subject listings.

8.2.5.1 Adverse Events

Treatment-emergent Adverse Event: A TEAE is defined as:

- A new event that occurs during or after treatment with study drug or
- Any event present at Baseline that worsens in either intensity or frequency after exposure to study drug.

Only TEAEs will be summarised.

The number and percentage of subjects experiencing TEAEs and serious TEAEs will be summarised by treatment group, and by MedDRA System Organ Class (SOC) and Preferred Term. The TEAEs will also be summarised by maximum severity and relationship to study medication in addition to SOC, Preferred Term and treatment group. Summaries will also be presented for serious TEAEs and for TEAEs leading to permanent discontinuation.

Medical history will be coded using the MedDRA latest version and listed for all subjects.

8.2.5.2 Safety Laboratory Tests

The results of safety laboratory tests will be summarised for each laboratory parameter and planned visit time point.

Continuous laboratory parameters will be summarised by visit time point using the number of subjects with non-missing data, mean, SD, median, minimum and maximum. Actual values as well as changes from Baseline will be summarised.

Categorical parameters will be summarised by the number and percentage of subjects within each category, relative to the total number of subjects in the SAF, with data available. In the event of missing test results, a "missing" category showing the number of subjects with missing test results at each level of summarisation will be presented.

Shift tables for specific time points versus baseline status will be presented for both continuous (categorised in accordance with study-specific reference ranges as Low, Normal, High) and categorical (using appropriate categories such as Normal, Abnormal) laboratory parameters. "Time point" in these tables may be either a specific visit, a final study visit or the entire study duration on-treatment.

8.2.5.3 Vital Signs and 12-lead ECG

Vital signs statistics will be presented in a similar way to the laboratory variables.

All ECG data results (normal/abnormal) will be summarised using frequency counts and percentages. Clinically significant abnormalities will be presented in by-subject listings.

8.2.5.4 Physical Examinations

Physical examination results will be summarised using frequency tables for normal/abnormal results per visits.

8.2.5.5 Concomitant Medications

All medications will be coded using the WHO Drug Dictionary and ATC system. Each medication will be classified as prior medication if it is stopped prior to the first dose of study medication, or as concomitant medication if it is ongoing at the time of the first dose or is started after the first dose of study medication. Prior and concomitant medications (other than permitted medications for the treatment of CD) will be summarised by treatment group by ATC level 2 categories and preferred name.

Permitted medications for the treatment of CD will be summarised separately.

8.2.6 Data To Be Analysed

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the SAP prepared by [redacted] and approved by the Sponsor before database lock.

8.2.7 Analysis Populations

Intent-to-Treat (ITT) population: The ITT population will include all randomised subjects. In this population, treatment will be assigned based upon the treatment arm to which subjects were randomised regardless of which treatment they actually received.

Per Protocol population (PP): The PP population will include all subjects who do not have major protocol violations that would affect the evaluation of the primary efficacy endpoint.

Safety population (SAF): The SAF population will include all randomised subjects who receive at least one dose of study drug. In this population, treatment will be assigned based upon the treatment subjects actually received, regardless of the treatment to which they were randomised.

Pharmacokinetic population (PK): The PK population will include all subjects in the SAF population who receive at least one dose of study drug and who have at least one post dose sample of serum and urine who do not have events or protocol deviations with the potential to affect PK concentrations.

8.2.8 Missing Data

Missing data handling and possible sensitivity analysis will be described in the SAP.

8.2.9 Subgroup Analysis

No subgroup analyses are planned.

8.3 Interim Analyses

No interim analysis for efficacy or safety is planned.

9.0 ETHICS

9.1 Institutional Review Board or Independent Ethics Committee

An ethics committee should approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will provide the Sponsor or [redacted] with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study site(s). The Investigator should submit the written approval to Sponsor or representative before enrolment of any subject into the study.

Sponsor or representative should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the Sponsor or [redacted] of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will promptly report any new information that may adversely affect the safety of subjects or the conduct of the study to the IRB/IEC. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

Sponsor or representative will provide Regulatory Authorities, ethics committees and Investigators with safety updates/reports according to local requirements, including SUSARs, where relevant.

Each Investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study drug. The Sponsor or representative will provide this information to the Investigator so that he/she can meet these reporting requirements.

9.2 Ethical Conduct of the Study

This study will be conducted, and the informed consent will be obtained, according to the ethical principles stated in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the applicable guidelines for good clinical practice (GCP) (CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations to assure

that the rights, safety and wellbeing of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

9.3 Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug. The Investigator will provide each subject with a copy of the signed and dated consent form.

A separate ICF will be used for subjects who elect to contribute samples for pharmacogenetic analyses.

9.4 Subject Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

The Sponsor or representative will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a Sponsor or representative physician or an Investigator might know a subject's identity and also have access to his or her genetic data. In addition, regulatory authorities may require access to the relevant files.

10.0 STUDY ADMINISTRATION

10.1 Administrative Structure

The administrative structure of this study is presented in .

10.2 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study site should plan to retain such documents for approximately 15 years after study completion. The study site should retain such documents until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any study records.

The U.S. Food and Drug Administration (FDA) regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of study drug (including eCRFs, consent forms, laboratory test results, and medication inventory records), must be retained by the Principal Investigator for 15 years after the last marketing application approval in an ICH region or after at least 15 years have elapsed since formal discontinuation of clinical development of the investigational product. The Sponsor will notify the Principal Investigator of these events.

No records should be disposed of without the written approval of the Sponsor.

For studies conducted outside the United States under a U.S. Investigational New Drug (IND) application, the Principal Investigator must comply with U.S. FDA IND regulations and with those of the relevant national and local health authorities.

10.3 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomised into the study.

The Investigator will allow the Sponsor, [redacted] and authorised regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate.

10.4 Investigator Information

10.4.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonised Tripartite Guideline for GCP (GCP, 1997); the U.S. CFR Title 21 parts 50, 56, and 312; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

10.4.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (see the Appendix, Section 12.3). By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any site where the Investigator has not signed the protocol.

10.4.3 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study site will be set forth in the Clinical Trial Agreement.

10.5 Financing and Insurance

The Sponsor will obtain liability insurance that covers this study as required by local law and/or national regulations and/or ICH guidelines whichever is applicable. The terms of the insurance will be kept in the study files.

11.0 REFERENCES

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12.0 APPENDICES

12.1 Sample Crohn's Disease Activity Index (CDAI) Score

	Factor
Number of liquid or soft stools each day for 7 days	×2
Abdominal pain (0-3 on severity) each day for 7 days	×5
Subjective general well-being (0=well to 4=terrible for each day for 7 days	×7
Presence of complications*	×20
Taking diphenoxylate or opiates for diarrhoea	×30
Presence of an abdominal mass (0=none; 2=questionable; 5=definite)	×10
Absolute deviation of haematocrit from 47% in men and 42% in women	×6
Percentage deviation from standard weight	×1

*One point each is added for each set of complications

- The presence of joint pain (arthralgia) or frank arthritis
- Inflammation of the iris or uveitis
- Presence of erythema nodosum, pyoderma gangrenosum or aphthous ulcers
- Anal fissures, fistulae or abscesses
- Other fistulae
- Fever (>37.8°C) during the previous week

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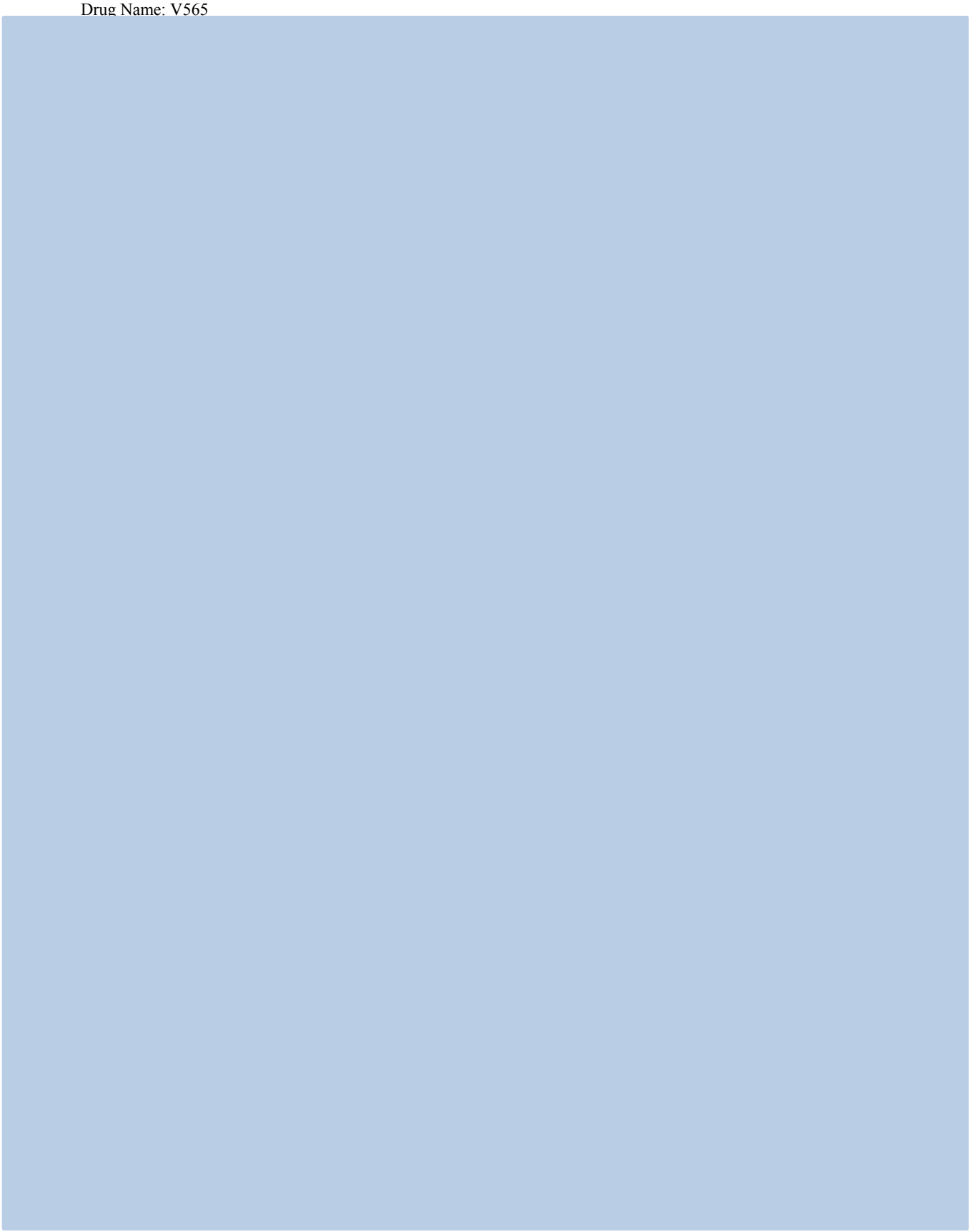

12.3 Signature of Investigator

PROTOCOL TITLE: A Phase 2 study to investigate the efficacy, safety, and tolerability of six weeks treatment with V565 in subjects with active Crohn's disease

PROTOCOL NO: V56502
Version 1.3 02 December 2016

This protocol is a confidential communication of VHsquared Ltd. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from VHsquared Ltd.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the study will be conducted. Return the signed copy to Quin

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

12.4 Protocol Amendment 1.3 Summary of Changes

The following non-substantial changes were implemented with Protocol Version 1.3:

1. Inclusion criterion 11(vii) amended to include reference to Section 6.2.2.
2. Section 6.2.2 additional detail provided for vasectomised partners and detailed definition of sexual abstinence.
3. Table 2: Activated partial thromboplastin time added to Safety Assessments.
4. Table 4: Activated partial thromboplastin time added to Additional Tests (Screening Only).