STATISTICAL ANALYSIS PLAN

V56502

A PHASE 2 STUDY TO INVESTIGATE THE EFFICACY, SAFETY, AND TOLERABILITY OF SIX WEEKS TREATMENT WITH V565 IN SUBJECTS WITH ACTIVE CROHN'S DISEASE

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0(Dated 12MAR2019) for Protocol V56502

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, pharmacokinetics (PK) and safety data for Protocol V56502. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 1.3, dated 24 August 2016 and amendment 02 December 2016.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is

- 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.

2.2. SECONDARY OBJECTIVES

The 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

2.3. PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective is

- To determine the concentration of V565 in serum and urine

2.4. EXPLORATORY OBJECTIVES

The exploratory objectives are

- 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
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-
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2.5. 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

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

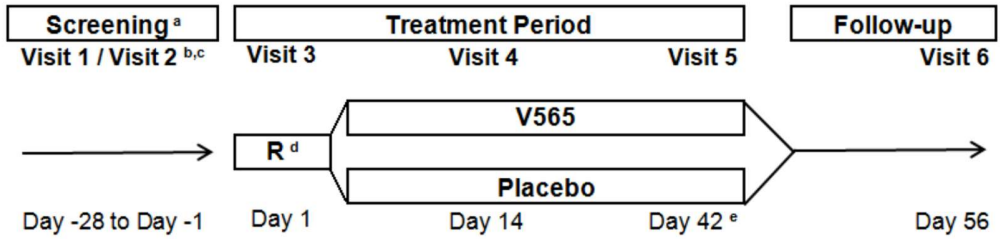
This study will be a multiple-site, double-blind, placebo-controlled, parallel-group proof-of-concept study in approximately 126 subjects with active CD. This study will include subjects who have a confirmed diagnosis of CD for at least three months and have CD involving the ileum and/or colon.

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 one of 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 (six weeks). The total daily V565 dose is 1665 mg.

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

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Table 2 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

In the protocol section 8.2.1 it is mentioned that the baseline CRP and baseline FCP results will be included as covariates in the statistical model for logistic regression. CRP or FCP will be used to determine inflammation status at baseline. Some subjects may appear 'normal' on the basis of their CRP result however the FCP measurement reveals the presence of inflammation. As FCP will be measured for subjects only if CRP is <5 mg/L, FCP will be missing for many subjects. In addition, the CRP result for subjects who entered on the basis of inflammation measured by a FCP result => 250 ug/g will not be meaningful as a reflection of inflammation status. For these reasons neither FCP nor CRP will be incorporated into the primary model fit. However, if a subject is enrolled in the study based on the baseline result of CRP the definition of response will incorporate a 40% reduction in CRP. If a subject is enrolled in the study based on the baseline result of FCP the definition of response will incorporate a 40% reduction in FCP.

4. PLANNED ANALYSES

4.1. DATA MONITORING COMMITTEE (DMC)

There is no DMC planned for this study.

4.2. INTERIM ANALYSIS

No interim analysis for efficacy or safety is planned for this study.

4.3. FINAL ANALYSIS

The final analyses identified in this SAP will be performed by Biostatistics following Sponsor Authorisation of this SAP, Database Lock, and Sponsor Authorisation of Analysis Sets and unblinding of Treatment.

5. ANALYSIS SETS

Agreement and authorisation of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the treatment allocations. A blinded data review plan will be created and further details related to analysis sets and major protocol deviations will be described in this plan.

5.1. INTENT-TO-TREAT (ITT) POPULATION

The ITT population will include all randomised subjects irrespective of whether any study medication was ingested. In this population, treatment will be assigned based upon the treatment arm to which subjects were randomised regardless of which treatment they actually received.

5.2. PER PROTOCOL POPULATION (PP)

The PP population will include all randomised subjects who do not have major protocol deviations that would affect the evaluation of the primary efficacy endpoint.

A major protocol deviation that is considered to affect the primary efficacy endpoint will lead to exclusion of subjects from the PP population. Major protocol deviations considered to affect the primary analysis include, but are not limited to, the following;

1. Violations of the inclusion/exclusion criteria
    a. The following inclusion criteria should be fulfilled:

i. Inclusion criterion 2: CDAI score of ≥220 to ≤450 during Screening

ii. Inclusion criterion 3: CRP ≥5 mg/L (or, if CRP is normal, FCP ≥250 µg/g) at screening.

iii. Inclusion criterion 4: Active CD of ileum and/or colon as determined by the baseline ileocolonoscopy

b. The following exclusion criteria should be absent in the data for the subjects:

i. Exclusion criterion 3: Any gastrointestinal (GI) manifestations of CD that might affect the evaluation of efficacy.

ii. Exclusion criterion 5: Prior primary efficacy failure of or secondary loss of response to anti-TNFα therapy, or any contraindication to anti-TNFα therapy

iii. Exclusion criterion 6: The use of medications prior to the study or during the study with the potential to affect the evaluation of efficacy.

2. Mishandling of the study drug which could have impacted the integrity of the study data such as non-allowable temperature deviations during storage or dispensing of study drug to the wrong subject
3. Non-compliance rate of <80% or >120% with study treatment.
4. Use of prohibited concomitant medications.
5. Study procedures done outside protocol-specified window period that are judged to affect study efficacy data.
6. Assessments for primary endpoint not done.

Protocol deviations will be reviewed prior to unblinding and individual subjects having protocol deviations will be evaluated for inclusion in the PP population. Any additional deviations not listed above will be documented at this time.

5.3. SAFETY POPULATION (SAF)

The SAF population will include all randomised subjects who receive at least one capsule of V565/placebo. In this population, treatment will be assigned based upon the treatment subjects actually received, regardless of the treatment to which they were randomised.

5.4. PHARMACOKINETIC POPULATION (PK)

The PK population will include all subjects in the SAF population who receive at least one capsule of V565 and who have at least one pre dose sample of serum or urine and who do not have events or protocol deviations with the potential to affect serum PK or urine PK concentrations.

Changes to the procedures or events, which may impact the quality of the PK data will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to,

1. sample processing errors that lead to inaccurate bioanalytical results,
2. inaccurate dosing on the day of PK sampling due to administration incidents or lack of compliance with

the protocol,

3. dosing date/time not available
4. blood/urine sampling date and time not available.

Affected data will be evaluated by the pharmacokineticist to determine whether or not they can be included in the PK analysis. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant protocol deviations. A common example of a non-significant protocol deviation is a missed blood sample or deviations from blood collection times.

Protocol deviations will be reviewed prior to unblinding and individual subjects having protocol deviations with the potential to affect PK concentrations will be evaluated during the blinded data review meeting for inclusion in the PK population.

5.5.

5.6. IMMUNOGENICITY POPULATION

The immunogenicity population will include all subjects in the SAF population who receive at least one capsule of V565/placebo and who have at least one pre dose sample of serum and who do not have events or protocol deviations with the potential to affect immunogenicity.

6. GENERAL CONSIDERATIONS

The following descriptive statistics will be presented in summary tables:

- Continuous variables: number (non-missing cases), mean, median, standard deviation (SD), minimum, and maximum
- Categorical variables: will be summarised by treatment group using frequency tables (frequencies and percentages). Percentages are routinely based on the total category count excluding the missing category if not otherwise mentioned. Missing category with zero count will not be presented

In general, the number of decimal places displayed for each statistic will be determined as follows with a maximum of three decimal places:

- Mean and median: one more than the number of decimal places allotted in the raw data received from data management
- SD: two more than the number of decimal places allotted in the raw data

- Minimum and maximum: equal to the number of decimal places allotted in the raw data
- Confidence Intervals (CIs) will be presented using the number of decimal places plus one as the parameters (e.g. mean) as appropriate
- P-values greater than or equal to 0.0001, in general, will be presented to four decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-value greater than ">0.9999" will be presented as 1.0000
- Percentages will be reported to one decimal place

In the case of normality assumption violations, appropriate non-parametric methods will be used for analysis as mentioned in section 15.2.3

Coding of adverse events and medications data (i.e. by Medical Dictionary for Regulatory Activities [MedDRA 19.1] or World Health Organization [WHO]-drug dictionary 01Sep2016E) will be included in the datasets.

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of study drug, (Day 1 is the day of the first dose of study drug)and will appear in every listing except medical history where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

  Study Day = (date of event – reference date) + 1
- If the date of the event is prior to the reference date then:

  Study Day = (date of event – reference date)

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in appendix 2; Partial Date Conventions.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to first administration of study drug (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and concomitant medications commencing on the reference start date will be considered post-baseline.

For the endpoints of CRP and FCP, the baseline score is the last non-missing measurement taken prior to Day 1 (including unscheduled assessments).

For the endpoints CDAI score and PRO-2, the screening score will be considered as baseline.

Listings will include scheduled and unscheduled data.

6.3. DERIVED TIMEPOINTS

Last observation carried forward (LOCF) method will be used for primary analysis. If any of the element (Patient reported data or Physician reported data or Haematocrit value) of primary endpoint is missing at Day 42, LOCF will be applied and that element will be carried forward from last available post-baseline visit.

Also, LOCF will be performed as part of sensitivity analysis for the primary and secondary efficacy endpoints. The missing CDAI scores, CRP and FCP will be carried forward from the last available post-baseline measurements.

In addition, the worst observation carried forward (WOCF) will also be performed as part of sensitivity analysis for the missing CDAI scores, CRP and FCP from the available baseline, post-baseline and the unscheduled assessments.

The descriptive summaries of derived timepoints provided for the primary efficacy variables will be summarised and named as “Day 42 (LOCF)” and “Day 42 (WOCF)”.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For by-visit summaries, data recorded at the nominal visit will be presented. Last non-missing value for a particular parameter will be included in by-visit summaries and listings. as well where unscheduled measurements will also be considered.

Subjects who prematurely discontinue from the study for any reason, will be scheduled for an Early Termination (ET) visit, at which time all of the assessments listed for that visit will be performed.

In by-visit summaries of all study objectives the Day 42 or ET visit will be summarised as follows “Day 42/Early Termination”.

Additionally, in by-visit summaries for primary efficacy variables CDAI score, CRP and FCP values “Day 42 (LOCF)” and “Day 42 (WOCF)” will also be summarised.

6.5. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.6. STATISTICAL TESTS

The default significance level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

Two-sided CIs will be assessed at the 5% significance and two-sided p-value will be reported.

6.7. COMMON CALCULATIONS

For quantitative measurements,

- change from baseline will be calculated as Test value at Day x – Baseline Value
- percent change from baseline will be calculated as

$$\frac{(\text{Test value at Day x} - \text{ Test value at Baseline})}{\text{Test value at baseline}} X\ 100$$

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis in Section 15.

- Treatment
- Prior anti-TNFα therapy
- Baseline CDAI score

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple sites and the summaries will not be presented by site. Randomisation to treatment arms is not stratified by center.

7.3. MISSING DATA

Missing safety data will not be imputed while missing dates will be imputed as per appendix 2.

Missing efficacy data will be handled as described in section 15.1.2 of this analysis plan.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

All statistical comparisons will be made at the 5% level. No adjustment will be made for multiple comparisons. Interpretation of the results should consider this

7.5. EXAMINATION OF SUBGROUPS

No subgroup analyses are planned for this study.

8. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study and the format and content of the summary tables and listings to be provided by IQVIA Biostatistics.

Tables will be presented by V565, Placebo and Total unless otherwise specified. For efficacy outputs, Total column will not be presented.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition including number and percentage of subjects screened, screen failures including reason as entered in “Eligibility” eCRF, randomised, treated, completed the study, discontinued early (including primary reason of discontinuation as mentioned in Disposition Study page of eCRF) will be tabulated by treatment group and Total.

Summaries for overview of disposition will be based on ITT subjects.

Number and percentage of subjects in each population and excluded subjects and the reason for exclusion from each population will also be summarised. Percentages for population exclusion will be based on ITT population.

Subjects who are excluded and reason for exclusion from safety, ITT, PP, PK and Immunogenicity population will be

listed.

Protocol deviations captured by the Clinical Trials Management System (CTMS) will be summarised and listed on ITT population. Percentages will be based on ITT population for protocol deviation summary.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT, SAF and PP populations.

No statistical testing is planned for demographic or other baseline characteristics.

Summaries for continuous and categorical variables (as described in section 6) will be presented for each treatment and Total.

Demographics and baseline characteristics will be presented in a listing by subject.

The following demographic and other baseline characteristics will be reported for this study

- Age (years) at screening as collected from eCRF
- Sex
- Race
- Ethnicity
- Body Weight (kg) at screening
- Height (cm) at screening as collected from eCRF
- BMI (kg/m^2) at screening as collected from eCRF
- Prior Anti-TNF Therapy
- Childbearing potential for female subjects
- Disease duration (months)
- Baseline CDAI score
- Baseline CRP for patients qualifying on CRP
- Baseline FCP for patients qualifying on FCP
- Baseline SES-CD score
- Prior CD medication use

11. DISEASE AND MEDICAL HISTORY

Disease and Medical History information will be presented for the ITT and PP population.

12. PREVIOUS IBD TREATMENT/THERAPY HISTORY

The previous IBD treatment and therapies as captured in the eCRF will be summarised by counts and percentages of subjects and also be listed on ITT population.

13. MEDICATIONS

Medications will be presented for the ITT population and coded using WHO Drug dictionary 01Sep2016E. See appendix 2 for handling of partial dates for medications

- 'Prior' medications are medications which started and stopped prior to the first capsule of study drug
- 'Concomitant' medications are medications which:

started prior to, on or after the first capsule of study drug or started before the end of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the study drug

- 'Post treatment' medications are medications which are started after the last capsule of study drug and at or before the follow up visit

Concomitant medications will be summarised by ATC level 2 and preferred term based on ITT population. Summary will be presented for each treatment and Total.

Details of prior, concomitant and post treatment medications will be listed.

The following permitted medications based on the preferred term will be summarised by ATC level 2 and preferred term based on ITT population.

- Oral Corticosteroids
- Oral Aminosalicylates
- Methotrexate
- Azathioprine/6-MP
- Oral Antibiotics
- NSAIDs such as low dose aspirin [<325 mg/day]
- Probiotics at an unchanged dose

14. STUDY DRUG COMPLIANCE

Compliance to study drug will be presented for the SAF population.

14.1. DERIVATIONS

Compliance with study drug based on the drug accountability data will be calculated as the number of capsules taken (total dispensed – total returned) divided by the prescribed number of capsules expressed as a percentage, see calculations below.

A listing of drug accountability will be presented on SAF population to account for all drug distributed to each subject, including the container number, total number capsules dispensed, returned, percentage compliance and compliant (yes/no).

$$\text{Overall Percentage Compliance} = \frac{\left\{\begin{array}{l}([\text{N of Capsules dispensed at Day 1}] - [\text{N of Capsules returned at Day 14}]+ \\ [\text{N of Capsules dispensed at Day 14}] - [\text{N of Capsules returned at Day 42}])\end{array}\right\}}{([\text{Date of Day 42}] - [\text{Date of Dispensing at Day 1}]+1) * \Theta} * 100$$

Where Θ = 9, Number of capsules required to be taken per day.

For subjects who discontinued from the study, the "Date of Day x" will be replaced by the date of study discontinuation where x= 14 and 42.

Each subject will be considered non-compliant if taking less than 80% or more than 120% of the expected capsules.

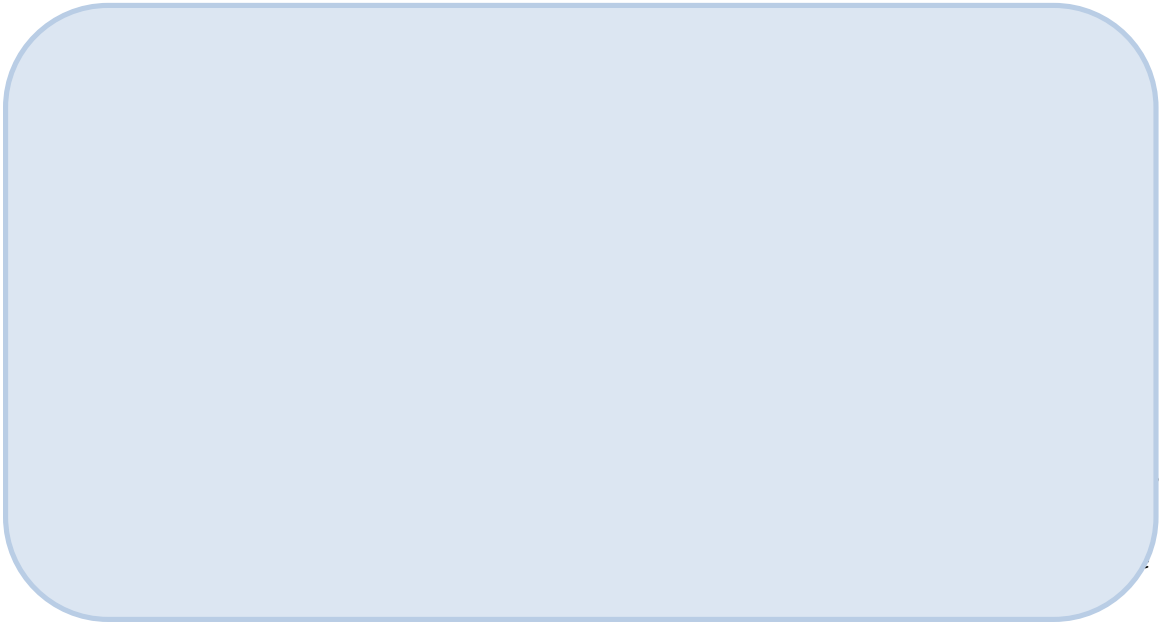
15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATIONS

The primary efficacy variable is Responders at Day 42

A Responder is 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 (where CRP at baseline => 5mg/dL) **or** FCP (where CRP at baseline <5mg/dL and FCP at baseline =>250 ug/g)



15.1.2. Missing Data Methods for Primary Efficacy Variable

Missing responder will be defined if at any visit either CDAI score or CRP/FCP values are missing. The missing responder status will then be imputed.

Missing primary efficacy data will be imputed using a LOCF method based on the following criteria -

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15.1.3. Primary Analysis of Primary Efficacy Variable(s)

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.

The primary efficacy analysis will be performed on ITT population. The primary endpoint will be analysed using a logistic regression model with treatment as the fixed effect and prior anti-TNFα therapy and baseline CDAI score 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% CI and 2-sided p-value. Two-sided 95% CIs for the odds ratio will be provided.

The SAS® procedure GENMOD that will be used is given in appendix 3The CDAI score, FCP, CRP results along with the change from baseline values will also be listed and summarised for the ITT population.

15.1.4. Sensitivity Analysis of Primary Efficacy Variable

The same primary efficacy analysis logistic regression model will be repeated using LOCF and WOCF on the ITT population.

The same primary efficacy analysis logistic regression model used for the ITT population will be repeated on the PP population. The same model used for primary efficacy will be used.

15.2. Secondary Efficacy

The secondary efficacy analyses will be performed and also be listed on ITT population.

15.2.1. Secondary Efficacy Variables & Derivations

The secondary efficacy variables are

Where subject achieving >=100 point reduction of CDAI score from baseline and a reduction of >=50% from the baseline value of CRP or FCP

Where subject achieving >=70 point reduction of CDAI score from baseline

Where subject achieving >=70 point reduction of CDAI score from baseline

Where subject's CDAI score at day 42 is < 150

- the total PRO-2 score is extracted from selected subject-reported variables of the CDAI included in the subject diary
- PRO-2 will be calculated at Day 14 and 42

15.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

Imputation of secondary efficacy variables will also follow the same procedure as primary efficacy variables.

15.3. EXPLORATORY EFFICACY

15.3.1. EXPLORATORY VARIABLES & DERIVATIONS

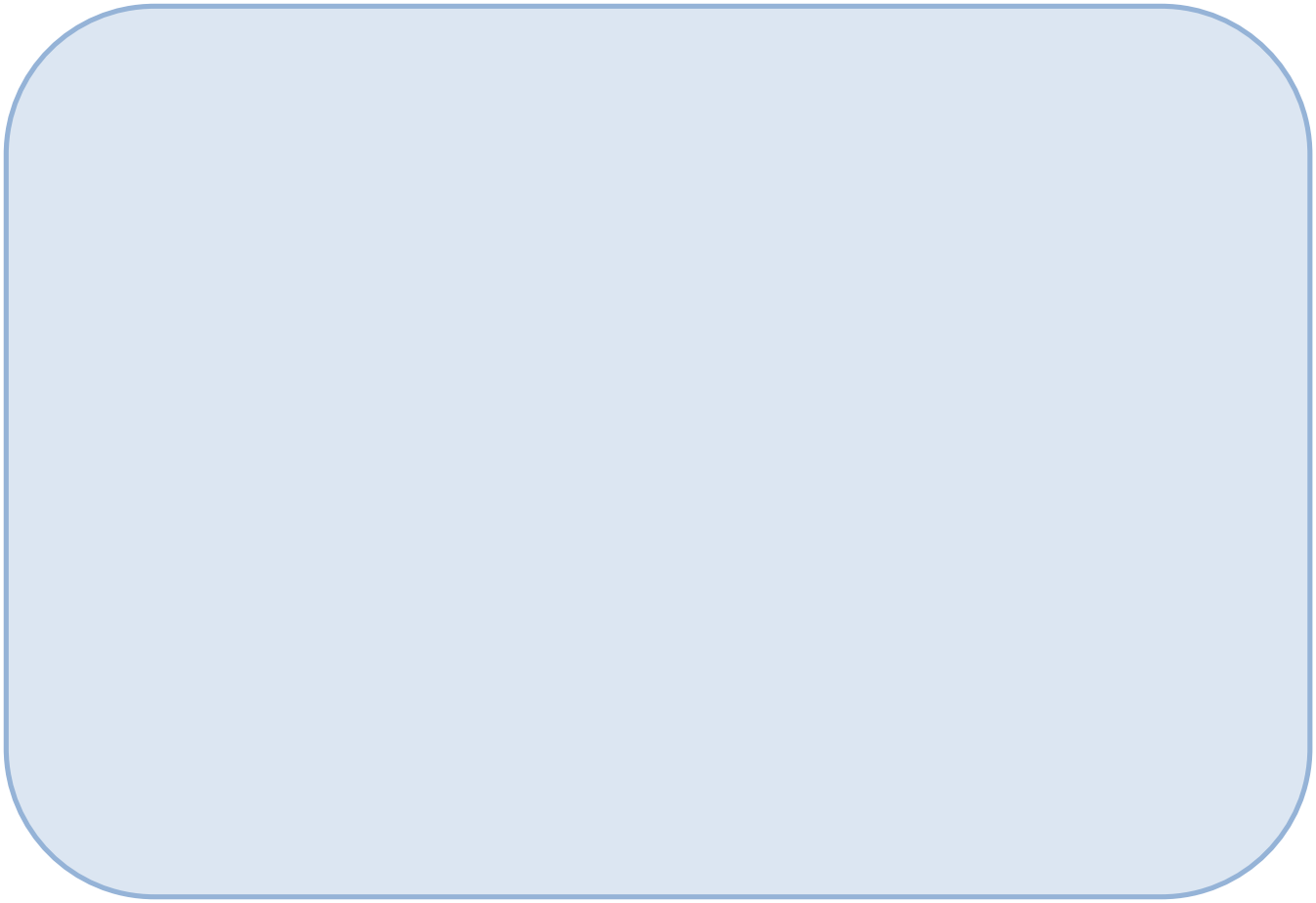
15.3.1.1. Proportion of subjects achieving CRP or FCP levels within protocol defined normal limits at Day 14 and Day 42

15.3.1.2. Changes from Baseline in CDAI score over time

- CDAI score is calculated at baseline, Day 14 and Day 42 as defined in the section 15.1.1
- Change from baseline at Day 14 and 42 are calculated using the formula mentioned in section 6.7

15.3.1.3. Changes from Baseline in CRP or FCP levels over time

- Change from baseline at Day 14 and 42 are calculated using the formula mentioned in section 6.7



15.3.1.7. Changes in Endoscopic Mucosal Appearance – endoscopic sub study patients only

- Change from baseline at Day 42 in overall Mucosal Appearance assessed as Markedly Better, Slightly Better, No Difference, Slightly Worse, Markedly Worse, Cannot be Determined

15.3.1.8. Changes in Endoscopic Score for Crohn's Disease (SES-CD) – endoscopic sub study patients only

- Change from baseline in SES-CD at day 42 for the subjects with an SES-CD ≥7, or ≥4 if only the ileum is involved using the formula mentioned in section 6.7

15.3.2. Missing Data Methods for Exploratory Variable(s)

Imputation of secondary efficacy variables will also follow the same procedure as primary efficacy variables.

15.3.3. ANALYSIS OF EXPLORATORY VARIABLES

15.3.3.1. The proportion of subjects achieving CRP (or FCP) levels within protocol defined normal limits at Day 14 and Day 42

- will be summarised using frequency and percentage and listed by subject for the ITT population

15.3.3.2. The endpoints evaluating changes in CDAI score over time and changes in CRP (or FCP) results over time

- will be summarised using descriptive statistics and listed by subject for the ITT population

15.3.3.6. Overall mucosal appearance

- The number and proportion of subjects in each of the categories defined in section 15.3.1.8 will be summarised for each treatment group at Day 42

15.3.3.7. Change from baseline of SES-CD

- will be summarised using descriptive statistics at Day 42

16. PHARMACOKINETIC ANALYSIS

Individual PK serum blood sample collection dates/times, and the associated V565 concentrations will be listed by visit for each subject.

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

Serum and urine V565 concentrations will be summarized using descriptive statistics by visit on the PK population.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

There will be no statistical comparisons between the treatment groups for safety data.

17.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA Version 19.1.

Treatment emergent adverse events (TEAEs) are 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.

17.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study drug.

17.1.2. TEAES LEADING TO DISCONTINUATION OF STUDY DRUG

For TEAEs leading to discontinuation of study drug, summaries of incidence rates (frequencies, percentages and events) by SOC and PT will be prepared.

17.1.3. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as ”Serious” on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared.

17.1.4. ADVERSE EVENTS LEADING TO DEATH

TEAEs leading to Death are those events which are recorded as ”Fatal” on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

17.2. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Haematology, Chemistry and Urinalysis. All laboratory assessments will be included in the outputs.

Presentations will use SI Units.

17.3. ECG EVALUATIONS

Results from the Electrocardiogram (ECG) as collected from eCRF will be included in the reporting of this study.

17.4. VITAL SIGNS

The following Vital Signs measurements as collected from eCRF will be reported for this study on SAF population:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (beats/min)
- Body Temperature (^{o}C)
- Weight (kg)
- BMI (kg/m^2)

17.5. PHYSICAL EXAMINATION

Physical examination findings as collected in eCRF and abnormalities associated, along with clinical significance will be tabulated and presented in the listings on SAF population.

17.6. OTHER SAFETY ASSESSMENTS

- The serum pregnancy test performed at Screening and a urine pregnancy test at Day 1, Day 42 (the end of the study) and at Day 56 (the Follow-up Visit) or ET visit will only be listed on SAF population
- The safety parameters Activated partial thromboplastin time, the Serology laboratory assessments (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 and QuantiFERON-TB Gold Test collected at screening visit as collected in eCRF will only be listed on SAF population
- The Pharmacogenetics sample data as collected in eCRF will only be listed on SAF population
- Titre values for anti drug antibodies for will be listed for all subjects both V565 and placebo at Day 1 (pre dose) and for V565 subjects only at Days, 14, 42 and 56. Results will be listed for each subject by visit and treatment on SAF population. Subjects who test positive for anti- drug antibodies will be tested to confirm whether the antibodies are neutralising.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT CONVENTIONS

Outputs will be presented according to the following:

DATES & TIMES

Depending on data available, dates and times will take the form dd-mmm-yyyy hh:mm:ss.

SPELLING FORMAT

English UK

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables and Graphs	For Listings (include if different to tables)
V565	V565	V565
Placebo	Placebo	Placebo

PRESENTATION OF VISITS

For outputs, visits will be represented as follows as applicable in the tables and listings and in that order:

Long Name (default)
Screening
Baseline
Day 1
Day 14
Day 42/Early Termination
Day 42 (LOCF)
Day 42 (WOCF)
Day 56

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Treatment
- Subject ID
- date (where applicable),

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
	Partial	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
	Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE

START DATE	STOP DATE	ACTION
		If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT DRUGS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment, assign as concomitant If stop date >= study drug start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment, assign as concomitant If stop date >= study drug start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior drug If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment, assign as concomitant If stop date >= study drug start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment, assign as concomitant If stop date >= study drug start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior drug If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant