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Efficacy and Safety of AbGn-168H in Patients with Moderate to Severe Active, Anti-TNFα and/or Anti-integrin Refractory Ulcerative Colitis: A 26-week, Open-label, Multi-center, Phase II Proof of Principle Trial

Statistical Analysis Plan

Version: 6.0

PAREXEL Project Number: 237705

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Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	06May2019	New document
1.1	30May2019	Implement Client Review Comments to V1.0 (internal review)
2.0	12June2019	Implement Client Review Comments to V1.0 and internal review comments to V1.1.
3.0	11July2019	Implement Client Comments to V2.0 of the SAP
4.0	30July2019	Implement Client Comments to V3.0 of the SAP
5.0	9June2020	Implement Client Comments to V4.0 of the SAP Implement Client Comments to V4.0 of the SAP and updated how to handle the local lab data provided in scanned PDF files.
6.0	12Oct2020	Based on Data Review Meeting Minutes, SAP amendment is needed to exclude Patient(10-10-001) from the m-ITT and PK sets but to include to Safety set

LIST OF ABBREVIATIONS

AE	Adverse Event
ADA	Anti-drug Antibody
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
Cmax	Maximum Drug Concentration
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Residual Drug Concentration
CV	Coefficient of Variation
ECG	Electrocardiograph
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart Rate
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IRB	Institutional Review Board
ITT	Intent-To-Treat
i.v.	intravenous
lb	pound
LNH	low/normal/high
LOCF	Last Observation Carried Forward
MCS	Mayo Clinic Score
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mITT	Modified Intent-To-Treat
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamics
PI	Principle Investigator
PK	Pharmacokinetic
PPS	Per Protocol Set
PsA	Psoriatic Arthritis
pMCS	Partial Mayo Clinic Score
QT	ECG trace rhythm: interval from onset of Q wave to the endpoint of S wave.
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
s.c.	subcutaneous
SOC	System Organ Class
SUSARs	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event

TNFα	Tumor Necrosis Factor-α
UC	Ulcerative Colitis
ULN	Upper Limit of Normal

1 AMENDMENT FROM PREVIOUS VERSION

The following are the changes from the Statistical Analysis Plan (SAP), v5.0, dated 09June2020:

- Added details of why Patient (10-10-001) need to exclude from the m-ITT analysis set to the section 5.15 "Changes in the Conduct of the Study or Planned Analysis" of the Version 5.0 of the SAP
- Added how Inflammatory Bowel Disease Questionnaire (IBDQ) numbers are structured to each of 4 subcategories to the section 5.11.2, "Quality of Life" of the Version 5.0 of the SAP.

2 INTRODUCTION

This study is designed to evaluate the efficacy and safety of Neihulizumab in patients with moderate to severe active ulcerative colitis (UC) who are refractory or intolerant to anti- TNFα and/or anti-integrin treatments.

The purpose of the statistical analysis plan (SAP) is to layout definitions and statistical methods for the planned analyses of primary, secondary, and exploratory endpoints. Anti-drug antibody (ADA) data will not be analyzed in this SAP. Those data will be included as an appendix in the final clinical study report.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version: Amendment 4 (November 01, 2018)
- Study Protocol, Version: Amendment 3 (April 03, 2018)
- Electronic Case Report Form (eCRF), Version 4.0 (February 20, 2019).

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to evaluate efficacy of AbGn-168H administered intravenously in patients with moderate to severe active ulcerative colitis who are refractory or intolerant to anti-TNF and/or anti-integrin treatments.

3.2 Secondary Objective

The secondary objective is to investigate safety, tolerability, and immunogenicity of intravenous AbGn-168H administration.

3.3 Exploratory Objective

Exploratory objective is to explore the change of biomarkers (faecal calprotectin and c-reactive protein) after intravenous AbGn-168H administration.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a single arm, open label, multiple dose, multi-center study to be conducted in 12-18 centers in United States (US) in 30-40 patients with a diagnosis of moderate to severe active ulcerative colitis, refractory or intolerant to anti-TNFα and/or anti-integrin treatments. Due to the COVID-19 pandemic, the holding of patient enrollment, as well as slow patient enrollment prior to the pandemic, the study has been closed out and the data will be analyzed at this time. Therefore, only available data from the patients will be included in the analysis.

Per protocol amendment 4, a total of 10 doses of Neihulizumab at 9 mg/kg will be administered to patients over 12 weeks on Day 1 (Week 0), Day 8 (Week 1), Day 15 (Week 2), Day 22 (Week 3), Day 29 (Week 4), Day 36 (Week 5), Day43 (Week 6), Day 50 (Week 7), Day 64 (Week 9), and Day 78 (Week 11).

Whereas the patients enrolled under Protocol amendments 1-3, a total of 8 doses of Neihulizumab at 9 mg/kg are administered on Day 1 (Week 0), Day 8 (Week 1), Day 15 (Week 2), Day 22 (Week 3), Day 29 (Week 4), Day43 (Week 6), Day 57 (Week 8), and Day 71 (Week 10).

Patients will be followed up on Day 84 (Week 12, End of Treatment, primary endpoint), Day 112 (Week 16), Day 140 (Week 20) and Day 182 (Week 26, End of Study) after the first dose of Neihulizumab.

4.1.1 Mayo Diary Card

During the screening visit, patients will be provided the Mayo diary card and instruction to fill the cards. Study coordinator will collect the Mayo diary card from patients at each visit to calculate Mayo Clinic Score (MCS) according to the subscores of stool frequency and rectal bleedings from the 3 consecutive days closest to the visiting day.

Rectal bleeding will be scored using 0-3 scale: 0 = no blood seen, 1 = streaks of blood with stool less than half the time, 2 = obvious blood with stools most of the time, 3 = blood alone passed.

Stool frequency will be recorded using 0 to 3 scale: 0 = normal, 1 = 1-2 stools/day more than normal, 2 = 3-4 stools/day more than normal, 3 = 5 or more stools/day more than normal.

4.1.2 Physician's assessment

Physician's assessment will be evaluated at each visit for the improvement of the disease activity. This score will be used to calculate the complete Mayo Clinic Score (cMCS) and partial Mayo Clinic Score (pMCS).

Physician global assessment will be evaluated by the investigator (or designee) at each visit using 4-point score system: 0 = normal, 1 = mild, 2 = moderate, 3 = severe.

4.1.3 Endoscopic Subscore

Endoscopic subscore will be assessed by a central reader.

Endoscopic findings will be evaluated using 4-point score system: 0 = normal or inactive disease, 1 = mild disease, 2 = moderate disease, 3 = severe disease.

An adjudication review will be triggered if there is a discrepancy of the change in endoscopic subscore between local and central reading. The central adjudicating reviewer will be blinded to which overall Mayo endoscopy subscore was provided by the site gastroenterologist or by the central reviewer. The adjudication assessment will be considered as final score.

4.1.4 cMCS and pMCS

The cMCS is calculated by summing the scores of following 4 assessments at Screening, W12 and W26 : Rectal bleeding, Stool frequency, Physician global assessment, and Endoscopic findings. The total score of cMCS is ranges from 0 to 12.

The pMCS will be calculated as the total of Rectal bleeding, Stool frequency, Physician global assessment without endoscopic subscore. The total score of pMCS ranges from 0 to 9.

4.2 Endpoints

4.2.1 Efficacy Variables

Efficacy will be assessed by cMCS, pMCS, endoscopy, biopsy, Inflammatory Bowel Disease Questionnaire (IBDQ), and Biomarkers (faecal calprotectin and c-reactive protein).

The **primary efficacy endpoint** is proportion of clinical responders at Week 12.

The clinical responder is defined as a $\geq$ 3-point reduction in MCS, a 30% or greater decrease from the baseline score, and with a 1-point or greater decrease of the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1 at Week 12.

Secondary efficacy endpoints are:

1. The proportion of patients with clinical response at Weeks 6, 7, 9 and 11 defined as a ≥2-point decrease in pMCS, and with a 1-point or greater decrease of the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1.
2. The proportion of patients with clinical remission, defined as MCS of 2 or lower (or pMCS of 1 or lower) and no subscore higher than 1 at Weeks 6, 7, 9, 11 and 12.
3. The proportion of responders who remain in clinical response and remission at Weeks 16, 20, and 26.
4. Flexible sigmoidoscopy subscore changes from baseline at Weeks 12 and 26.
5. The proportion of patients with sigmoidoscopic improvement, defined as any decrease in MCS endoscopic subscore, at Week 12 and 26.
6. The proportion of patients with mucosa healing defined as an absolute subscore for endoscopy of 0 or 1 at Weeks 12 and 26.
7. Change of histological activity grade from baseline at Weeks 12 and 26 using the Geboes system.
8. The proportion of patients with histological healing defined as histological grade = 0 at Weeks 12 and 26.
9. Change of Inflammatory Bowel Disease Questionnaire (IBDQ) from baseline at Weeks 12 and 26.
10. The proportion of patients with IBDQ response, defined as an increase from baseline of at least 16 points at Weeks 12 and 26.

Above time points are for the patient enrolled under Protocol Amendment 4. The time points for the patient enrolled under Amendments 1-3 are given in the table in the SAP section 4.5.2 as well as in Appendix 1 'Schedule of Assessments (Protocol Amendment 1-3)' and Appendix 2 'Schedule of Assessments (Protocol Amendment 4)'.

4.2.2 Safety Variables

Safety will be assessed by adverse event (AE) monitoring, laboratory tests, vital signs, physical examinations, discontinuation of treatment due to AE and immunogenicity.

4.2.2.1 Adverse Events

Adverse event (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. AE will be graded according to CTCAE Version 4.03.

An AE will be considered treatment-emergent (TEAE) if it occurs on or after the first dose of the study medication or it started before the date of the first dose of study medication and worsened after the date of first dose.

Drug-related adverse events are those assessed by investigator as being definitely related, probably related, or possibly related.

Where dates are missing or partially missing, AEs will be assumed to be TEAE, unless there is clear evidence to suggest that AE started prior to the first dose of study treatment. Imputation of partial missing dates will be discussed in section 4.2.1.

Missing relationship to study drug is considered as treatment related in the analyses.

4.2.2.2 Laboratory Safety Tests

Following laboratory safety tests will be performed:

- **Hematology**: Haematocrit (Hct), Haemoglobin (Hb), Red Blood Cell / Erythrocytes Count, White Blood Cells / Leucocytes Count Platelet / Thrombocytes Count.
- **Diff Automatic**: Neutrophils (Relative and absolute Count), Eosinophils (Relative and absolute Count), Basophils (Relative and absolute Count), Monocytes (Relative and absolute Count), Lymphocytes (Relative and absolute Count).
- **Diff Manual (if Diff Automatic is abnormal)**: Neutrophils, Bands (Stabs), Neutrophils, Polymorphonuclear (PMN), Eosinophils, Basophils, Monocytes, Lymphocytes.
- **Enzymes**: AST/GOT, SGOT, ALT/GPT, SGPT, Alkaline Phosphatase (AP/ALP), Lactic Dehydrogenase (LDH).
- **Substrates:** Glucose, Creatinine, Blood urea nitrogen, Bilirubin Total, Bilirubin Direct, Protein Total.
- **Hormones:** Serum ß-Human Chorionic Gonadotrophin (pregnancy test) (only female patients of childbearing potential).
- **Electrolytes:** Calcium, Sodium, Potassium

4.2.2.3 Vital Signs, Physical Examination and Electrocardiograph

Vital signs: Per protocol amendment 4, the vital signs will be evaluated at screening, baseline (week 0), weeks 1, 2, 3, 4, 5, 6, 7, 9, 11, 12 [end of treatment (EOT)], 16, 20 and 26 [end of study (EOS)]. Whereas the patients enrolled under Protocol amendments 1-3, vital signs will be evaluated at screening, baseline, weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 26 (EOS). Vital signs will include systolic and diastolic pressure, temperature, hart rate, and respiratory rate.

Physical examination: The patients enrolled under protocol amendment 4, full physical examination will be performed at screening, baseline, week 12 (EOT) and week 26 (EOS). The partial physical examination will be performed at weeks 1, 2, 3, 4, 5, 6, 7, 9, 11, 16 and 20. All clinically significant abnormal findings at the screening visit will be recorded in the Medical History form. Any clinically significant changes from the screening visit will be recorded.
The patients enrolled under protocol amendment 1-3, full physical examination will be done at same time points as subject enrolled under amendment 4. However, the partial physical examination will be performed only at weeks 1, 2, 3, 4, 6, 8, 10, 16, and 12.

Electrocardiograph (ECG): 12-Lead resting ECG will be performed at Screening visit.

4.2.3 Exploratory Efficacy Biomarkers

Exploratory efficacy endpoints are faecal calprotectin and c-reactive protein changes at Weeks 4, 9, 12, 16, 20, and 26.

4.2.4 Pharmacokinetic and Anti-drug Assessments

Blood samples for Pharmacokinetic (PK) determinations will be drawn approximately 15 minutes before dosing and 2 hours post dosing at Visits 2, 9 and 11, 15 minutes before dosing at Visits 3, 4, 5, 6, 7, 8 and 10, and at Visits 12, 13 and 14. The plasma concentration (Cmax) and associated parameters will be calculated at Day 1, Day 50, and Day 78. The PK profile will be monitored as specified in Table 1 of the Appendix 1 Schedule of assessments of the SAP.

Anti-drug antibodies (ADA) will be determined in all patients before dosing at Visits 2, 6, 10 and at Visits 12-15.

5 STATISTICAL METHODS

5.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

5.2 General Presentation Considerations

Due to the small number of patients expected to be enrolled at each center, all summaries and analyses will be performed using pooled patients across centers.

Unless otherwise specified, continuous data will be summarized with the number of non-missing observations, in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts.

Confidence intervals will be presented to one more decimal place than the raw data.

The patients enrolled under Protocol amendments 1-3 were administered 8 doses of study medication over 11 weeks whereas the patients enrolled under amendment 4 will be administered

10 doses over 12 weeks. Therefore, the statistical analyses and summary tables will be performed by following groups: Group 1: the patients enrolled under amendments 1 to 3, Group 2: the patients enrolled under amendment 4.

5.2.1 Missing or Partial Dates

In general, imputation of partial missing dates will be made for AE onset date, start and end dates of concomitant therapy, and date of initial diagnosis of UC.

For AE onset date, the global standard AE imputation rules listed below will be applied.

- Partial AE onset dates will be imputed as follows:
  - If the onset date of an adverse event is missing day only, it will be set to:
    - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the first dose date;
    - The day of first dose date, if the month/year of the onset of AE is the same as month/year of the first dose date and month/year of the AE resolution date is different;
    - The day of first dose date or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dose date and month/year of the AE resolution date are same
  - If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
    - January 1 of the year of onset, as long as this date is after the first dose date;
    - Month and day of the first dose date, if this date is the same year that the AE occurred;
    - The AE resolution date
  - Completely missing onset dates will not be imputed.
- Partial AE resolution dates not marked as ongoing will be imputed as follows:
  - If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month;
  - If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year;
  - Completely missing resolution dates will not be imputed;

For start and end dates of concomitant therapies, the global standard AE imputation rules listed above will be applied accordingly.

For date of initial diagnosis of UC, the following rule will be applied.

- If date is completely missing, no imputation will be made;
- If year is missing, no imputation will be made;
- If only year is present, but month and day are missing, then June 30th will be used;
- If only day is missing but year and month are available, then the 15th of the month will be used;

However, the above imputations will be modified by the following rules:

- If such imputed date for initial diagnosis is on or after study consent date, then consent date - 1 will be used.

5.3 Software

All report outputs will be produced using Statistical Analysis System (SAS®) version 9.2 or a later version in a secure and validated environment.

5.4 Study Patients

5.4.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

Following summaries will be provided.

- A summary of the number of patients screened for entry into the study and the number and percentage of patient screen failures by major reason and overall (Analysis set: All Patients)
- A summary of the number of patients enrolled per center, and per country if appropriate [Analysis set: All Patients in intent to treat (ITT) population]
- A summary of the number of patients enrolled, the number and percentage of patients treated (with at least one dose of study medication) and the number and percentage of patients entering, withdrawing from study treatment, withdrawing from the study and completing each visit. Withdrawals from study treatment and from the study should also be summarized by major reason.

By-patient listings of visit dates and withdrawal/study completion details (including reason for discontinuation and duration of treatment prior to discontinuation) should be provided.

5.4.2 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on patient's right, safety, well-being and/or the validity of data for analysis.

Major protocol deviations and any action to be taken regarding the exclusion of patients or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification. The final determination of major protocol deviations and the exclusion of patients from any of the analysis sets will be made prior to database lock.

A summary of the number and percentage of patients with a major protocol deviation as well as by type of deviation will be provided. Also, a by-patient listing of all protocol deviations will be provided. The patients whose PDs related to Covid-19 pandemic will also be included in the listings.

5.5 Data Conventions and Analysis Sets

Unscheduled assessments (laboratory data, ECG, or vital signs associated with non-protocol clinical visits or obtained during investigating or managing adverse events) will be included in listings, but not summaries. If more than one laboratory value is available for a given visit, the last valid observation will be used in summaries and all observations will be presented in listings. If it is not possible to determine which is the first measurement due to missing times, then the average of all measurements for that time point will be used as the value for that time point.

5.5.1 Analysis Sets

The study populations include the ITT, modified ITT (mITT), safety, and PK sets.

Intent-to-Treat Set: The ITT population is defined as all patients who are enrolled irrespective of treatment received or not.

Modified Intent-to-Treat Set: The mITT set is defined as all patients who are enrolled and have received at least one dose of Neihulizumab treatment.

The efficacy analyses will be based on the modified ITT set. Summaries of patient disposition, demographics, and disease characteristics, assessments of physical condition and functionality, and dosing of study drug will be provided in this population.

Safety Set: Safety set includes all patients in mITT. This analysis set will be used for all safety analyses and analysis of exposure.

Pharmacokinetic Set: This set will include all patients in mITT who provide at least one post-baseline evaluable drug concentration value.

5.5.2 Visit Windows

'Baseline' is defined as the last available pre-treatment assessment. 'End of Study' is defined as the last available post-treatment assessment. 'Treatment Day' will be calculated relative to the date of first dose i.e. Treatment Day = Assessment Date –First dose date + 1.

The visit windows and study relative days are given in below table. Assessments at early termination and any deviation of scheduled visits will be slotted based on the following visit window but unscheduled visits will not be slotted to analysis visit as below.

Period	Analysis Visit Protocol Amendments 1-4	Analysis Visit Protocol Amendments 1-3	Analysis Visit Protocol Amendment 4	Target day (relative to first dose date)	Study Day** ranges
Screening Period	Week -4 to -1	Week -4 to -1	Week -4 to -1		-28 to -1
Treatment Period	Week 0	Week 0	Week 0	1	<=1
	Week 1	Week 1	Week 1	8	2-11
	Week 2	Week 2	Week 2	15	12-18
	Week 3	Week 3	Week 3	22	19-25
	Week 4	Week 4	Week 4	29	26-32
	Week 5		Week 5	36	33-39
	Week 6	Week 6	Week 6	43	40-47
	Week 7		Week 7	50	48-53
	Week 8	Week 8		57	54-60
	Week 9		Week 9	64	61-67
	Week 10	Week 10		71	68-74
	Week 11		Week 11	78	75-81
EOT	Week 12	Week 12	Week 12	84	82-104
Follow-up	Week 16	Week 16	Week 16	112	105-132
	Week 20	Week 20	Week 20	140	133-174
EOS	Week 26	Week 26	Week 26	182	175-212

**Study Day=Visit Date-First dose Date+1

5.6 Demographic and Other Baseline Characteristics

The following demographic and baseline characteristics will be summarized for patients in the ITT set:

- Age at time of informed consent (in years, as a continuous variable)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Hawaiian Native or Other Pacific Islander, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown).
- Weight at screening (in kilograms)
- Baseline cMCS and pMCS
- Baseline IBDQ

- Duration of history of patient's ulcerative colitis.

By-patient listings of demographic data and other baseline characteristics will be provided.

5.7 Medications and Medical History

5.7.1 Prior and Concomitant Medications

Start and stop dates of medications or medical and surgical procedures will be compared to the date of first dose of study drug to allow them to be classified as either Prior or Concomitant. Medications or medical and surgical procedures that start and stop prior to the date of first dose of study drug will be classified as Prior.

If start and/or stop dates of medications or medical and surgical procedures are missing or partial, the dates will be compared as far as possible with the date of first dose of study drug. Medications or medical and surgical procedures will be assumed to be Concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that they started and stopped prior to the first dose of study treatment.

Medications are coded using World Health Organization Drug Dictionary (WHO DD: SEP 2017) summaries showing number of patients and percentage taking each medication will be provided for each preferred medication term. This will be done separately for prior and for concomitant medications.

A by-patient listing of all prior and concomitant medication data will also be provided.

5.7.2 Medical History

Medical history from the screening visit will be summarized. Medical history will be coded using the MedDRA version 20.1. The number and percentage of subjects experiencing at least one such diagnosis will be summarized by the MedDRA system organ class (SOC) and preferred term (PT).

Summary (n, %) may be presented according to MedDRA groups for specific MH analyses.

By subject listings of medical history will be provided.

5.8 Treatment Compliance

The compliance rate will be assessed as:

Compliance Rate (%) is defined as: (Actual Total Volume (mL) / Prescribed Total Volume) x 100, where Actual Total Volume (mL) is defined as the sum of the real volume injected according to

the case report form records and Prescribed Total Volume (mL) is defined as number of total injections x (Weight of the patient in kg x 0.225 ml/Kg)).
If the compliant rate is <80% then the patient is considered as non-compliant to study treatment. Otherwise, the patient will be considered compliant with the study treatment.

A summary of the treatment compliance measures including the number and percentage of compliant and non-compliant patients will be provided.

A by-patient listing of treatment compliance data will be provided.

5.9 Efficacy Evaluation

5.9.1 Analysis and Data Conventions

5.9.1.1 Handling missing data for Efficacy

All missing values will be treated as a non-responder for primary and secondary binary endpoints. A supportive analysis will be performed using only observed data for the primary and secondary binary endpoints. The primary imputation method for any missing data for continuous variable for secondary efficacy endpoints will be the last observation carried forward (LOCF) approach.

If percentage of missing values at Week 12 and 26 is above 10% overall, then multiple imputation analysis will be performed.

5.9.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of clinical responders at week 12. The clinical response is a composite measurement of MCS and the rectal bleeding score. It is defined as:

a) ≥ 3-point reduction in MCS, a 30% or greater decrease from the baseline score,

AND

b) 1-point or greater decrease of the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1 at Week 12.

The proportion of response rate will be summarized with frequencies and percentages along with 2-sided 95% exact Clopper-Pearson confidence interval at Week 12.

5.9.3 Secondary Efficacy Endpoints

The secondary endpoints (1, 2, 3, 5, 6, 8, 10) of clinical outcomes listed in Section 3.2.1 will be summarized with frequencies and percentages along with 2-sided 95% exact Clopper-Pearson confidence interval at given weeks.

The changes from baseline of secondary endpoints (4,7, 9) including total score of IBDQ at Weeks 12 and 26 will be analysed separately using Analysis of Covariance model (ANCOVA) with baseline value as covariate. The descriptive statistics and the absolute change from baseline will be presented for each time point. Least square means and 95% confidence interval (CI) will also be provided at each assessment time point.

The estimated proportion of primary and secondary end points and 95% CI at each week will be displayed graphically using line graph. A line plots showing the mean change and 95% CI from baseline vs. time in weeks for secondary endpoints will be produced for mITT population.

5.9.4 Exploratory Efficacy Variables

The change of biomarkers of faecal calprotectin and c-reactive protein (CRP) at Week 4, 9, 12, 16, 20, and 26 will be to summarized using descriptive statistics. The association between biomarkers andCmax and the primary efficacy endpoint of UC will be examined.

5.10 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.5.

5.10.1 Extent of Exposure

A by-patient listing of the duration of exposure (total number of days and total dose (mg) will be provided

5.10.2 Adverse Events

All TEAE summaries will include the frequency count of patients with TEAE and the percentage. Patients with multiple TEAEs will be counted only once for each TEAE category.

An overall summary of TEAE will include number of patients in the following TEAE categories:

- Any TEAE
- Any TEAE with Grade ≥ 3
- Any treatment related TEAE by study medication
- Any treatment related TEAE with Grade ≥ 3 by study medication
- Any TEAE leading to treatment discontinuation
- Any TEAE leading to dose reduction or interruption
- Any serious AE
- Any treatment related serious AE by study medication
- Any AE with outcome of death

TEAE will also be summarized by MedDRA system organ class (SOC) and preferred term (PT) for the following TEAE categories:

- Any TEAE
- TEAEs with Grade ≥ 3
- Treatment related TEAE
- Any TEAE leading to discontinuation
- Any TEAE leading to dose reduction or interruption
- Any serious AE

Alldeath and SAEs will be listed.

5.10.3 Adverse Events of Special Interests

Potential significant risks due to infusion toxicities and infection related to immunosuppression of Neihulizumab will be summarized by SOC and PT. A by-patient listings will also be provided.

5.10.4 Clinical Laboratory Evaluation

Laboratory results will be summarized using standard international (SI) units, as appropriate. For all quantitative parameters listed in 3.2.2.2, the actual value and the change from baseline to each post-baseline visit and to the EOT will be summarized by visit using descriptive statistics. Qualitative parameters listed in 3.2.2.2 will be summarized using frequencies (number and percentage of patients), and changes from baseline to each post-baseline visit and to the EOT will be reported using shift tables. Percentages will be based on the number of patients with both non-missing baseline and relevant post-baseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the values are below (L), within (N), or above (H) the laboratory parameter's reference range. Similar shift tables will be used to compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

A by-patient listing of laboratory will be provided with abnormal values flagged.

5.10.5 Vital Signs, Physical Examination and ECG

Over-time summary statistics (n, mean, SD, median and range) of vital signs (temperature, heart rate, respiratory rate, and systolic/diastolic blood pressure) will be provided for each scheduled visit. A separate summary will be produced for vital signs at baseline, maximum, minimum, change to maximum, change to minimum, last value, and change to last value.

Baseline physical examination findings will be summarized. New or worsened physical examination abnormalities will be analyzed as adverse events (AEs).

Descriptive statistics of ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QT_C interval) will be presented.

5.11 Other Analyses

5.11.1 Pharmacokinetics

Plasma concentration-time data for Neihulizumab will be summarized by nominal time using descriptive statistics. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero.

Patients who are considered as not evaluable will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment. A patient is not evaluable if the patient has a protocol violation relevant to the evaluation of pharmacokinetics.

The PK parameters derived using non-compartmental techniques in Phoenix™ WinNonlin® (Version 8.0 or higher, Certara USA, Inc., Princeton, NJ). The following PK parameters will be assessed (other parameters at the discretion of the PK Scientist):

- Cmax: The observed peak drug concentration
- C_{trough}: The residual drug concentration

The above PK parameters will be summarized using descriptive statistics (n, arithmetic mean, SD, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, geometric coefficient of variation). Geometric means and between-patient coefficients of variation (CV_b) will be calculated for $\log_e$-transformed C_{trough} and C_{max} where:

Geometric mean = exp(mean on log scale)

CV_b (%) = sqrt[exp(SD^2) - 1] x 100,

where: SD is the standard deviation of the $\log_e$-transformed data.

Mean plasma concentration-time data will be presented graphically on linear and semi-logarithmic scales using nominal time. Individual concentration-time data and graph of C_{trough} will be presented for all patients plotted grouped together on linear and semi-logarithmic scales using nominal times. No data monitoring committee (DMC) review meetings are planned. However, Primary internal data monitoring will be performed continuously over the accrual and follow-up periods by the site PI and the Study Coordinator.

5.11.2 Quality of Life

To examine the quality of life in the patient population, a self-administered IBD questionnaire containing 32 questions identifiable to four dimensions: systemic symptoms (S), bowel symptoms (B), social Function (SF), and emotional function (E) will be used. The score of the questionnaire will be used to determine subjective health status for patients with inflammatory bowel disease over time.

IBDQ four dimensions:

- Bowel symptoms (B) – Question #s: 1, 5, 9, 13 17, 20, 22, 24, 26, and 29
- Emotional function(E) – Question #s: 3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32
- Systemic symptoms (S) – Question #s: 2, 6, 10, 14, 18
- Social function (SF) –Question #s: 4, 8, 12, 16, and 28.

The scoring of each question is in 1-7 scale. The higher the score the less quality of life is impaired. The IBDQ is calculated by summing the score of each question resulting in a maximum 224 and minimum of 32. If >50% of the questions are left unanswered the total will be treated as missing. The IBDQ questions with above 4 dimensions will be given in the Appendix 1.

Total IBDQ and the change of it from baseline will be summarized by each visit (Baseline, Week 12, and EOS/Week 26) using descriptive statistics. The number and proportion of patients with total IBDQ increased at least 16 points from baseline will also be summarized. Improvement or deterioration of each dimension from baseline to EOT will be compared using paired t-test. By subject listings of these data should be provided.

5.12 Immunogenicity (Anti-drug Antibody)

Results of ADA concentration will be described in the bioanalytical report, which will be included as an appendix in the final clinical study report.

5.13 Data Monitoring Plan

No data monitoring committee (DMC) review meetings are planned. However, Primary internal data monitoring will be performed continuously over the accrual and follow-up periods by the site PI and the Study Coordinator.

5.14 Determination of Sample Size

The primary endpoint is overall responsive rate at Day 84. Assuming placebo effects of 25% (historical data) and AbGn-168H responsive rate of 45%, 40 patients have > 80% power to detect an alpha of 0.1 (two sided).

5.15 Changes in the Conduct of the Study or Planned Analysis

- Regarding the local lab results provided scanned results saved as PDF files for Dr. Scherl's subjects (10-11-002 & 10-11-003) will not be include into the analysis. These pdf files (scanned results) may be included as attachments/appendices to CSR.
- Based on the Inclusion/Exclusion criteria, the patient (10-10-001) must have central read endoscopic score of 2 or higher to include to the study. But patient (10-10-001) was enrolled because endoscopic score was 2 by LOCAL read and was treated, but later the endoscopic score was determined to be 1 by CENTRAL read. This patient was not eligible

based on the I/E criteria and shouldn't have been enrolled in the study. Therefore, this patient is excluded from the analysis set (mITT) as well as from the Pharmacokinetic set (PK) but included to Safety set.

6 REFERENCES

[1] Phoenix™ WinNonlin® (Version 8.0, Certara USA, Inc., Princeton, NJ)

[2] SAS® Version 9.2 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

[3] Little RJ, Rubin DB. Statistical analysis with missing data, John Wiley & Sons (New York; Chichester), 2002.

[4] Clopper, C. and Pearson, S. The use of confidence or fiducial limits illustrated in the case of the Binomial. Biometrika 26: 404-413, 1934.

[5] Guyatt, G et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 3: 809-810, 1989.

Appendix 1: IBDQ Questionnaire Summary

Appendix: Inflammatory Bowel Disease Questionnaire (IBDQ) Summary

The IBDQ includes 32 questions. The wording is deliberately repetitious, as experience has taught us that the repetition ensures subjects' understanding. The questions are grouped into four categories: bowel symptoms (B), systemic symptoms (S), emotional function (E), and social function (SF). Response options are consistently presented as seven-point scales. An example of the way the questions are structured follows:

(B) 1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from the WHITE card in front of you.
- 1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
- 2 EXTREMELY FREQUENT
- 3 VERY FREQUENT
- 4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
- 5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
- 6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
- 7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

The working structure of the other questions is identical, and appropriate seven-point scales are offered for each question. The content of the remaining 31 questions is as follows:

(S) 2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last two weeks?
(E) 3. How often during the last two weeks have you felt frustrated, impatient, or restless?
(SF) 4. How often during the last two weeks have you been unable to attend school or work because of your bowel problem?
(B) 5. How much of the time during the last two weeks have your bowel movements been loose?
(S) 6. How much energy have you had during the last two weeks?
(E) 7. How often during the last two weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem?
(SF) 8. How often during the last two weeks have you had to delay or cancel a social engagement because of your bowel problem?
(B) 9. How often during the last two weeks have you been troubled by cramps in your abdomen?
(S) 10. How often during the last two weeks have you felt generally unwell?
(E) 11. How often during the last two weeks have you been troubled because of fear of not finding a washroom?
(SF) 12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last two weeks?
(B) 13. How often during the last two weeks have you been troubled by pain in the abdomen?

(S) 14. How often during the last two weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night?
(E) 15. How often during the last two weeks have you felt depressed or discouraged?
(SF) 16. How often during the last two weeks have you had to avoid attending events where there was no washroom close at hand?
(B) 17. Overall, in the last two weeks, how much of a problem have you had with passing large amounts of gas?
(S) 18. Overall, in the last two weeks, how much of a problem have you had maintaining, or getting to, the weight you would like to be at?
(E) 19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about have a relapse. In general, how often during the last two weeks have you had felt worried or anxious?
(B) 20. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?
(E) 21. How often during the last two weeks have you felt relaxed and free of tension?
(B) 22. How much of the time during the last two weeks

have you had a problem with rectal bleeding with your bowel movements?

(E) 23. How much of the time during the last two weeks have you felt embarrassed as a result of your bowel problem?

(B) 24. How much of the time during the last two weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels are empty?

(E) 25. How much of the time during the last two weeks have you felt tearful or upset?

(B) 26. How much of the time during the last two weeks have you been troubled by accidental soiling of your underpants?

(E) 27. How much of the time during the last two weeks have you felt angry as a result of your bowel problem?

(SF) 28. To what extent has your bowel problem limited sexual activity during the last two weeks?

(B) 29. How much of the time during the last two weeks have you been troubled by feeling sick to your stomach?

(E) 30. How much of the time during the last two weeks have you felt irritable?

(E) 31. How often during the last two weeks have you felt lack of understanding from others?

(E) 32. How satisfied, happy, or pleased have you been with your personal life during the past two weeks?

Appendix 2 Schedule of assessments (Protocol Amendment 1-3)

TABLE 1 (Scheduled Events of Treatment Period)

Trial Periods	Screening V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**84 EOT [1]**	**112**	**140**	**182 EOS**
Week	**-4 to -1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**26**
Time window (days)	**N.A.**	**± 0**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 2**	**± 4**	**± 4**	**±4**
Informed Consent	x												
Check of Eligibility	x												
Patient Medical History	x												
Patient Ulcerative Colitis History	x												
Inclusion/Exclusion Criteria	x	x											
Concomitant Therapy[2]	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess for Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x
Diary instruction/review	x												
Demographics/Weight	x	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]			
Full Physical Examination	x	x								x			x
Partial Physical Examination			x	x	x	x	x	x	x		x	x	
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead Resting ECG	x												
Flexible sigmoidoscopy[4]	x[5]									x			x
Administer AbGn-168H		x	x	x	x	x	x	x	x				
Complete Mayo Clinic score[4]	x									x			x
Partial Mayo Clinic score[6]		x	x	x	x	x	x	x	x		x	x	
Histopathological analysis	X[7]									x			x
Inflammatory Bowel Disease Questionnaire (IBDQ)	x									x			x
Stool screening[8]	x												
Fecal calprotectin and CRP	x					x		x		x	x	x	x
PK sampling[9]		x	x	x	x	x	x	x	x	x	x	x	
ADA		x				x		x		x	x	x	x
Safety Lab Tests	x	x	x	x	x	x	x	x	x	x	x	x	x
HbA1c test	x												
QuantiFERON® test for tuberculosis	x												
Pregnancy/Hormone Test[10]	x	x	x	x	*x*	x	x	x	x	x			x
Drug and viral screening	x												

Footnotes:

1. Patients who completed the treatment (8 doses) should continue in the study and attend visits through EOS. Patients who discontinue before the completion of 8 doses will be encouraged to continue the visit until EOS. If patients are unable to continue the visits until EOS, the last visit should be considered as EOS and EOS assessments should be completed.
2. Any over-the-counter and/or prescription medications, including dietary supplements taken within 30 days prior to Screening, any ulcerative colitis medications taken 3 months prior to Screening OR any prohibited medications (as outlined in the protocol) that were washed out prior to Screening should be recorded in the eCRF.
3. Weight will be reassessed before administration of AbGn-168H and at EOT.
4. MCS endoscopic subscore will be assessed by a central reader. It is allowed if a full colonoscopy is deemed necessary at screening (V1) per investigator's discretion. However, the endoscopic subscore will be determined by rectum, sigmoid and descending colon only.
5. The screening sigmoidoscopy must be performed at least 14 days before Visit 2/Day 1 (or within 2 weeks after the ICF is signed), since it may take up to 14 days for sites to receive the results of the CMV assessment of intestinal mucosa biopsy.
6. To be done before the infusion of AbGn-168H.

7. CMV assessment of intestinal mucosa biopsy will be performed at screening only.
8. Stool screening include ova and parasites, stool culture for pathogens, stool toxin assay for *Clostridium difficile* to be performed at screening
9. PK sampling will be done at 15±10 mins predose and 2 hrs±15 mins after the end of infusion at Visits 2, 6 and 9. At Visits 3, 4, 5, 7 and 8, PK sample will be done at 15±10 mins predose.
10. Serum pregnancy test will be performed at Screening (Visit 1) for females of childbearing potential. Pregnancy test or confirmation of birth control should be recorded in the source document as available. Urine pregnancy test will be performed prior to drug administration at Visits 2~9, Visit 10 (EOT) and Visit 13 (EOS).

Appendix 3 Schedule of assessments (Protocol Amendment 4)

TABLE 1 (Scheduled Events of Treatment Period)

Trial Periods	Scre	V	V	V	V	V	V	V	V	V	V	V	V	V
Day	-28 to -1	1	8	15	22	29	36	43	50	64	78	84 EOT[1]	112	140	182 EO
Week	-4 to -1	0	1	2	3	4	5	6	7	9	11	12	16	20	26
Time window (days)	N.A.	± 0	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 2	± 4	± 4	±4
Informed Consent	x														
Check of Eligibility	x														
Patient Medical	x														
Patient Ulcerative Colitis History	x														
Inclusion/Exclusion Criteria	x	x													
Concomitant	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess for Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demographics/Wei	x	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]	x [3]			
Full Physical Examination	x	x										x			x
Partial Physical Examination			x	x	x	x	x	x	x	x	x		x	x	
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead Resting	x														
Flexible	x[5]											x			x
Administer AbGn-		x	x	x	x	x	x	x	x	x	x				
Diary	x														
Diary	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physician Global Assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Complete Mayo Clinic score[4]	x											x			x
Partial Mayo Clinic score[6]		x	x	x	x	x	x	x	x	x	x		x	x	
Histopathological analysis	x[7]											x			x
Inflammatory Bowel Disease Questionnaire	x											x			x
Stool screening[8]	x														
Fecal calprotectin	x					x				x		x	x	x	x
PK sampling[9]		x	x	x	x	x	x	x	x	x	x	x	x	x	
ADA		x				x				x		x	x	x	x
Safety Lab Tests (Hematology and Chemistry)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis[10]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
HbA1c test	x														
QuantiFERON® test for tuberculosis	x														
Pregnancy/H ormone	x	x	x	x	x	x	x	x	x	x	x	x			x
Drug Screening[12]	x														
Viral screening	x														

Footnotes:

1. Patients who completed the treatment (10 doses) should continue in the study and attend visits through EOS. Patients who discontinue before the completion of 10 doses will be encouraged to continue the visit until EOS. If patients are unable to continue the visits until EOS, the last visit should be considered as EOS and EOS assessments should be completed.
2. Any over-the-counter and/or prescription medications, including dietary supplements taken within 30 days prior to Screening, any ulcerative colitis medications taken 3 months prior to Screening OR any prohibited medications (as outlined in the protocol) that were washed out prior to Screening should be recorded in the eCRF.
3. Weight will be reassessed before administration of AbGn-168H and at EOT.
4. MCS endoscopic subscore will be assessed by a central reader. It is allowed if a full colonoscopy is deemed necessary at screening (V1) per investigator's discretion. However, the endoscopic subscore will be determined by rectum, sigmoid and descending colon only.

5. The screening sigmoidoscopy must be performed at least 14 days before Visit 2/Day 1 (or within 2 weeks after the ICF is signed), since it may take up to 14 days for sites to receive the results of the CMV assessment of intestinal mucosa biopsy.
6. To be done before the infusion of AbGn-168H.
7. CMV assessment of intestinal mucosa biopsy will be performed at screening only.
8. Stool screening include ova and parasites, stool culture for pathogens, stool toxin assay for Clostridium difficile to be performed at screening
9. PK sampling will be done at 15±10 mins predose and 2 hrs±15 mins after the end of infusion at Visits 2, 9 and 11. At Visits 3, 4, 5, 6, 7, 8, and 10, PK sample will be done at 15±10 mins predose.
10. If urinalysis stix assay is abnormal, a microscopic examination of urine sediment should be perform at local laboratory.
11. Serum pregnancy test will be performed at Screening (Visit 1) for females of childbearing potential. Pregnancy test or confirmation of birth control should be recorded in the source document as available. Urine pregnancy test will be performed prior to drug administration at Visits 2~11, Visit 12 (EOT) and Visit 15 (EOS).
12. Medical use of marijuana, benzodiazepine and amphetamine is allowed, the rest (barbiturate, cocaine, methadone, and opiate)

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