Clinical Trial Protocol

Sponsor	AbGenomics International, Inc.
Trial No.:	2017.008.01
Investigational Product(s):	**Neihulizumab** (AbGn-168H)
Study Title:	**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**
Clinical Phase:	II
Lead Investigator	Dr. David Rubin
Trial Medical Monitor:	Dr. Shipra Patel Dr. Shih-Yao Lin
Status:	*Official Protocol*
Version and Date:	**Version: Amendment 4** **Date: 2018-11-01**
	Page 1 of 78

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: AbGenomics International, Inc.		**Tabulated Trial Protocol**	
Name of finished product: Neihulizumab			
Name of active ingredient: AbGn-168H			
Protocol date (Original): 2017.09.26	**Trial number:** 2017.008.01		**Revision date (Amendment 4):** 2018.11.01

Title of trial:	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.
Lead Investigator:	David Rubin
Trial site(s):	Multi-center trial
Clinical phase:	II
Objective(s):	**Primary Objectives:** To evaluate the efficacy of AbGn-168H administered intravenously in patients with moderate-to-severe active ulcerative colitis (UC) who are refractory or intolerant to anti-TNFα and/or anti-integrin treatments. **Secondary Objective:** To investigate safety, tolerability, and immunogenicity of intravenous AbGn-168H administration.
Methodology:	A Phase II, single arm, open-label, multiple dose, multi-center study
Study Design:	Open-label
Number of Centers:	Around 12-18
No. of Patients:	A minimum of 30 patients and a maximum of 40
Diagnosis:	Moderate to severe active ulcerative colitis refractory or intolerant to anti-TNFα and/or anti-integrin treatments.

Name of company: AbGenomics International, Inc. **Name of finished product:** Neihulizumab **Name of active ingredient:** AbGn-168H		**Tabulated Trial Protocol**	
Protocol date (Original): 2017.09.26	**Trial number:** 2017.008.01		**Revision date (Amendment 4):** 2018.11.01
Main criteria for inclusion:	1) Patients must provide written informed consent; 2) Age 18-75 years; 3) Diagnosis of UC ≥ 12 weeks prior to screening by full colonoscopy (i.e., ≥ 12 weeks after first diagnosis by a physician according to American College of Gastroenterology guidelines); 4) Moderate-to-severe active UC, at time of screening, defined as: a) Mayo Clinic Score (MCS) of 6 points or higher, AND b) a centrally read MCS endoscopic subscore of grade 2 or higher, AND c) MCS rectal bleeding subscore of 1 point or higher, AND d) disease extending 15 cm or more from the anal verge; 5) Stable doses of concomitant medications, including : a) Stable oral corticosteroids (i.e., ≤ 20 mg/day of prednisone, ≤ 9 mg/day of budesonide) ≥ 2 weeks before D1 dosing; Taper of oral corticosteroids per Investigator's discretion during the study is allowed; b) Stable oral 5-amyinosalicylic acid dose ≥ 2 weeks before D1 dosing; c) Stable immunosuppressant including azathioprine, mercaptopurine, or methotrexate ≥ 8 weeks before D1 dosing. Patients taking methotrexate also are advised to take folic acid 1 mg/day or equivalent if there is no contraindication; d) Stable doses of probiotics ≥ 2 weeks before D1 dosing; e) Stable anti-diarrheas ≥ 2 weeks before D1 dosing; 6) Patients must have previously received anti-tumor necrosis factor alpha (anti-TNFα) and/or anti-integrin therapy for UC and demonstrated an inadequate response, loss of response, or intolerance, and must have discontinued therapy ≥ 8 weeks before D1 dosing; 7) Patients previously treated with cyclosporine or tacrolimus must have discontinued therapy ≥ 4 weeks before D1 dosing; 8) Topical corticosteroids and topical 5-amyinosalicylic acid preparations must have been withdrawn ≥ 2 weeks before D1 dosing; 9) Nonsteroidal anti-inflammatory drugs (NSAIDs) must have been discontinued ≥ 4 weeks before D1 dosing; 10) Tofacitinib or other Janus kinase (JAK) inhibitors must have been discontinued ≥ 2 weeks before D1 dosing; 11) Patients previously treated with tube feeding, defined formula diets, or parenteral alimentation/nutrition must have discontinued treatment 3 weeks before D1 dosing; 12) Females with reproductive potential must have a negative pregnancy test result before enrollment. Men and women with reproductive potential have to be willing to use a highly effective method of contraception from study start to ≥ 3 months after the final dose of the study drug. A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year).		

<table>
<tr><td colspan="2">Name of company:
AbGenomics International, Inc.</td><td>Tabulated
Trial Protocol</td><td></td></tr>
<tr><td colspan="2">Name of finished product:
Neihulizumab</td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td colspan="2">Name of active ingredient:
AbGn-168H</td></tr>
<tr><td>Protocol date (Original):
2017.09.26</td><td>Trial number:
2017.008.01</td><td></td><td>Revision date (Amendment 4):
2018.11.01</td></tr>
<tr><td>Main criteria for exclusion:</td><td colspan="3">GI related exclusion criteria:
1) Indeterminate colitis (Inflammatory bowel disease unclassified, IBD-U) or suspected Crohn’s disease
2) Any history of colectomy
3) Presence of an ileostomy or colostomy
4) A history or evidence of colonic mucosal dysplasia
5) Short gut syndrome</td></tr>
<tr><td></td><td colspan="3">General health related exclusion criteria:
6) Pregnant or lactating
7) Inability to comply with study protocol in the opinion of the investigator
8) History of dysplasia or malignancy in recent 5 years, except completely excised basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix
9) Cirrhosis or active alcohol abuse per the judgement of investigator
10) Poorly controlled diabetes (HbA1c > 8.0%)
11) Significant screening ECG abnormalities, including evidence of acute myocardial infarction, complete left bundle branch block, second-degree heart block, or complete heart block
12) Impaired renal function (calculated creatinine clearance < 60 mL/min)
13) Impaired hepatic function in the absence of diagnosis of primary sclerosing cholangitis, serum transaminase > 2.5x Upper Limit Normal (ULN), alkaline phosphatase > 2.5x ULN, or increased total bilirubin judged by the investigator to be clinically significant, or a diagnosis of primary sclerosing cholangitis, serum transaminases > 3x ULN, alkaline phosphatase > 3x ULN, or total bilirubin > 2.5x ULN judged by the investigator to be clinically significant
14) Moderate to severe anemia (Hb < 8g/dL)
15) Thrombocytopenia (platelet count < 75,000/uL)
16) Evidence of current or previous clinically significant disease, medical condition or finding in the medical examination that in the opinion of the investigator, would compromise the safety of the patient or quality of the data
17) Requiring parenteral corticosteroid treatment.
18) Received any investigational product within 1 year.
19) History of drug abuse according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria within 12 months prior to screening or positive drug screening tests.</td></tr>
</table>

Name of company: AbGenomics International, Inc. **Name of finished product:** Neihulizumab **Name of active ingredient:** AbGn-168H		**Tabulated Trial Protocol**	
Protocol date (Original): 2017.09.26	**Trial number:** 2017.008.01		**Revision date (Amendment 4):** 2018.11.01
Main criteria for exclusion:	Infection related exclusion criteria: 20) Human immune deficiency virus (HIV) infection or known HIV-related malignancy. 21) Acute or chronic hepatitis B or C, or carrier status. Patients with anti-HBc Ab but with undetectable anti-HBs Ab should also be excluded. 22) Positive IgM antibody titers in the presence of negative IgG titers to Epstein-Barr virus 23) Positive stool test for ova or parasites, positive stool culture for pathogens, or positive stool toxin assay for *Clostridium difficile* at screening. Patients with the positive stool toxin assay *for C. difficile* at screening could be rescreened if they are being treated for *C. difficile* and a repeat stool toxin assay at least 4 weeks after the completion of treatment is negative with no evidence of recurrence. 24) Intestinal mucosa biopsy positive for cytomegalovirus (CMV) at screening. 25) Positive screening test for latent *Mycobacterium tuberculosis* (TB) infection. Patients with a history of latent TB infection who received an appropriate and documented course of therapy can be included if the screening examination and a chest x-ray performed ≤ 3 months before screening revealed no evidence of current active infection. If a Quantiferon TB test is indeterminate, the test should be repeated, and if the result is again indeterminate, such patient should be excluded. 26) History of any opportunistic infection ≤ 12 weeks before D1 dosing. 27) Any current or recent (≤ 4 weeks before D1 dosing) symptoms/signs of infection. 28) Received oral antibiotics ≤ 4 weeks before D1 dosing or intravenous antibiotics ≤ 8 weeks before D1 dosing. 29) Received a live attenuated vaccine ≤ 4 weeks before D1 dosing. 30) Neutropenia (absolute neutrophil count < 1,500/uL). 31) Lymphocytopenia (absolute lymphocyte count < 500 /uL).		
Dose:	9 mg/kg; Total 10 doses 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).		
Mode of Administration:	Intravenous infusion, infusion time approximately 1 hour		

Name of company: AbGenomics International, Inc. **Name of finished product:** Neihulizumab **Name of active ingredient:** AbGn-168H		**Tabulated Trial Protocol**	
Protocol date (Original): 2017.09.26	**Trial number:** 2017.008.01		**Revision date (Amendment 4):** 2018.11.01
Duration of treatment and follow-up:	Patients receive a total of 10 doses, 9 mg/kg of Neihulizumab, administered over 12 weeks. Patients will be evaluated at the beginning of Week 0 (Day 1), Week 1 (Day 8), Week 2 (Day 15), Week 3 (Day 22), Week 4 (Day 29), Week 5 (Day 36), Week 6 (Day 43), Week 7 (Day 50), Week 9 (Day 64), Week 11 (Day 78), Week 12 (Day 84, End of Treatment), Week 16 (Day 112), Week 20 (Day 140), and Week 26 (Day 182, End of Study).		
Criteria for efficacy:	**Primary endpoint**: The proportion of patients with **clinical response**, defined as defined as a ≥ 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 subscore or an absolute rectal bleeding score of 0 or 1 at Week 12. **Secondary endpoints:** (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. **Exploratory endpoints:** Faecal calprotectin and c-reactive protein changes at Week 4, 9, 12, 16, 20, and 26.		

<table>
<tr><td colspan="2">Name of company:

AbGenomics International, Inc.</td><td>Tabulated

Trial Protocol</td><td></td></tr>
<tr><td colspan="2">Name of finished product:

Neihulizumab</td><td rowspan="3"></td><td rowspan="3"></td></tr>
<tr><td colspan="2">Name of active ingredient:

AbGn-168H</td></tr>
<tr><td>Protocol date (Original):

2017.09.26</td><td>Trial number:

2017.008.01</td><td>Revision date (Amendment 4):

2018.11.01</td></tr>
<tr><td>Criteria for safety:</td><td colspan="3">Physical examination, vital signs, safety laboratory tests, adverse events and tolerability.</td></tr>
<tr><td>Pharmacokinetics parameters:</td><td colspan="3">C_{max} and associated parameters</td></tr>
<tr><td>Immunogenicity:</td><td colspan="3">The Immunogenicity (anti-drug antibody; ADA) of AbGn-168H will be evaluated by a qualitative bridging immunoassay with electrochemiluminescence detection.</td></tr>
<tr><td>Statistical methods:</td><td colspan="3">Determination of sample size: 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).

All patients who receive AbGn-168H treatment (modified Intent to Treat set, mITT) will be included in all analyses.

Summaries of patient disposition, demographics, disease characteristics, assessments of physical condition and functionality. Summary statistics for the time from the first dosing date to the last dosing date will be provided as the extent of drug exposure.

Descriptive statistics with appropriate plots will be employed in the analysis of all efficacy, PK, PD biomarkers (Fecal calprotectin and CRP), and immunogenicity (ADA) data.

AEs will be listed by body system using MedDRA terms. Descriptive statistics will be provided for clinical laboratory test results by scheduled time of evaluation, as well as for the change from baseline.

Summary statistics of continuous variables including numbers, means, standard deviations, median, minimum and maximum will be calculated. Categorical variables will be presented as number and percentages.</td></tr>
</table>

CLINICAL STUDY PROTOCOL APPROVAL/ACKNOWLEDGMENT

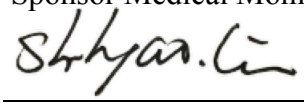
APPROVAL STATEMENT OF ABGENOMICS

On behalf of AbGenomics, only the Sponsor Medical Monitor is authorized to approve the Clinical Study Protocol and any subsequent amendment(s).

The following person has approved this Clinical Study Protocol using signatures as presented below:

Shih-Yao Lin, MD

Sponsor Medical Monitor's Name (Print)



Sponsor Medical Monitor's Signature

31 Oct 2018

Date of Signature
(DD MMM YYYY)

APPROVAL STATEMENT OF THE LEAD INVESTIGATOR

It is the responsibility of the Lead Investigator to approve the Clinical Study Protocol and any subsequent amendment(s).

The following person has approved this Clinical Study Protocol using signatures as presented below:

David Rubin, MD

Lead Investigator's Name (Print)

Lead Investigator's Signature

06 Nov 2018

Date of Signature
(DD MMM YYYY)

ACKNOWLEDGE STATEMENT INVESTIGATOR(S)

Each participating investigator must agree to the approved Clinical Study Protocol and any subsequent amendment(s) by signing the Investigator Clinical Study Protocol Agreement Form.

TABLE 1 (Scheduled Events of Treatment Period)

Trial Periods	Screening V1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**64**	**78**	**84 EOT[1]**	**112**	**140**	**182 EOS**
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 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	x	x
Assess for Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demographics/Weight	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 ECG	x														
Flexible sigmoidoscopy[4]	x[5]											x			x
Administer AbGn-168H		x	x	x	x	x	x	x	x	x	x				
Diary Instruction/review	x														
Diary collection/review	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 (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	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/Hormone Test[11]	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) is exclusionary.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
ADA	Anti-drug Antibody
ADCC	Antibody-dependent Cellular Cytotoxicity
AICD	Activation-induced Cell Death
CDC	Complement-dependent Cytotoxicity
CHO	Chinese Hamster Ovary
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSR	Clinical Study Report
DTH	Delayed-type Hypersensitivity
ECG	Electrocardiograph
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
Fas-L	Ligand for Fas molecule
FDA	Food and Drug Administration
GvHD	Graft versus Host Disease
GWAS	Genome-wide Association Study
GCP	Good Clinical Practice
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease

IBDQ	Inflammatory Bowel Disease Questionnaire
IEC	Independent Ethics Committee
IFNγ	Interferon Gamma
IL	Interleukin
IL18RAP	Interleukin 18 Receptor Accessory Protein
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	intravenous
JAK	Janus kinase
lb	pound
MCS	Mayo Clinic Score
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NOAEL	No Observed Adverse Effect Level
NOD2	Nucleotide-binding Oligomerization Domain-Containing Protein 2
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PI	Principle Investigator
PK	Pharmacokinetics
pMCS	Partial Mayo Clinic Score
PPS	Per Protocol Set
PRO	Patient-reported Outcome
PsA	Psoriatic Arthritis
PSGL-1	P-selectin Glycoprotein Ligand-1
SAE	Serious Adverse Event

s.c.	subcutaneous
sr-aGvHD	steroid-refractory acute Graft versus Host Disease
SRD	Single Rising Dose
SUSARs	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TLPL	T-Lamina Propria Lymphocytes
TNFα	Tumor Necrosis Factor-α
UC	Ulcerative Colitis
ULN	Upper Limit of Normal
5-ASA	5-aminosalicylic Acid
6-MP	6-mercaptopurine

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Ulcerative colitis (UC) is a lifelong, chronic inflammatory disease affecting colorectal mucosa. The hallmark clinical symptom is bloody diarrhea, rectal urgency and tenesmus. Anatomically, UC involves the rectum in about 95% of cases and may extend to proximally to the proximal portion of the large intestine. At extreme, UC may involve the entire colon. Ulcerative colitis is associated with significant morbidity. Typically, UC patients go through cycles of exacerbations and emissions, which may occur spontaneously or in response to treatment changes or concurrent illnesses. If poorly controlled, UC can significantly affect a person's social and psychological wellbeing. An estimated 50% of people with ulcerative colitis will have at least one relapse per year[1]. About 80% of these are mild to moderate and about 20% are severe[2].

UC was estimated to affect approximately 500,000 individuals in the United States. The incidence of UC is about 8-12 per 100,000 population per year[3]–[7]. The direct medical costs alone exceed four billion dollars annually, comprising estimated hospital costs of over US$960 million[8] and drug costs of $680 million[9]. The social economic cost associated UC is high. A quarter million physician visits, 30,000 hospitalizations, and loss of over a million workdays per year are contributed by UC[10].

The pathogenesis of ulcerative colitis is complex and not completely known, but accumulating evidence suggests that environmental factors contribute to trigger in genetically predisposed individuals **an overly aggressive T cell mediated immune-inflammatory response** against components of the luminal flora, which eventually leads to mucosa damage [11]–[13]. From genome-wide association study (GWAS) data, hundreds of disease-associated loci have been identified. Although the molecular functions of many identified UC-related genes are not clear, the molecular functions of several genes (e.g., NOD2, IL23R, and IL10) are involved in **inflammation against bacteria** and **T cell-mediated cytokines production**[14]. Environmental factors and microbiota within colon also contributes significantly to colon mucosal inflammation, especially in genetically predisposed individuals. It is postulated that in the colon of genetically susceptible individual, special inflammation triggering bacteria may emerge in the presence of environmental factors, such as high fat diet and antibiotics use. Through an elusive mechanism, these bacteria activate **gut mucosa homing T cells** to secret an array of inflammatory cytokines: IL1, IL2, IL12B, IL18RAP, IL21, IFNγ, IL10, IL27, causing the breakdown of colorectal mucosa[15].

T cell involvement in UC has been substantiated by several observations[16]. First, UC is associated with a single nucleotide polymorphism on a T cell specific transcription factor T-bet binding site that controls the expression of *IL18RAP*[17]; UC is frequently associated with other T-cell mediated diseases such as psoriasis[16] and multiple sclerosis[18]; research has further shown that colitis can be induced in immune deficiency mice by native T cell transfer [18], and a novel helper T cell subset expressing the transcription factor PU.1 and IL9 consequently named Th9 cells was identified in patients with UC, and was shown to play an important role in driving UC by regulating the function of the intestinal epithelial barrier[19], [20]; and finally, inhibitors

of T cell proliferation and activation such as cyclosporine[21] and tacrolimus[22], or blocking T cell influx into colorectal mucosa by vedolizumab (an anti α4β7 integrin antibody)[23], [24] or etrolizumab (an anti-β7 integrin antibody)[25], has been proved to be effective in control disease activity. In line with the pathogenesis role of T cell, blocking TNFα, which is secreted by activated T cells, among other cells, is also effective in controlling UC activities [26]–[30], so is Tofacitinib, an oral inhibitor of JAK pathways which modulate the signaling of IL2, IL4, IL9, IL21, among other cytokines and interfere with Th2 and Th17 differentiation.

The treatment goal in ulcerative colitis is the induction and maintenance of clinical/patient-reported outcome remission (PRO), defined as resolution of rectal bleeding and diarrhea/altered bowel habit, and endoscopic remission, defined as a Mayo endoscopic subscore of 0-1. Histological remission was considered as a adjunctive goal[31]. The primary drugs used in ulcerative colitis include 5-aminosalicylic acid (5-ASA), steroids, and immunomodulators such as azathioprine and 6-mercaptopurine (6-MP)[32]. However, most of these conventional medications provide symptomatic improvement but fail to stop the underlying inflammatory process and do not change the disease course[33]. In addition, 20-40% of UC patients do not respond to conventional medications[34]. The advent of biologics such as anti-TNFα agents has dramatically changed the outcome of UC since they changed both disease course (fewer surgeries, less hospitalization, steroid sparing, greater clinical remission and mucosal healing rates) and patients' life (quality of life and work productivity)[26], [35]. However, with all current available biologics, more than 50% of UC patients failed to reach remission (Table 2 and Table 3), with 10-20%/year the loss of response rate and withdrawal due to intolerance is frequent in the long term[36]. In the safety prospective, long term use of TNFα inhibitors is associated with increased risk of opportunistic infection and even cancer[37]–[40]. All these clinical experiences demonstrate there are still significant unmet medical needs for ulcerative colitis and underscores the need for new medications which could provide therapeutic efficacy without compromising the protective immunity.

Table 2: Response rates (2A) and Remission rates (2B) in UC patients naïve to biological treatments.

(2A) Response Rates

TNFα naïve	**Induction Response rate at/within W12**		**Maintenance Response rate at/beyond W52**	
	Treatment	Placebo	Treatment	Placebo
Infliximab **ACT 1** **ACT 2**	69.4% (W8) 64.5% (W8)	37.2% (W8) 29.3% (W8)	45.5% (W54) 47.1% (W30)	19.8% (W54) 26.0% (W30)
Adalimumab **ULTRA 1** **ULTRA 2**	53.8% (W8) 59.3%	43.1% (W8) 38.6%	36.7%	24.1%
Golimumab **PURSUIT**	52.9% (W6)	30.3% (W6)	48.4% (W54)	31.2% (W54)
Vedolizumab **GEMINI 1**	53.1%	26.3%	60.7%	26.6%

(2B) Remission rates

TNFα naïve	**Induction** **Remission rate at/within W12**		**Maintenance** **Remission rate at/beyond W52**	
	Treatment	Placebo	Treatment	Placebo
Infliximab **ACT 1** **ACT 2**	39% (W8) 33.9% (W8)	14.9% (W8) 5.7% (W8)	34.7% (W54) 35.8% (W30)	16.5% (W54) 10.6% (W30)
Adalimumab **ULTRA 1** **ULTRA 2**	18.5% (W8) 21.3% (W8)	9.2% (W8) 11% (W8)	22% (W52)	12.4% (W52)
Golimumab **PURSUIT**	17.9% (W6)	6.4% (W6)	33.8% (W54)	22.1% (W54)
Vedolizumab **GEMINI 1**	23.1% (W6)	6.6% (W6)	46.9% (W52)	19.0% (W52)
Etrolizumab	44% (W10)	0% (W10)		

Table 3: Response rates (3A) and Remission rates (3B) in UC patients refractory to TNFα treatment.

(3A) Response rates

TNFα exposed	**Induction Response rate at/within W12**		**Maintenance Response rate at/beyond W52**	
	Treatment	Placebo	Treatment	Placebo
Adalimumab **ULTRA 2**	36.7%	28.7%	20.4%	9.9%
Vedolizumab **GEMINI 1**	39.0%	20.6%	44.6%	15.8%

(3B) Remission rates

TNFα exposed	**Induction Remission rate at/within W12**		**Maintenance Remission rate at/beyond W52**	
	Treatment	Placebo	Treatment	Placebo
Adalimumab **ULTRA 2**	9.2%	6.9%	10.2%	3%
Vedolizumab **GEMINI 1**	9.8%	3.2%	36.1%	5.3%
Etrolizumab	5%	0%		

T cell apoptosis is a critical mechanism aimed at preserving immune homeostasis by preventing uncontrolled lymphocyte proliferation. Activation-induced cell death (AICD) is a specialized form of T cell apoptosis which follows antigen-induced T cell stimulation, and is mediated by

Fas (CD95) on T cells, among other molecules. AICD machinery is particularly relevant in the context of chronic antigenic stimulation, such as that occurring in the intestinal track, where the mucosal immune system is constantly exposed to luminal antigens deriving from bacterial flora and diet. While normal intestinal T-lamina propria lymphocytes (T-LPL) undergo apoptosis when stimulated in vitro with the ligand for Fas molecule (Fas-L), intestinal T-LPL of IBD patients are shown to be resistant to Fas-mediated cell death[41], [42].

Neihulizumab (AbGn-168H), the development candidate, is a humanized IgG4κ monoclonal antibody (mAb) directed against the surface adhesion molecule, P-selectin glycoprotein ligand-1 (PSGL-1). Binding of PSGL-1 by cross-inked Neihulizumab preferentially induces apoptosis (programmed cell death) of late stage activated T cells while sparing resting T cells and other immune cells[43]. In fact, Neihulizumab delivers apoptosis signal to late stage activated T cells, similar to similar to Fas/Fas-L mediated AICD in late stage activated T cells. More importantly, our research data also demonstrated that Neihulizumab induced apoptosis in T cells isolated from lamina propria of the intestinal lesion sites in Pts with Crohn's disease, one form of IBD closely related to UC (data not yet published). This data suggested that Neihulizumab can deliver apoptosis signal and restore immune homeostasis even in cells where Fas/Fas-L mediated AICD are impaired, suggesting a potential therapeutic effect in IBD.

With this novel mechanism of action Neihulizumab is anticipated to be effective in treating T-cell mediated autoimmune diseases such as psoriasis, psoriatic arthritis, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, type-1 diabetes and GvHD. Indeed animal model studies have demonstrated the potential therapeutic effects of Neihulizumab in arthritis (data not yet published), diabetes and GvHD[44], among others. Other than providing a potential new therapeutic effect via a new MOA, Neihulizumab also provides two possible additional advantages over all currently available biologics: First, while all the current available biologics need to be continuously used, the elimination (apoptosis induction) of activated antigen-specific, pathogenic T cells is anticipated to create a long-term disease-free period (remission); Second, equally important, since AICD could be induced only after the completion of protective immunity, Neihulizumab administration should have reduced risk of opportunistic infection and cancer compared to currently available biologics which generate a general immune suppression to some degree.

Two randomized, double blind, placebo-controlled Phase II studies (**Study No. 2012.005.01** and **Study No. 2014.002.01**, **IND No. 115535)** have demonstrated **clinical proof of principle** and the safety profile of Neihulizumab in psoriasis patients[45], [46]. **Clinical proof of principle** was also clearly demonstrated in psoriatic arthritis via a phase II open-label, multiple center trial (**Study 2014.009.01**)[47]. Neihulizumab for **steroid-refractory acute graft-versus-host disease (sr-aGvHD)** in patients undergoing allogeneic hematopoietic cell transplantation was tested in **Study BMT-285**[48], and detailed in *clinical studies*. A new study design (**Study 2017.002.01**)

is being prepared to address PK, PD, safety and efficacy points of view of Neihulizumab in sr-aGvHD.

To establish the therapeutic effect of Neihulizumab in ulcerative colitis, a Phase II, open label, single arm, multiple dose proof of principle study is designed in patients with moderate to severe active ulcerative colitis and who has failed or are intolerant to anti-TNFα and/or anti-integrin therapy.

1.2 DRUG PROFILE

Drug Substance and Drug Product

Neihulizumab (AbGn-168H) is derived from AbGn-168, a humanized monoclonal antibody of the IgG4 subclasses which binds to human CD162 (PSGL-1). The AbGn-168H molecule is composed of two heterodimers. Each of the heterodimers is composed of a heavy and a light polypeptide chain. The four polypeptide chains of the antibody molecule are linked together by disulfide bonds. In order to reduce the in vivo occurrence of half molecules (also known as shuffling) of wild type IgG4 antibodies such as AbGn-168, a serine to proline (S228P) mutation was introduced in the hinge region of AbGn-168H heavy chain by PCR mutagenesis. This mutation was shown to stabilize the intermolecular disulfide bonds and eliminate IgG4 shuffling in vivo. The heavy chains are glycosylated and there are two binding sites for CD162 per antibody molecule. The antibody protein has a molecular mass of approximately 148 kDa.

AbGn-168H is expressed in Chinese hamster ovary (CHO) cells. It is manufactured using standard mammalian cell culture techniques, followed by a series of protein purification steps including several chromatography steps, as well as steps for removal and inactivation of potential viruses.

The current formulation of the AbGn-168H drug product is a solution for injection at a concentration of 40 mg/mL.

Pharmacology and Safety Pharmacology

AbGn-168H binds to PSGL-1 and preferentially induces apoptosis of activated T cells and spares primary peripheral T cells, the majority of which are resting T cells. The *in vivo* pharmacologic effects have been demonstrated in a murine model of DTH (*trans-vivo* Delayed-type Hypersensitivity) and a DTH model in cynomolgus monkey, the relevant animal species, indicating a pharmacologically relevant effect can be achieved *in vivo*.

As an IgG4 antibody, AbGn-168H does not mediate ADCC (Antibody-dependent Cellular Cytotoxicity) or CDC (Complement-dependent Cytotoxicity). Additional studies done with AbGn-168, which support the safety assessment of AbGn-168H include the demonstration that no apoptosis induction occurs in other PSGL-1 expressing cells, including neutrophils, B cells and monocytes, after AbGn-168 treatment. *In vitro* binding by AbGn-168 does not interfere with

the interaction of P-selectin with PSGL-1, a key function associated with PSGL-1 and a requirement for efficient localization of activated T cells and neutrophils to target tissues. In addition, there is no *in vitro* cytokine release from purified CD4+ T cells or PBMC when treated with AbGn-168 or AbGn-168H (see also Toxicology). Furthermore, administration of AbGn-168H surrogate antibody in mice (cTAB4) does not have significant impact on the disease progression of *C. difficile* infection.

Toxicology

AbGn-168H toxicity evaluations include studies supporting the use of the cynomolgus monkey as the toxicologically relevant species, a study investigating the potential for cytokine release in humans, and 4-week intravenous and subcutaneous repeat-dose toxicity studies in cynomolgus monkeys. Relevant studies with AbGn-168 which support the safety assessment of AbGn-168H include additional cytokine release studies, intravenous repeat-dose toxicity evaluations up to 13 weeks with a 39-week recovery period, evaluation of effects on the hematopoietic system (including stem cells and platelet), and local tolerance assessment.

AbGn-168H administered over 4 weeks by twice weekly intravenous infusion or subcutaneous administration to cynomolgus monkeys caused no adverse effects at dose levels up to 100 mg/kg, and administration of AbGn-168 twice weekly at dose levels up to 100 mg/kg for 4- or 13 weeks likewise caused no adverse effects in monkeys. The 13-week repeat-dose study in cynomolgus monkeys with AbGn-168 showed no effect on a T-cell dependent antibody response or on NK cell cytolytic activity. **Therefore, the No Observable Adverse Effect Level (NOAEL) of AbGn-168H was greater than 100 mg/kg, twice per week.**

There was no evidence of any treatment-related effect *in vivo* on circulating cytokines in the 4-week studies with AbGn-168H or AbGn-168, or in a separate DTH monkey study with AbGn-168 that simulated the conditions of an activated immune system. In addition, there was no evidence for *in vitro* cytokine release in whole blood from healthy donors exposed to AbGn-168H or AbGn-168, or in whole blood from psoriatic patients exposed to AbGn-168. Taking the results from all of these studies together, the weight of evidence suggests that treatment with AbGn-168H in humans has a low risk of inducing cytokine release.

Studies to test the potential effects of AbGn-168 on bone marrow demonstrated that AbGn-168 binds to human and cynomolgus monkey CD34+ stem cells but does not appear to affect hematopoiesis. The effect of AbGn-168 on platelet function was evaluated and data showed that AbGn-168 did not bind platelets that were either untreated or thrombin activated.

AbGn-168H was well tolerated locally in cynomolgus monkeys when administered by repeated intravenous or subcutaneous administration twice per week over 4 weeks. AbGn-168 formulation, very similar to that of AbGn-168H, was well tolerated locally in cynomolgus monkeys at concentrations of 10 and 40 mg/mL when administered by intravenous, intramuscular, and subcutaneous routes. AbGn-168 did not cause hemolysis of human whole blood *in vitro* and was compatible with human plasma.

AbGn-168H is immunogenic in cynomolgus monkeys. Repeat dose administration of AbGn-168H to cynomolgus monkeys resulted in an immunogenic response. However, such immunogenicity does not appear to have been a seriously limiting factor for other humanized monoclonal antibodies taken into the clinic.

No developmental or reproductive toxicology studies have been conducted to date. No treatment-related effects on the reproductive tissues of male and female monkeys when administered AbGn-168H for up to 4 weeks or AbGn-168 for up to 13 weeks were observed, with the caveat that many of these animals were sexually immature. Based on the biophysical nature of monoclonal antibodies and the demonstrated mode of action for AbGn-168H, genetic toxicology studies are not warranted and have not been performed. Carcinogenicity studies have not been conducted to date.

Non-clinical Pharmacokinetics

The pharmacokinetics of AbGn-168H was studied in CD57BL/6 mice and cynomolgus monkeys and was compared with the pharmacokinetics of AbGn-168 in those species. Exposures for AbGn-168H were quite similar to those for AbGn-168 in these studies. Whereas AbGn-168 undergoes IgG_4 shuffling in cynomolgus monkeys, AbGn-168H exhibits little if any IgG_4 shuffling.

In the 4- and 13-week studies with AbGn-168H and AbGn-168, the highest dose level tested of 100 mg/kg was a NOAEL. At the NOAEL, AbGn-168H mean exposures on Day 25 in the 4-week intravenous study were approximately 5,230,000 ng/mL (C_{max}) and 308,500,000 ng·hr/mL ($AUC_{0\text{-}72hr}$) and mean exposures on Day 22 of the 4-week subcutaneous study were approximately 4,450,000 ng/mL (C_{max}) and 353,000,000 ng·hr/mL ($AUC_{0\text{-}96hr}$). Exposure levels of AbGn-168H in the 4-week study were comparable to levels of total AbGn-168 (intact + shuffled) in 4- and 13-week studies. The results of the 4-week studies in cynomolgus monkeys with AbGn-168H, including exposure levels, mirror those of 4- and 13-week repeat-dose toxicity studies with AbGn-168.

Clinical Studies

AbGn-168H was first tested in a single rising dose (SRD) **trial (Study 1304.1)**[49] in 36 healthy volunteers in doses up to 2000 µg/kg i.v. and 125 and 1000 µg/kg s.c.. AbGn-168H was well tolerated in the SRD trial. There was no evidence of cytokine release and no critical change in laboratory parameters.

The PK analysis of trial 1304.1 demonstrated that no shuffling with AbGn-168H occurred. After i.v. dosing, AbGn-168H C_{max} or $AUC_{0\text{-}\infty}$ exposure increased in a close to dose-proportional manner. The terminal half-life of the antibody increased somewhat with dose up to the 500 µg/kg dose and then remained relatively constant at higher doses (40-45 h), which is relatively short compared to published values of endogenous IgG4 half-life. This suggests that AbGn-168H may be cleared by target-mediated clearance. Following s.c. dosing, bioavailability for the 125 µg/kg

and 1000 µg/kg s.c. doses of AbGn-168H is 33% and 42%, respectively. These values may be relatively low because of the relatively rapid clearance of AbGn-168H. In trial 1304.1, Anti-Drug Antibody (ADA) responses were only observed in 1 subject dosed at 125 µg/kg s.c. AbGn-168H.

Multiple doses of AbGn-168H were first tested in two randomized, double blind, placebo-controlled Phase II studies in patients with moderate to severe chronic plaque psoriasis **(Study No. 2012.005.01** and **Study No. 2014.002.01)**[45], [46]. In **study 2012.005.01**, six consecutive weekly doses of AbGn-168H at 0.5 mg/kg (19 patients) or 3 mg/kg (18 patients) were well tolerated. There was no evidence of cytokine release or any critical change in lab parameters, although a mild, clinically insignificant, transient, and reversible decreases in the mean and median total leukocyte counts were observed in the 3 mg/kg group. Signs of clinical efficacy (median PASI score over time, % of PASI50 responders, and improved TLPSS assessment) were observed at 3 mg/kg compared to Placebo group. **Clinical proof of principle was considered demonstrated in psoriasis** [45].

Analysis of the pharmacokinetic parameters for AbGn-168H revealed that increasing the concentration of AbGn-168H from 0.5 mg/kg to 3 mg/kg disproportionately increased both the plasma concentration (C_{max}) and the exposure (AUC). Of the 19 patients in the AbGn-168H 0.5 mg/kg group and the 18 patients in the AbGn-168H 3 mg/kg group, 3 (15.8%) patients in the AbGn-168H 0.5 mg/kg group and 7 (38.9%) patients in the AbGn-168H 3 mg/kg group were confirmed positive for ADA (titer $\leq$ 625) at one or more visits.

In **Study 2014.002.01**, 4 doses of 6 mg/kg (17 patients) and 9 mg/kg (16 patients) given to patients with moderate to severe chronic plaque psoriasis on Day 1 (W0), Day 8 (W1), Day 29 (W4) and Day 36 (W5) was well tolerated. There was no evidence of cytokine release or any critical change in lab parameters, although a mild, clinically insignificant, transient and reversible decreases in the mean and median total leukocyte counts were observed in both the 6 mg/kg and 9 mg/kg groups. Although results for the primary efficacy endpoint, the frequency of PASI75 at Week 10, were unremarkable, a consistently greater number of patients in the AbGn-168H groups achieved a PASI50 compared with the placebo group at every assessment time point except Week 1 (for the 9 mg/kg group compared with placebo) and Week 5 (for the 6 mg/kg group compared with placebo). **Clinical proof of principle is considered proven once again for psoriasis** [46].

Analysis of the pharmacokinetic parameters for AbGn-168H revealed that increasing the concentration of AbGn-168H from 6 mg/kg to 9 mg/kg increased both the plasma concentration and exposure (approximately 2.8 times). The steady-state $T_{1/2}$ was also increased from 113.9 hr in the AbGn-168H 6 mg/kg group to 132.1 hr in the AbGn-168H 9 mg/kg group. Of the 17 patients in the AbGn-168H 6 mg/kg group and the 16 patients in the AbGn-168H 9 mg/kg group, 4 (23.5%) patients in the AbGn-168H 6 mg/kg group and 5 (31.2%) patients in the AbGn-168H

9 mg/kg group were confirmed ADA positive at some time during the study. The ADA titer was generally low (≤3125) with the exception of 1 patient in the 9 mg/kg group who had an ADA titer of 15625 at Week 20.

Study 2014.009.01 is a phase II open-label, multi-center, proof of principle trial for psoriatic arthritis in which Seven (7) doses of AbGn-168H at 9 mg/kg was administered in 20 patients with moderately to severely active psoriatic arthritis. AbGn-168H were well tolerated and no safety concerns for AbGn-168H administration at this dose. Forty percent (40%) of all patients treated with study agent in this open label study demonstrated meaningful responses by week 12, suggesting the clinical utility with AbGn-168H for the treatment of psoriatic arthritis. **Clinical proof of principle is considered proven also for psoriatic arthritis [47].** There was only one positive ADA response (Ab titer is 125) detected at Week 12 from 1 patient who had received all 7 doses of the study drug.

Since AbGn-168H demonstrated proof of clinical principle in treating T-cell mediated diseases such as psoriasis and psoriatic arthritis, a dose escalation/de-escalation study using AbGn-168H to treat steroid-refractory acute graft-versus-host disease (sr-aGvHD) in patients undergoing allogeneic hematopoietic cell transplantation was initiated **(Study BMT-285)**. Patients received up to 4 infusions of up to 9 mg/kg of AbGn-168H. Four (4) patients were enrolled and received at least one infusion of AbGn-168H.

The AEs observed in this small group of patients were consistent with what would be expected in this patient population. The most frequently occurring AEs were diarrhea (n=3), elevated bilirubin levels (n=3), ileus (n=2), septic shock (n=2) and respiratory distress (n=2). There were no cytokine release reactions or infusion reactions observed with AbGn-168H and there was no apparent association between increasing dose of AbGn-168H and increasing incidence or severity of adverse events. No DLTs attributed to AbGn-168H were observed in this study. Three patients died during the study due to complications arising from disease progression of severe aGvHD.

The mortality in this study triggered an accrual pause to conduct safety review by protocol, and was subsequently placed on Clinical Hold by the FDA on April 8, 2016, although the continuation of the study was concurred by the Institute DSMC. After a face-to-face discussion with FDA on Nov. 15, 2016, a newly designed study protocol (Study 2017.002.01) was resubmitted on May 1, 2017. May proceed letter was received on May 18, 2017 and the study is currently ongoing.

This **Study 2017.008.01** is a Phase II, open label, single arm, multiple dose proof of principle study to test the therapeutic effect of Neihulizumab in patients with moderate to severe ulcerative colitis and who has failed or are intolerant to anti-TNFα and/or anti-integrin therapy. This study is to be conducted in compliance with Good Clinical Practice (GCP). For further details see "*Investigator's Brochure*"[50].

2. RATIONALE, OBJECTIVES, AND BENEFIT-RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Therapeutic rationale for AbGn-168H in anti-TNFα and/or anti-integrin refractory ulcerative colitis

As discussed previously, the pathological process that causes mucosa damage in ulcerative colitis is substantially involved with T cell accumulation and T cell mediated immune-inflammatory response. The important role of T cells in the pathogenesis of ulcerative colitis has been suggested in the literature and therapies that target T cell mediated inflammatory response and T cell trafficking have demonstrated efficacy to treat UC[24]–[28]. However, with all the biologics available to date, more than 50% of UC patients failed to reach remission and hence a new therapeutic agent with a different mode of action is required for this unmet medical need. Anti-TNFα and/or anti-integrin agents are the major biologics available in UC treatments and therefore patients who are refractory to these two types of biologics are selected as the target population for this study.

AbGn-168H is an agonistic mAb to PSGL-1 (CD162) which has been shown to induce apoptosis of late-stage activated T-cells *in vitro* but spare naïve T cells and other hematopoietic cells. This mode of action can be applied in UC to target this specific T-cell population which is driving pro-inflammatory reactions but spares those naive T cells which are for protective immunity, so without increasing the risk of infections. AbGn-168H showed in *vivo efficacy* in the *trans-vivo* DTH models which are models of T-cell dependent inflammatory disease. Clinical proof of principle is also obtained in T cell-mediated diseases such as psoriasis and psoriatic arthritis. All these results justify the adding on of AbGn-168H in the treatment of ulcerative colitis.

Justification for doses

The highest dose of AbGn-168H used in the 4-week intravenous and subcutaneous toxicity studies (100 mg/kg; twice weekly) was also the NOAEL. Table 4 depicts safety margins extrapolated from 4th doses of AbGn-168H in humans (Study 2012.005.01 and Study 2014.002.01) *versus* the monkey NOAEL weekly dose and systemic exposure after 4-weeks of intravenous dosing. Although an adverse effect level was not reached with AbGn-168H in monkeys, it is clear that safety margins projected for the highest dose of 9 mg/kg based on body weight dose, C_{max}, and AUC comparisons for patients in this Phase I trial should be considered adequate. Safety evaluation from Study 2014.009.01 which was only 1 dose less than dosing regimen proposed in study also substantiates the safety of the current 8 dose regimen.

Table 4 Safety Margins from 4-Week Monkey Study (IV) with AbGn-168H estimated based on trial 2014.002.01

Species	Route of Admin	Maximum Dose	Weekly Dose	Dosing duration	C_{max} (ng/mL)	AUC (ng·hr/mL)	Safety Margins Vs Maximum Human Dose		
							Weekly Dose	C_{max}	AUC
Monkey	IV	100 mg/kg	200 mg/kg	4 weeks	5,230,000	308,500,000			
Human Patients	IV	9 mg/kg	9 mg/kg	8 weeks	751,750*	151,862,500*	>22X	>6X	>2X

*extrapolated data from 4st doses in Phase II studies (Study 2014.002.01) in psoriatic patients at 9 mg/kg iv.

2.2 TRIAL OBJECTIVES

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

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

2.3 BENEFIT - RISK ASSESSMENT

With this novel mechanism of action Neihulizumab is anticipated to be effective in treating T-cell mediated autoimmune diseases. In both Studies 2012.005.01 and 2014.002.01, signs of efficacy were clearly observed for psoriasis. Study 2014.009.01 also demonstrated clinical efficacy for psoriatic arthritis (see Section clinical studies). Patients of UC might benefit from the trial because T cells play a pivotal role in the pathogenesis of UC, and based on Neihulizumab's novel mechanism of action it is expected that patients with UC are going to benefit from the treatment of Neihulizumab.

Risk of hematopoietic cell depletion

In Study 1304.1, Study 2012.005.01, Study 2014.002.01 and Study 2014.009.1, Neihulizumab single or multiple doses were well tolerated. No cytokine release syndrome or hematopoietic cell depletion was observed in these four studies. A mild, clinically insignificant, transient, and reversible decrease in the mean and median total leukocyte counts was observed in the 3 mg/kg group in trial 2012.005.01 and in the 6 mg/kg and 9 mg/kg groups in trial 2014.002.01, and in study 2014.009.01 where 7 doses of Neihulizumab at 9 mg/kg were administered. Although the risk that Neihulizumab will affect stem cells is convincingly low, it is still critical that careful long-term monitoring of peripheral blood cells is carried out to rule out a clinically significant adverse effect of Neihulizumab on bone marrow stem cells *in vivo*.

Risk of impaired immune function

Neihulizumab has been demonstrated to induce apoptosis selectively in late stage activated T-cells. This selectivity suggests that naïve and resting memory T-cells would be spared from deletion by Neihulizumab, and therefore that Neihulizumab may be less immunosuppressive than pan-T-cell depleting mAbs or the systemic immunomodulating agent such as cyclosporine. However, it cannot be ruled out that depletion of activated T-cells by Neihulizumab may lead to a transiently increased risk of infection. This risk will be addressed by clinical monitoring for adverse events during the treatment and observation periods.

Treatment of psoriasis and psoriatic arthritis with systemic immunomodulatory therapies such as TNFα antagonists has been associated with an increased risk of tuberculosis, and as a result, current guidelines recommend screening patients for latent tuberculosis infection prior to treatment with such agents. As it is not known if a similar risk would be posed by Neihulizumab administration, patients with tuberculosis, history of tuberculosis, or a positive Quantiferon test will be excluded (Exclusion Criterion 24).

Risk of hypersensitivity reactions

As with any systemically administered biologic agent, there is a risk of local or systemic hypersensitivity reactions. Local reactions to intravenously or subcutaneously administered biologic agents are uncommon, and are usually limited to redness, swelling or induration at the injection site. Manifestations of systemic hypersensitivity reactions include anaphylaxis, pruritus, hypotension, and respiratory distress, but these occur uncommonly. Both local and systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard medical treatment. No such events occurred in Neihulizumab related trials (trials 1304.1, 2012.005.01, 2014.002.01, 2014.009.01 and trial BMT-285) up to date.

Summary of benefit-risk assessment

Patients might benefit from the trial, because it is expected that UC may improve. The risks of participation in the trial include the risks associated with the study procedures (e.g. blood drawing and i.v. infusion) which are similar to other trials of investigative agents. The specific risks that can be anticipated in patients receiving Neihulizumab are described above. The study has been designed and will be conducted in such a manner as to minimize these risks as much as possible. Therefore, the benefit-risk assessment is considered acceptable for the current multiple dose trial in human.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This will be an open label, multiple dose, multi-centre study to be conducted in around 12-18 centres 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.

Dose of Neihulizumab will be 9 mg/kg iv. Patients will receive a total of 10 doses on Day 1 (Week 0), Day 8 (Week 1), Day15 (Week 2), Day 22 (Week 3), Day 29 (Week 4), Day 36 (Week 5), Day 43 (Week 6), Day 50 (Week 7), Day 64 (Week 9) and Day 78 (Week 11). 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.

In some case, patient may be allowed to continue the treatment of study drug in the judgment of the investigator and sponsor medical monitor.

Blood samples for PK determinations will be drawn approximately 15 minutes before dosing and 2 hours post doing at Visits 2, 9 and 11, 15 minutes before doing at Visits 3, 4, 5, 6, 7, 8 and 10, and at Visits 12, 13 and 14. Anti-drug antibodies (ADA) will be determined in all patients before dosing at Visits 2, 6, 10 and at Visits 12-15. Efficacy will be assessed by Mayo Clinic Score (Complete and Partial), endoscopy, biopsy, Inflammatory Bowel Disease Questionnaire (IBDQ) and Biomarkers (faecal calprotectin and c-reactive protein). Safety will be assessed by adverse event (AE) monitoring, laboratory tests, vital signs, physical examinations, discontinuation of treatment due to AE and immunogenicity.

3.2 DISCUSSION OF TRIAL DESIGN

The planned study design including endpoints and methodology is in compliance with regulatory recommendations and consistent with other recently completed phase II studies investigating the efficacy and safety of novel agents in the treatment of UC.

3.3 SELECTION OF TRIAL POPULATION

It is planned that a minimum of 30 and a maximum of 40 patients with moderate to severe UC refractory to anti-TNFα and/or anti-integrin treatments will be entered into this trial. A patient will be considered “enrolled” if they have signed consent and successfully passed the screening phase. Enrollment will be competitive. Approximately 12-18 US sites are planned for this trial.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main Diagnosis for Study Entry

Moderate to severe active ulcerative colitis refractory or intolerant to anti-TNFα and/or anti-integrin treatments

3.3.2 Inclusion Criteria

1. Patients must provide written informed consent;

2. Aged 18-75 years;

3. Diagnosis of UC ≥ 12 weeks prior to screening by full colonoscopy (i.e., ≥ 12 weeks after first diagnosis by a physician according to American College of Gastroenterology guidelines);

4. Moderate-to-severe active UC, at time of screening, defined as:
   a) Mayo Clinic Score (MCS) of 6 points or higher, AND
   b) a centrally read MCS endoscopic subscore of grade 2 or higher, AND
   c) MCS rectal bleeding subscore of 1 point or higher, AND
   d) disease extending 15 cm or more from the anal verge;

5. Stable doses of concomitant medications, including :
   a) Stable oral corticosteroids (i.e., ≤ 20 mg/day of prednisone, ≤ 9 mg/day of budesonide) ≥ 2 weeks before D1 dosing. Taper of oral corticosteroids per Investigator's discretion during the study is allowed;
   b) Stable oral 5-amyinosalicylic acid dose ≥ 2 weeks before D1 dosing;
   c) Stable immunosuppressant including azathioprine, mercaptopurine, or methotrexate ≥ 8 weeks before D1 dosing. Patients taking methotrexate also are advised to take folic acid 1 mg/day or equivalent if there is no contraindication;
   d) Stable doses of probiotics ≥ 2 weeks before D1 dosing;
   e) Stable anti-diarrheas ≥ 2 weeks before D1 dosing;

6. Patients must have previously received anti-tumor necrosis factor alpha (anti-TNFα) and/or anti-integrin therapy for UC and demonstrated an inadequate response, loss of response, or intolerance, and must have discontinued therapy ≥ 8 weeks before D1 dosing;

7. Patients previously treated with cyclosporine or tacrolimus must have discontinued therapy ≥ 4 weeks before D1 dosing;

8. Topical corticosteroids and topical 5-amyinosalicylic acid preparations must have been withdrawn ≥ 2 weeks before D1 dosing;

9. Nonsteroidal anti-inflammatory drugs (NSAIDs) must have been discontinued ≥ 4 weeks before D1 dosing;

10. Tofacitinib or other Janus kinase (JAK) inhibitors must have been discontinued ≥ 2 weeks before D1 dosing;

11. Patients previously treated with tube feeding, defined formula diets, or parenteral alimentation/nutrition must have discontinued treatment 3 weeks before D1 dosing;

12. Females with reproductive potential must have a negative pregnancy test result before enrollment. Men and women with reproductive potential have to be willing to use a highly effective method of contraception from study start to ≥ 3 months after the final dose of the study drug. A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year).

3.3.3 Exclusion Criteria

GI related exclusion criteria:

1. Indeterminate colitis (IBD-U) or suspected Crohn's disease;

2. Any history of colectomy;

3. Presence of an ileostomy or colostomy;

4. A history or evidence of colonic mucosal dysplasia;

5. Short gut syndrome.

General health related exclusion criteria:

6. Pregnant or lactating;

7. Inability to comply with study protocol in the opinion of the investigator;

8. History of dysplasia or malignancy in recent 5 years, except completely excised basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix;

9. Cirrhosis or active alcohol abuse per the judgement of investigator;

10. Poorly controlled diabetes (HbA1c > 8.0%);

11. Significant screening ECG abnormalities, including evidence of acute myocardial infarction, complete left bundle branch block, second-degree heart block, or complete heart block;

12. Impaired renal function (calculated creatinine clearance < 60 mL/min);

13. Impaired hepatic function in the absence of diagnosis of primary sclerosing cholangitis serum transaminase > 2.5x ULN, alkaline phosphatase> 2.5x ULN, or increased total bilirubin judged by the investigator to be clinically significant, or a diagnosis of primary

sclerosing cholangitis, serum transaminases > 3x ULN, alkaline phosphatase > 3x ULN, or total bilirubin > 2.5x ULN judged by the investigator to be clinically significant;

14. Moderate to severe anemia (Hb < 8g/dL);

15. Thrombocytopenia (platelet count < 75,000/uL);

16. Evidence of current or previous clinically significant disease, medical condition or finding in the medical examination that in the opinion of the investigator, would compromise the safety of the patient or quality of the data;

17. Requiring parenteral corticosteroid treatment.

18. Received any investigational product within 1 year
19. History of drug abuse according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria within 12 months prior to screening or positive drug screening tests.

Infection related exclusion criteria:

20. Human immune deficiency virus (HIV) infection or known HIV-related malignancy;

21. Acute or chronic hepatitis B or C, or carrier status. Patients with anti-HBc Ab but with undetectable anti-HBs Ab should also be excluded;

22. Positive IgM antibody titers in the presence of negative IgG titers to Epstein-Barr virus;

23. Positive stool test for ova or parasites, positive stool culture for pathogens, or positive stool toxin assay for *Clostridium difficile* at screening. Patients with the positive stool toxin assay for *C. difficile* at screening could be rescreened if they are being treated for *C. difficile* and a repeat stool toxin assay at least 4 weeks after the completion of treatment is negative with no evidence of recurrence;

24. Intestinal mucosa biopsy positive for cytomegalovirus (CMV) at screening;

25. Positive screening test for latent *Mycobacterium tuberculosis* (TB) infection. Patients with a history of latent TB infection who received an appropriate and documented course of therapy can be included if the screening examination and a chest x-ray performed ≤ 3 months before screening revealed no evidence of current active infection. If a Quantiferon TB test is indeterminate, the test should be repeated, and if the result is again indeterminate, such patient should be excluded;

26. History of any opportunistic infection ≤ 12 weeks before D1 dosing;

27. Any current or recent (≤ 4 weeks before D1 dosing) symptoms/signs of infection;

28. Received oral antibiotics ≤ 4 weeks before D1 dosing or intravenous antibiotics ≤ 8 weeks before D1 dosing;

29. Received a live attenuated vaccine ≤ 4 weeks before D1 dosing;

30. Neutropenia (absolute neutrophil count < 1,500/uL);

31. Lymphocytopenia (absolute lymphocyte count < 500 /uL);

3.3.4 Patient Withdrawal and Trial Discontinuation

3.3.4.1 Patients withdrawal from the treatment or trial

Patients should make every attempt to complete the protocol as specified. Investigators should encourage compliance with the dosing schedule and completion of all study visits.
It is the right and the duty of the investigator or sub-investigator to interrupt treatment of any patient if they feel that study discontinuation is necessary to protect the patient, or that there are unmanageable factors, that may interfere significantly with the study procedures and/or the interpretation of results. If a patient is withdrawn from study drug, he/she will be encouraged to continue the rest of the visits in Table 1, without receiving study drug.
In accordance with the Declaration of Helsinki, patients have the right to withdraw their consent to participate in the trial at any time, for any reason. In addition, the investigator also has the right to withdraw patients from the study for any legitimate reason.

The patient must be withdrawn from treatment with the study drug in the following cases:

- The patient withdraws consent
- The patient has a worsening in his/her ulcerative colitis (partial Mayo Clinic Score ≥ 2 increase compared to baseline)
- The patient is no longer able to participate in the trial for any reason (e.g. surgery, concomitant diseases, concomitant therapies required not allowed by trial or administrative reasons). The patient delays dosing for more than 10 days from the previous dose, or noncompliance while on study
- Patient lost to follow-up
- Investigator's discretion.
- Female participant becomes pregnant

Should a patient decide to withdraw from the study, or should a patient have to be withdrawn from the study, the date (considered End of Study) and the reason for discontinuation shall be recorded on the eCRF, and observation / assessment shall be recorded as thoroughly as possible. All patients withdrawing prior to Day 182 (End of Study) will be asked to allow follow up for

AEs for a minimum of 28 days after the last dose. AEs must be followed until the event has been resolved or no further follow-up is required in the judgment of the investigator and sponsor medical monitor

Patients withdrawn from the trial due to an adverse event must be followed until the event has been resolved or no further follow-up is required in the judgment of the investigator and the trial medical monitor.

The investigator should inform the sponsor immediately when a patient needs to be withdrawn from the trial.

3.3.4.2 Trial discontinuation by the sponsor

AbGenomics reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons as long as patients' health/welfare is not compromised:

1. Failure to meet expected enrolment goals overall or at a particular trial site,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial.
3. Violation of GCP, Clinical Trial Protocol, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The study medication is produced by Boehringer Ingelheim Pharma GmbH & Co. KG.

All doses will be calculated based on mg/kg body weight.

4.1.1 Identity of AbGenomics' Investigational Product

The characteristics of the study medication are listed below

Substance:	AbGn-168H monoclonal antibody (mAb)
Pharmaceutical form:	Infusion concentrate
Chemical name:	Anti-human CD162 (P-selectin glycoprotein ligand-1; PSGL-1) monoclonal antibody (mAb)
Manufacturer:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit Strength:	Each 2 mL vial contains approximately 1 mL of 40 mg/mL solution
Posology:	Multiple doses
Route of administration:	i.v. (approximately 60 minutes)

4.1.2 Packaging, Labeling, and Re-supply

Drug supplies will be provided by Sponsor's designated CRO. The clinical trial supplies are packaged in a box containing 6 vials. The required information according to the United States Law as well as FDA and other applicable Guideline will be on the boxes and vials.

Each box and vial is labeled with:

- Study number
- Name of product and strengths
- Pharmaceutical dosage form, quantity of dosage units
- Term "for clinical trial use only"
- Sponsor name and address
- Manufacture name and address

- Storage conditions
- Batch number

Label examples are given in the Investigator Site File (ISF).

4.1.3 Storage Conditions

Drug supplies will be kept in their original packaging under the recommended storage conditions, i.e. in a refrigerator with limited access, between + 2°C and + 8°C. A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The study medication must be stored securely, e.g. at a secure pharmacy. It may only be dispensed to trial patients according to the protocol by authorized personnel as documented in the form "Investigator's Trial Staff".

All unused medication must be returned to the sponsor/sponsor designated facility or destroyed on-site per site's standard operation procedure. Receipt, usage and return of study medication must be documented on the respective forms. Account must be given for any discrepancies.

4.1.4 Drug Accountability

The investigator is fully responsible for the investigational products at the trial site. Dispensing of investigational products will be delegated to delegated site staff. The person responsible for dispensing the investigational products will be responsible for maintaining adequate control of the investigational products and for documenting all transaction with them.

The *investigator* and/or *pharmacist* and/or *study medication storage manager* will receive the study medications delivered by the sponsor or sponsor assigned CRO when the following requirements are fulfilled:

- approval of the study protocol by the IRB /ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor or the sponsor assigned CRO and the Trial Centre,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae and medical license of the principal investigator,
- availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol, <in exceptional cases, medication could already be sent to the site, before its activation >

- availability of the Form 1572 and financial disclosure.

Investigational product will be accounted for by the field CRA with the help of delegated site staffs for dispensing the medication. Accountability will be documented by the use of drug accountability forms. The *investigator* and/or *pharmacist* and/or *study medication storage manager* must maintain records (drug accountability forms) of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s).

These records will include dates, quantities, batch/serial numbers, expiry ('use by') or retest dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The *investigator/pharmacist/study medication storage manager* will maintain records that document adequately that the patients were provided the doses specified by the clinical trial protocol and reconcile all investigational product(s) received from the sponsor or sponsor assigned CRO.

An inventory must be available for inspection during monitoring visits and will be checked by the field CRA to ensure correct dispensing of the investigational product.

At the time of return to sponsor/sponsor assigned CRO or destruction on-site, the *investigator/pharmacist/study medication storage manager* must verify that all unused or partially used drug supplies have been returned or destroyed and that no remaining supplies are in the investigator's possession.

4.2 TREATMENTS SCHEME, DOSING DELAY AND DISCONTINUATION

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). Neihulizumab will be administered intravenously in a total volume of approximately 100 mL over about 1 hour (60 minutes) at a rate of approximately 1.6 to 1.7 mL/min. See Appendix 10.1 for the detailed procedures for preparing Neihulizumab for intravenously administration.

Dosing delay

After the initial infusion, subsequent Neihulizumab infusions can be delayed up to 10 days period due to reversible medical conditions or adverse events or any other reason. If a grade 3 -5 adverse event attributable to the study drug (probably, or definitely related) is observed, additional doses for that patient will be held until the adverse event has returned to baseline. After the adverse reaction is resolved or stabilized, dosing may be restarted if continued

treatment is determined appropriate by the investigator. (unless the adverse reaction is a grade 3 to 5 cytokine release or hypersensitivity reaction, see *Treatment discontinuation* below).

Treatment discontinuation (see also 4.3 Concomitant Therapy and Restrictions and 5.2.2.3 Adverse event and serious adverse event monitoring and reporting)

Any patient who experiences a grade 3 to 5 cytokine release or hypersensitivity reaction will be permanently discontinued from Neihulizumab, and withdrawn from the treatment portion of the study. Patients with unambiguous evidence of progression may discontinue Neihulizumab treatment and receive additional therapy per standard institutional guidelines.

4.3 CONCOMITANT THERAPY AND RESTRICTIONS

4.3.1 Concomitant therapy

Stable doses of concomitant medications is allowed, including:

a) Stable oral corticosteroids (i.e., ≤ 20 mg/day of prednisone, ≤ 9 mg/day of budesonide) ≥ 2 weeks before D1 dosing; Taper of oral corticosteroids per Investigator's discretion during the study is allowed
b) Stable oral 5-amyinosalicylic acid dose ≥ 2 weeks before D1 dosing;
c) Stable immunosuppressant including azathioprine, mercaptopurine, or methotrexate ≥ 8 weeks before D1 dosing. Patients taking methotrexate also are advised to take folic acid 1 mg/day or equivalent if there is no contraindication;
d) Stable doses of probiotics ≥ 2 weeks before D1 dosing;
e) Stable anti-diarrheas ≥ 2 weeks before D1 dosing.

Any additional concomitant medication and therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation are permissible. In case of adverse events in need of treatment, appropriate therapy according to the judgment of the investigator will be permitted. However, all concomitant medications being taken by eligible patients must be carefully evaluated, and questions on the use of concomitant medications should be discussed with the trial medical monitor. All concomitant therapies will be recorded on the appropriate pages of the eCRFs.

Prophylaxis for hypersensitivity reactions/cytokine release syndrome

Patients who experience a grade 2 hypersensitivity reaction/cytokine release syndrome may continue treatment if the event is resolved, and they may receive prophylactic pre-medications prior to the next infusion. Any patient who experiences a grade 3 to 4 hypersensitivity

reaction/cytokine release syndrome will be permanently discontinued from Neihulizumab, and withdrawn from the treatment portion of the study.

In addition, enrollment will be paused pending a protocol amendment if there are 2 grade 3-5 infusion reactions/cytokine release syndrome in the patients. In order to re-start enrollment, the protocol will be amended with a premedication regimen that will be based in part on the observed symptoms of affected patients. Until the protocol amendment, presently enrolled patients will be informed, but permitted to re-consent and continue treatment with pre-medication at the investigator's discretion. If there are 2 or more grade 3 to 5 infusion reactions/cytokine release syndrome despite the use of pre-medications, the accrual will be stopped. Regardless of relationship, FDA will be informed via expedited reporting of a serious adverse event ("IND Safety Report per 21CFR§312.32) if 2 grade 3 to 5 cytokine release / infusion reactions occur (see Section 5.2.2.3 Adverse event and serious adverse event monitoring and reporting).

4.3.2 Restricted Medications

The medications (or classes of medication) listed in Table 4.3.2: 1 must not be taken for the specified times before treatment and for the whole duration of the study. If patients take restricted medications due to experiencing an intolerable increase of UC disease activity according to the investigator's judgment, patients will have to be withdrawn from the trial after the use of these restricted medications.

Patients taking the restricted medications of biologics, Cyclosporine/Tacrolimus or investigational products for medical reasons other than UC will also need to be withdrawn from the trial.

Table 4.3.2:1 Restricted medications

- Any biologics, including anti-TNFα, anti-integrin and anti-IL23 antibodies	8 weeks before D1 dosing and during the whole trial duration
- Tofacitinib or other JAK inhibitors	2 weeks before D1 dosing and during the whole trial duration
- Cyclosporine, Tacrolimus	4 weeks before D1 dosing and during the whole trial duration.

- Rectal corticosteroids or rectal 5-amyinosalicylic acid preparations	2 weeks before D1 dosing and during the whole trial duration
- Antibiotics	Oral antibiotics: 4 weeks before D1 dosing; intravenous antibiotics: 8 weeks before D1 dosing; all antibiotics during the whole trial duration
- Investigational products	1 year prior to and during the whole trial duration
- Nonsteroidal anti-inflammatory drugs (NSAIDs)	4 weeks before D1 dosing and during the whole trial duration
- Opiates/Methadone	During the whole trial duration

4.4 TREATMENT COMPLIANCE

Patients who are non-compliant, e.g., they do not appear for treatment (temporary treatment interruption for more than 10 days from the previous dose), must be withdrawn from the trial and the eCRF will be completed accordingly. Compliance will be assured by administration of all study medication under supervision of the investigating physician or a designee.

5. VARIABLES AND THEIR ASSESSMENT

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-TNFα and/or anti-integrin treatments. The secondary objective is to investigate safety, tolerability, and immunogenicity of intravenous AbGn-168H administration.

5.1 EFFICACY

5.1.1 Endpoint(s) of efficacy

The primary efficacy endpoint is the proportion of patients with clinical response, defined as defined as a ≥ 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 subscore 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 Weeks 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.

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

5.1.2 Mayo Diary Card

During Screening Visit, subjects will be provided the Mayo diary card and an instruction to fill the card. In brief, patient should record in the Mayo diary card with information including the day(s) having a clear liquid diet, the total number of stool in 24 hours per day and the amount of blood having in the stools each day for 7 consecutive days prior to a visit with the exception of the preparation day of endoscopic examination. Study Coordinator will collect the Mayo diary card from subjects at each visit to calculate Mayo Clinic Score according to the subscores of stool frequency and rectal bleedings from the 3 consecutive days closest to the visiting day.

5.1.3 Reading of MCS Endoscopic Subscore/ Flexible Sigmoidoscopy

MCS endoscopic subscore will be assessed by a central reader. At Screening Visit, if there is difference in confirmation of study inclusion criteria of MCS endoscopic subscore of grade 2 or higher, an adjudication review will be triggered. At Visit 10 (EOT, Week 12) and Visit 13 (EOS, Week 26), if there is a discrepancy of the change in overall MCS endoscopic subscore, an adjudication review will be triggered. 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 will be considered as final. If a full colonoscopy is deemed necessary at Screening Visit per investigator's discretion, it is allowed, however, the endoscopic subscore will be determined by rectum, sigmoid and descending colon only.

5.2 SAFETY

5.2.1 Safety Endpoints

Safety assessments will consist of evaluating physical examination, vital signs, safety laboratory tests, adverse events, immunogenicity and tolerability.

Safety endpoints include:

- Adverse events (AEs) graded according to CTCAE v4.03.
- Discontinuation of therapy due to AEs
- Changes in safety laboratory analysis
- Changes in vital signs and physical examination
- Immunogenicity
- Tolerability

5.2.2. Adverse Events

5.2.2.1 Definitions of adverse events

Adverse event

Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Serious adverse event

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

Events reported by the patient or observed by the (sub) investigator and that fall into any of the above definitions must be recorded on the adverse event page of the eCRF and should be described in the following manner:

Nature of adverse event

The nature of the event will be described in precise English medical terminology (i.e. not necessarily the exact words used by the patients). Whenever possible, a specific diagnosis should be stated (e.g. allergic contact dermatitis).

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity, and may warrant intervention.

Severe: Incapacitating or causing inability to work or to perform usual activities, or significantly affects clinical status, and warrants intervention.

Duration of adverse event

The duration of the event will be reported as the start date and stop date of the event.

Causal relationship of adverse event

The relationship between an AE and the use of the investigational product will be determined by a medically qualified Investigator on the basis of his/her clinical judgment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history, with the following definitions and causality rating scale (1-3 related; 4-5 not related):

1. Definitely Related: There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. De-challenge is positive. Re-challenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
2. Probably related: There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. De-challenge (if performed) is positive.
3. Possibly related: There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. De-challenge (if performed) is positive.
4. Probably not related: There is evidence of exposure to the test drug. There is another more likely cause of the AE. De-challenge (if performed) is negative or ambiguous. Re-challenge (if performed) is negative or ambiguous.
5. Definitely not related: The patient did not receive the test drug, or temporal sequence of the AE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE.

Assessment of causal relationship should be recorded in the case report forms.

Outcome of adverse event

The outcome of the event will be classified and handled as follows:

Recovered/resolved	The event has stopped. The stop date of the event must be recorded.
Recovering/resolving	The patient is clearly recovering from an event. The event is, however, not yet completely resolved. Follow-up on the event is required until final outcome is established.
Not recovered/not resolved	Event is still ongoing. Follow-up on the event is required until final outcome is established.
Recovered with sequelae	The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke. The stop date of the event must be recorded.
Fatal	The patient has died as a consequence of the event. Date of death is recorded as stop date for the adverse event.
Unknown	Unknown to investigator, e.g. patients lost to follow-up.

5.2.2.1.1 Adverse Events of Special Interests

Potential significant risks from infusion of Neihulizumab that are described in the informed consent:

1) **Infusional toxicities**.
2) **Infection:** Related to immunosuppression.

5.2.2.2 Listed adverse events

No AEs are classified as listed for Neihulizumab and the current study.

5.2.2.3 Adverse event and serious adverse event monitoring and reporting

All adverse events occurring from the administration of study medication and all serious adverse events occurring during the course of the clinical trial from signing the informed consent onwards through Day 182 will be collected, documented and reported to the sponsor via the clinical trial CRO by the investigator on the appropriate CRF(s)/eCRFs/SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the ISF.

For each adverse event, the investigator will provide the onset date, end date, severity, treatment required, outcome, seriousness, and action taken with the study medication. The investigator will determine whether it is unexpected according to the Informed Consent, Protocol, or Investigator's Brochure, the underlying disease and concomitant treatment and the relationship of the study medication to all AEs as defined in Section 5.2.2.1.

Adverse event grading

Adverse event will be graded according to CTCAE v4.03.

Development of Infusion-Related Reactions

The incidence of infusion-related reactions will be assessed as the combined incidence for acute cytokine release syndrome, infusion reactions, and hypersensitivity related to Neihulizumab. The following Stopping Rule will apply: enrolment will be paused pending a protocol amendment if there are 2 or more grade 3-5 infusion reactions/cytokine release syndrome observed during the study period. In order to re-start enrolment, the protocol will be amended with a premedication regimen that will be based in part on the observed symptoms of affected patients. If there are 2 or more grade 3 to 5 infusion reactions/cytokine release syndrome despite the use of pre-medications, the accrual will be stopped.

Observed cases of Grade 3 to 5 Infusion Reactions in Safety Analysis Cohort	**Action**
2 or more Grade 3-5 on an ongoing basis	Pause accrual; Conduct Safety Review; Amend protocol to add premedication regimen
2 or more events on an ongoing basis, despite the use of pre-medications	Stop accrual

5.2.3 Assessment of safety laboratory parameters

The safety laboratory tests will be performed at the visits as indicated in the Table 1 and as listed in Tables 5.2.3: 1 and 5.2.3: 2.

Table 5.2.3: 1 Routine laboratory tests

Category	**Test name**
Haematology	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)
Hormones	Serum ß-Human Chorionic Gonadotrophin (pregnancy test) (only female patients of childbearing potential, only as indicated in Table 1)
Substrates	Glucose Creatinine Blood urea nitrogen Bilirubin Total Bilirubin Direct Protein, Total
Electrolytes	Calcium Sodium

	Potassium
Urinalysis (Stix)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine Hemoglobin (RBC) Urine Leukocyte Esterase (WBC) Urine pH
Urin-Sediment (microscopic examination) *(if urine analysis abnormal)*	Urine Sediment Bacteria Urine Cast (hyaline, WBC, RBC, waxy and granular) in Sediment Urine Squamous Epithelial Cells Urine Sediment Crystals (calcium oxalate, uric acid and triphosphate) Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leucocytes

The tests shown in Tables 5.2.3: 1 and 5.2.3: 2 will be done at screening. The tests shown in Table 5.2.3: 1 will also be performed at the other visits as indicated in Table 1. The tests listed in Table 5.2.3: 2 constitute exclusionary laboratory tests that will be done only at screening. These tests may be repeated as required. The results will not be included into the CSR.

Urine sediment will only be done if there is a positive finding on the urinalysis (stix).

Table 5.2.3: 2 Exclusionary testing

Category	**Test name**
Drug Screening (Urine)	Amphetamines Barbiturates Benzodiazepine Cannabis Cocaine Methadone Opiates
Viral screening	Hepatitis B HBc Antibody (qualitative) Hepatitis B HBs Antibody (qualitative) Hepatitis C Antibodies (qualitative) HIV-1 and HIV -2 Antibody (qualitative) Epstein-Barr virus IgM and IgG Antibody (qualitative) Cytomegalovirus (CMV) assessment of intestinal mucosa biopsy
Stool screening	Ova Parasite Pathogen (stool culture) *Clostridium difficile* toxin
Diabetes screening	HbA1c test
Tuberculosis screening	QuantiFERON® test for *Mycobacterium tuberculosis*

5.2.4 Electrocardiogram

5.2.4.1 ECG (12-lead)

12 lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a standard 12 lead ECG machine.

Electrode placement will be performed according to the method of Wilson, Einthoven and Goldberg.

The site personnel will be instructed to assure a relaxed and quiet environment and that all patients are at complete rest during the recordings.

ECG recordings may be repeated for quality reasons like alternating current artifacts, muscle movements and electrode dislocation.

All locally printed ECGs will be evaluated by the site investigator or a designee. Additional (unscheduled) ECGs can be recorded for safety reasons at any time based on the judgment of the investigator.

Clinically relevant abnormal findings will be reported as medical history if detected at visit 1.

5.2.5 AE and SAE reporting

5.2.5.1 Reporting to AbGenomics

The site PI is responsible for adhering to the timelines for reporting SAEs and clinical outcomes to the sponsor. Any AEs reported to the sponsor during this phase must be documented in the electrical database system.

If not stipulated differently in the Investigator Site File (ISF), Pursuant to 21CFR§312.64, the investigator must report the following events using paper process SAE form via fax or email to sponsor appointed CRO immediately (within 24 hours or the next business day): SAE, grade 3-5 cytokine release/infusion reactions, and AE of special interest (see 5.2.2.1.1). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship.

With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

5.2.5.2 Reporting to FDA

1. Events that are serious, related and unexpected as assessed by the site investigator should be reported to the sponsor appointed CRO and sponsor's medical monitor within 24 hours after the site investigator has become aware of the event. The sponsor's medical monitor will review these events to determine whether expedited reporting to all sites and the FDA is required. Sponsor appointed regulatory CRO will submit each SAEs to FDA pursuant to IND Safety Report per 21CFR§312.32.
2. FDA will be informed via expedited reporting (IND Safety Report per 21CFR§312.32) if, regardless of relationship, two grade 3 to 5 cytokine release / infusion reactions occur, and for each additional such reaction, if any.
3. In the event the “Grade 3 to 5 Infusion Reaction stopping rule” is invoked or if 2 grade 3-5 grade 3 to 5 cytokine release / infusion reactions occur despite the use of pre-medication , FDA will be informed via an expedited safety report (IND Safety Report per 21CFR§312.32).

5.2.5.2.1 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the MedWatch 3500A report will include the following information.

- Protocol number
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics, if known
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

MedWatch 3500A (Mandatory Reporting) form is available at:

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf.

5.2.5.3 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

5.2.5.4 Other events to be reported

Changes in vital signs, physical examination, and laboratory test results

Changes in vital signs, physical examination and laboratory test results will be recorded as an AE or SAE in the (e)CRF , if they are judged clinically relevant by the investigator.

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an AE or SAE in the (e)CRF through the Follow-Up period.

Overdose

Any overdose defined as any higher dose than prescribed for the individual patient must be reported on the adverse event form of the eCRF book. AEs originating in the overdose must be documented on a separate line.

Pregnancy

Pregnancy Test or Confirmation of Birth Control: Performed at indicated study visits (Table 1). Record of a pregnancy test or confirmation of birth control will be recorded as available at each study visit. This information will be kept in the source documents and not recorded in the eCRF.

Once a female patient has been enrolled into the clinical trial and has received study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor appointed CRO. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) by the treating physician or designee to the sponsor appointed CRO when the treating physician or designee first becoming aware of the occurrence. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up through to resolution. In the absence of an AE or SAE, only the Pregnancy Monitoring Form for Clinical Trials must be completed.

If an SAE occurs in conjunction with the pregnancy, then the reporting time frame for an SAE (within 24 hours or next business day whichever is shorter) must be met. The SAE form is to be completed. The sponsor or designee will provide instructions on how to collect pregnancy information. Follow-up, information on the outcome of the pregnancy is also required be forwarded to the sponsor's designee. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials.

5.3 IMMUNOGENICITY (ANTI-DRUG ANTIBODY)

ADA samples will be collected at approximately 15 min. before Neihulizumab administration on Day 1, Day 29, Day 57 and also at EOT (Day 84), 28, 56 and 98 days after EOT (Days 112, 140 and 182) for each patient in a non-anticoagulant serum drawing tube to produce about 1.0 mL of serum. Instructions for handling and shipping specimens will be provided in detail in the Laboratory Manual.

5.4 PHARMACOKINETICS END POINTS

If feasible, the following PK parameters will be calculated:

Day 1, Day 50 and Day 78: C_{max} and associated parameters

For quantification of analyte plasma concentrations, PK blood samples will be taken from a forearm vein in an EDTA (ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube at the time points specified in Table 1.

Instructions for handling and shipping specimens will be provided in detail in the Laboratory Manual.

5.5 OTHER ASSESSMENT (S)

A medical examination will be carried out within 28 days before visit 2 (i.e., during the screening period before the infusion of Neihulizumab). Screening activities will include documentation of information provided to patients, informed consent, review of demographics including weight, relevant medical history, ulcerative colitis history, concomitant medication, inclusion/exclusion criteria, vital signs (BT, BP, PR, RR, and oxygen saturation), 12-lead ECG and laboratory (including safety, drug and viral screening, stool screening, QuantiFERON® test and pregnancy), physical examination, flexible sigmoidoscopy, complete Mayo Clinical Score, IBDQ, biomarkers (fecal calprotectin and CRP), and histopathological analysis. The weight will be reassessed before administration of Neihulizumab in order to confirm the dosage. The EOS examination will include physical examination, vital signs, flexible sigmoidoscopy, complete Mayo Clinic Score, IBDQ, biomarkers (fecal calprotectin and CRP), histopathological analysis, safety lab, ADA test and pregnancy.

5.6 APPROPRIATENESS OF ASSESSMENTS

All assessments performed during this trial are standard and will be performed in order to monitor efficacy and safety aspects relevant to Neihulizumab administration in an appropriate way. The scheduled assessments are appropriate to observe drug related changes over time. Therefore, all assessments taken in this trial are appropriate.

5.7 BIOMARKERS

Biomarker studies for faecal calprotectin and c-reactive protein (CRP) will be performed to monitor ulcerative colitis activities.

5.8 PHARMACODYNAMICS

5.8.1 Pharmacodynamic endpoints

None.

5.9 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Not applicable.

6. INVESTIGATIONAL PLAN

All patients must provide written informed consent before any study-specific procedures or assessments are performed. Day 1 (Visit 2) will occur as soon as possible and within 28 days after the initial screening visit (Visit 1) has verified eligibility and documented informed consent.

6.1 VISIT SCHEDULE

6.1.1 Screening period

After the patients have been informed about the trial, all patients will have given their **written informed consent** in accordance with GCP and the local legislation prior to enrolment to the study. The following Screening laboratory tests/evaluations will be performed within 4 weeks (28 days) prior to the infusion of Neihulizumab (Week 0). A single retest for screening laboratory retest is allowed per investigator's discretion.

- Assignment of patients number
- Review of inclusion and exclusion criteria
- Demographic data (e.g., sex, age, race/ethnicity)
- Complete medical history
- Patient ulcerative colitis history
- Concomitant medications
- Complete physical examination-including weight and vital signs.
- 12-lead ECG
- Safety lab tests (Hematology and Chemistry)
- Urinalysis
- Drug and viral screening
- Serum pregnancy test, if applicable
- Provide and review the diary instruction and diary sheet to patients
- Flexible sigmoidoscopy
- Collect the filled diary card from patient
- Physician Global Assessment
- Complete Mayo Clinic Score assessment
- Histopathological analysis
- IBDQ assessment
- Stool screening
- Fecal calprotectin and CRP tests

- HbA1c test
- QuantiFERON® test for Tuberculosis

6.1.2 Study period

Patients who meet the inclusion/exclusion criteria will receive one dose of Neihulizumab intravenously starting from Day 1 (Week 0). It is preferred but not required that the drug administration should occur at the similar time of each visit day. See Appendix 10.1 for the detailed procedures for preparing Neihulizumab for intravenously administration. Administration of the study drug will be repeated on Day 8 (Week1), Day 15 (Week 2), Day 22 (Week 3), Day 29 (Week 4), Day 36 (Week 5), Day 43 (Week 6), Day 50 (Week 7), Day 64 (Week 9), and Day 78 (Week 11).

The measurements performed during the study period are specified in Section 5 of this protocol and Table 1.

All assessments should be performed prior to drug administration unless it is specified.

Visit 2/Day 1

Procedures at Visit 2/Day 1 should preferably be done in the sequence specified. Drug administration and blood sampling should adhere as closely as possible to the time schedule given in Table 1

- Urine pregnancy test, if applicable
- Review of inclusion and exclusion criteria
- Collect the filled diary card from patient
- Physician Global Assessment
- Partial Mayo Clinic Score assessment
- Concomitant medications
- Adverse events
- Full physical examination including weight and vitals
- Safety lab tests (Hematology and Chemistry)
- Urinalysis
- Blood sampling for anti-drug antibody (ADA) test at -15 min (prior to Neihulizumab infusion)
- PK sampling: -15min (prior to Neihulizumab infusion), and 2 hrs after the end of Neihulizumab infusion

- Administration of Neihulizumab: Study drug will be administered by approximately 1hr (60-minute) i.v. infusion. Patients should remain at the clinical site for at least 1 hour after the infusion for observation.

Visit 3/Day 8, Visit 4/Day 15, Visit 5/Day 22, Visit 7/Day 36, Visit 8/Day 43, Visit 9/Day 50, and Visit 11/Day 78

- Urine pregnancy test, if applicable
- Concomitant medications
- Adverse events
- Partial physical examination including, weight and vitals
- Collect the filled diary card from patient
- Physician Global Assessment
- Partial Mayo Clinic Score assessment
- Safety lab tests (Hematology and Chemistry)
- PK sampling: -15min (prior to Neihulizumab infusion) and 2 hrs after the end of Neihulizumab infusion for Visit 9 and 11. Fifteen (15) minutes prior to Neihulizumab infusion for Visits 3, 4, 5, 7 and 8
- Administration of Neihulizumab: Study drug will be administered by approximately 1hr (60-minute) i.v. infusion. Patients should remain at the clinical site for at least 1 hour after the infusion for observation.

Visit 6/Day 29 and Visit 10/Day 64

- Urine pregnancy test, if applicable
- Concomitant medications
- Adverse events
- Partial physical examination including weight and vitals
- Collect the filled diary card from patient
- Physician Global Assessment
- Partial Mayo Clinic Score assessment
- Safety lab tests (Hematology and Chemistry)
- Urinalysis
- Fecal calprotectin and CRP tests
- Blood sampling for anti-drug antibody (ADA) test at -15min (prior to Neihulizumab infusion)

- PK sampling: Fifteen minutes prior to Neihulizumab infusion (-15 min).
- Administration of Neihulizumab: Study drug will be administered by approximately 1hr (60-minute) i.v. infusion. Patients should remain at the clinical site for at least 1 hour after the infusion for observation.

Visit 12/Day 84 (End of Treatment)

- Urine pregnancy test, if applicable
- Concomitant medications
- Adverse events
- Full physical examination including weight and vitals
- Flexible sigmoidoscopy
- Collect the filled diary card from patient
- Physician Global Assessment
- Complete Mayo Clinic Score assessment
- Histopathological analysis
- IBDQ assessment
- Fecal calprotectin and CRP assessments
- PK sampling
- Safety lab tests (Hematology and Chemistry)
- Urinalysis
- Blood sampling for anti-drug antibody (ADA) test

Visit 13/ Day 112 and Visit 14/Day 140

- Concomitant medications
- Adverse events
- Partial physical examination including vitals
- Collect the filled diary card from patient
- Physician Global Assessment
- Partial Mayo Clinic Score assessment
- Fecal calprotectin and CRP tests
- Blood sampling for anti-drug antibody (ADA) test.
- Safety lab tests (Hematology and Chemistry)
- Urinalysis
- PK sampling

Visit 15/Day 182 (End of Study)

- Urine pregnancy test, if applicable
- Concomitant medications
- Adverse events
- Full physical examination including vitals
- Flexible sigmoidoscopy
- Collect the filled diary card from patient
- Physician Global Assessment
- Complete Mayo Clinic Score assessment
- Histopathological analysis
- IBDQ assessment
- Fecal calprotectin and CRP tests
- Safety lab tests (Hematology and Chemistry)
- Urinalysis
- Blood sampling for anti-drug antibody (ADA) test

7. STATISTICAL CONSIDERATIONS

This is a phase II, open labelled, multiple dose study to be held at multiple study centers. The trial was designed to assess the efficacy and safety of Neihulizumab treatment in moderate-severe ulcerative colitis patients. Due to the small number of patients expected to be enrolled at each center, all summaries and analyses will be performed using data pooled across centers. Unless otherwise specified, continuous variables will be summarized with the number of non-missing observations, mean, standard deviation, median, maximum and minimum displayed. Categorical data will be summarized as counts and percentages. Missing data will not be estimated or carried forward in any of the analyses.

Patient data will be listed, sorted by investigative center and patient number. Deviations from the statistical analysis plan will be documented in the clinical trial report.

Except where other software may be deemed more appropriate (e.g., S-Plus or R), all analyses will be performed using SAS Version 9.2 statistical software (SAS Institute, Cary, NC). Details of the statistical analysis (beyond those specified below) will be defined in the TSAP.

7.1 PLANNED ANALYSES

Intent to Treated Set

The ITT set is defined as all patients who are enrolled irrespective of treatment received or not.

Modified ITT (or Analyzable Set)

The mITT set is defined as all patients who are enrolled and have received at least one dose of Neihulizumab treatment.

The statistical analysis will be based on the modified ITT set. Summaries of patient disposition, demographics, disease characteristics, assessments of physical condition and functionality, and dosing of study drug will be provided.

7.1.1 Pharmacokinetic analyses

The following PK parameters will be assessed:
1. C_{max},
2. Any additional parameters as relevant

The PK profile will be monitored as specified in Table 1 till Day 140 so that the profile of C_{max} and associated parameters can be determined.

All evaluable patients who received Neihulizumab will be included in the pharmacokinetic analysis. 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 considered to be not evaluable if the patient has a protocol violation relevant to the evaluation of pharmacokinetics.

Drug plasma concentrations

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Only concentrations within the validated concentration range will be used for the calculation of pharmacokinetic parameters.

Plasma concentrations will be plotted graphically versus time for all patients as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic mean, geometric mean and the planned blood sampling times will be used.

Drug plasma concentrations and pharmacokinetic parameters

The following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, geometric coefficient of variation.

The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

7.1.2 Safety analyses

Safety analyses will be performed based on the mITT set. No hypothesis testing is planned prospectively.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA). Adverse events occurring prior to drug administration will be assigned to the screening period. All other adverse events will be assigned to the treatment periods for evaluation.

Independent of this rule, the relationship of an adverse event to the study drug treatment will be assessed by the investigator. The evaluation of adverse events will comprise various frequency tabulations.

Descriptive statistics of demographic data, of time-courses and of changes from baseline of vital signs and physical examination will be provided.

Descriptive statistics of laboratory values over time and for the difference from baseline will be provided. Frequency tables of changes with respect to the reference range between baseline and last value on treatment will also be presented.

Relevant findings in ECG measurements will be reported under “Relevant Medical History /Baseline Conditions” (at screening).

7.1.3 Efficacy analyses

Efficacy analyses will be performed based on the mITT set.

Summary statistics for efficacy endpoints will be provided.

7.1.4 Anti-drug Antibody

Human ADA concentrations will be determined by an ADA ELISA. The plate-specific, screening assay cut point will be set by a statistician to achieve a 5% false positive rate and was derived from assays using samples from naïve human donors. Study samples screened with signals below the cut point will be deemed negative for the presence of ADA, while samples at or above the cut point will be deemed putative positive for the presence of ADA.

All putative positive samples will be analyzed in a confirmation assay which is designed to test whether an excess of Neihulizumab added to the putative positive sample can inhibit the Neihulizumab response by a percentage greater than or equal to the confirmation cut point, thus confirming the presence of specific Neihulizumab antibodies. In addition, a titer, defined as the reciprocal of the lowest dilution of the sample whose signal fell below the cut point, will be determined for those samples that were confirmed to be positive for ADA.

A listing will be made of all patients with ADA values above the established cutoff level, along with their titers.

7.2 PATIENT REPLACEMENT

Patients receiving less than 6 doses (60% planned dosing) will be replaced.

7.3 DETERMINATION OF SAMPLE SIZE

The primary endpoint is overall responsive rate at Day 84. Assuming Neihulizumab has a responsive rate of 44.6% (6.8 % higher than conventional treatment and 20% higher than control rate), 40 patients in Neihulizumab treatment is estimated to have > 80% power to detect the difference with a 1 sided significance level of $\alpha = 0.1$

8. REGULATORY CONSIDERATIONS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study patients against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the clinical trial contract with the trial institute and/or investigator. As a general rule, no trial results should be published prior to finalization of the Clinical Trial Report.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF or upon request.

8.1 INSTITUTIONAL REVIEW

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the IRB. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The site PI will disseminate the protocol amendment information to all participating investigators.

8.2 INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country.

Informed consent will be obtained from the HCT patient patients by the investigator or his representative. The rationale, risks and benefits, and study procedures will be reviewed with the patient. Alternative therapies will be discussed. Patients will be given ample time to ask questions and do not need to sign the consent form until they are ready to proceed. Patients will be notified that they may withdraw their consent any time during the study.

The patient must be informed that his/her personal trial-related data will be used by AbGenomics in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors (CRA) or Clinical Quality Assurance auditors appointed by AbGenomics, by appropriate *IRB/IEC* members, and by inspectors from regulatory authorities.

During the consent process, the investigator or his representative will ask the patient questions to assess their understanding of the study and consent. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. The investigator will store the original, signed informed consent form and any additional patient-information form per institutional policy. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative. This process will be documented in the patient's record.

For patients who are not fluent in English, the consent procedure will be performed with an interpreter present (or via telephone), or a sign language-capable interpreter for those that are hearing-impaired.

8.3 DATA MONITORING PLAN

Primary internal data monitoring will be performed continuously over the accrual and follow-up periods by the site PI and the Study Coordinator. The site PI will review data to assure the validity of data, as well as the safety of the patients. The site PI will also monitor the progress of the trial. The site PI will be responsible for maintaining the clinical protocol, reporting adverse event, assuring the consent is obtained and documented, reporting of unexpected outcomes and reporting the status of the trial in the continuing renewal report submitted annually to the IRB and SRC if applicable.

8.4 DATA MANAGEMENT PLAN

This study will use Case Report Forms (CRFs) to record all protocol-related and study specific information on each trial participant, for data analysis.

8.5 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have

access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.6 REPORTING MECHANISM

The site PI (or designee) will be responsible for the coordination of all protocol amendments. Any changes to the protocol or consent will be approved by IRB prior to implementation. This process will be included in the monitoring plan. Changes or amendments to the protocol or consent will be reported to the IRB and FDA. All IRB actions will be reported to FDA.

8.7 TRIAL RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture. For drug accountability, refer to Section 4.1.4. Research records will be maintained in a secure office, and electronic data will be maintained in a study-specific, secure database.

8.7.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

For eCRFs, all data must be derived from source documents. Data entered in the eCRFs must be consistent with the source documents or the discrepancies must be explained. The investigator needs to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

8.7.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs/eCRFs and all source documents, including related medical records, progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA)/on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.7.1.

8.8 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial must be available for inspection on request by the participating physicians, the sponsor's representatives, by the *IRB/IEC* and the regulatory authorities.

9. REFERENCES

[1] C. Mowat *et al.*, "Guidelines for the management of inflammatory bowel disease in adults," *Gut*, vol. 60, no. 5, pp. 571–607, May 2011.

[2] S. P. L. Travis *et al.*, "European evidence-based Consensus on the management of ulcerative colitis: Current management," *J. Crohns Colitis*, vol. 2, no. 1, pp. 24–62, Mar. 2008.

[3] E. V. Loftus, M. D. Silverstein, W. J. Sandborn, W. J. Tremaine, W. S. Harmsen, and A. R. Zinsmeister, "Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival," *Gut*, vol. 46, no. 3, pp. 336–343, Mar. 2000.

[4] M. D. Kappelman *et al.*, "The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States," *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.*, vol. 5, no. 12, pp. 1424–1429, Dec. 2007.

[5] C. G. Loftus *et al.*, "Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000," *Inflamm. Bowel Dis.*, vol. 13, no. 3, pp. 254–261, Mar. 2007.

[6] L. J. Herrinton, L. Liu, J. D. Lewis, P. M. Griffin, and J. Allison, "Incidence and prevalence of inflammatory bowel disease in a Northern California managed care organization, 1996-2002," *Am. J. Gastroenterol.*, vol. 103, no. 8, pp. 1998–2006, Aug. 2008.

[7] L. J. Herrinton *et al.*, "Estimation of the period prevalence of inflammatory bowel disease among nine health plans using computerized diagnoses and outpatient pharmacy dispensings," *Inflamm. Bowel Dis.*, vol. 13, no. 4, pp. 451–461, Apr. 2007.

[8] G. C. Nguyen, A. Tuskey, T. Dassopoulos, M. L. Harris, and S. R. Brant, "Rising hospitalization rates for inflammatory bowel disease in the United States between 1998 and 2004," *Inflamm. Bowel Dis.*, vol. 13, no. 12, pp. 1529–1535, Dec. 2007.

[9] M. D. Kappelman *et al.*, "Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults," *Gastroenterology*, vol. 135, no. 6, pp. 1907–1913, Dec. 2008.

[10] A. Sonnenberg and J. Chang, "Time trends of physician visits for Crohn's disease and ulcerative colitis in the United States, 1960-2006," *Inflamm. Bowel Dis.*, vol. 14, no. 2, pp. 249–252, Feb. 2008.

[11] M. L. Chen and M. S. Sundrud, "Cytokine Networks and T-Cell Subsets in Inflammatory Bowel Diseases," *Inflamm. Bowel Dis.*, vol. 22, no. 5, pp. 1157–1167, May 2016.

[12] R. B. Sartor, "Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis," *Nat. Clin. Pract. Gastroenterol. Hepatol.*, vol. 3, no. 7, pp. 390–407, Jul. 2006.

[13] F. Caprioli, I. Marafini, F. Facciotti, F. Pallone, and G. Monteleone, "Targeting T cells in Chronic Inflammatory Bowel Diseases," *J. Clin. Cell. Immunol.*, vol. 4, no. 4, Jul. 2013.

[14] R. Duchmann, I. Kaiser, E. Hermann, W. Mayet, K. Ewe, and K. H. Meyer zum Büschenfelde, "Tolerance exists towards resident intestinal flora but is broken in active inflammatory bowel disease (IBD)," *Clin. Exp. Immunol.*, vol. 102, no. 3, pp. 448–455, Dec. 1995.

[15] L. Jostins *et al.*, "Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease," *Nature*, vol. 491, no. 7422, pp. 119–124, Nov. 2012.

[16] N. Skroza *et al.*, "Correlations between psoriasis and inflammatory bowel diseases," *BioMed Res. Int.*, vol. 2013, p. 983902, 2013.

[17] K. Soderquest *et al.*, "Genetic variants alter T-bet binding and gene expression in mucosal inflammatory disease," *PLoS Genet.*, vol. 13, no. 2, p. e1006587, Feb. 2017.
[18] C. S. Pokorny, R. G. Beran, and M. J. Pokorny, "Association between ulcerative colitis and multiple sclerosis," *Intern. Med. J.*, vol. 37, no. 10, pp. 721–724, Oct. 2007.
[19] K. Gerlach *et al.*, "TH9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells," *Nat. Immunol.*, vol. 15, no. 7, pp. 676–686, Jul. 2014.
[20] N. Nalleweg *et al.*, "IL-9 and its receptor are predominantly involved in the pathogenesis of UC," *Gut*, vol. 64, no. 5, pp. 743–755, May 2015.
[21] S. Campbell, S. Travis, and D. Jewell, "Ciclosporin use in acute ulcerative colitis: a long-term experience," *Eur. J. Gastroenterol. Hepatol.*, vol. 17, no. 1, pp. 79–84, Jan. 2005.
[22] H. Ogata *et al.*, "A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis," *Gut*, vol. 55, no. 9, pp. 1255–1262, Sep. 2006.
[23] B. G. Feagan *et al.*, "Vedolizumab as induction and maintenance therapy for ulcerative colitis," *N. Engl. J. Med.*, vol. 369, no. 8, pp. 699–710, Aug. 2013.
[24] B. G. Feagan *et al.*, "Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists," *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.*, vol. 15, no. 2, p. 229–239.e5, Feb. 2017.
[25] S. Vermeire *et al.*, "Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial," *Lancet Lond. Engl.*, vol. 384, no. 9940, pp. 309–318, Jul. 2014.
[26] P. Rutgeerts *et al.*, "Infliximab for induction and maintenance therapy for ulcerative colitis," *N. Engl. J. Med.*, vol. 353, no. 23, pp. 2462–2476, Dec. 2005.
[27] W. J. Sandborn *et al.*, "Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis," *Gastroenterology*, vol. 142, no. 2, pp. 257-265.e1–3, Feb. 2012.
[28] W. J. Sandborn *et al.*, "Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis," *Gastroenterology*, vol. 146, no. 1, pp. 85-95; quiz e14–15, Jan. 2014.
[29] W. J. Sandborn *et al.*, "Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis," *Gastroenterology*, vol. 146, no. 1, p. 96–109.e1, Jan. 2014.
[30] "Adalimumab in the Treatment of Moderate-to-Severe Ulcerative Colitis: ULTRA 2 Trial Results," *Gastroenterol. Hepatol.*, vol. 9, no. 5, pp. 317–320, May 2013.
[31] L. Peyrin-Biroulet *et al.*, "Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target," *Am. J. Gastroenterol.*, vol. 110, no. 9, pp. 1324–1338, Sep. 2015.
[32] E. F. Stange and S. P. L. Travis, "The European consensus on ulcerative colitis: new horizons?," *Gut*, vol. 57, no. 8, pp. 1029–1031, Aug. 2008.
[33] D. Burger and S. Travis, "Conventional medical management of inflammatory bowel disease," *Gastroenterology*, vol. 140, no. 6, p. 1827–1837.e2, May 2011.
[34] S. C. Park and Y. T. Jeen, "Current and emerging biologics for ulcerative colitis," *Gut Liver*, vol. 9, no. 1, pp. 18–27, Jan. 2015.

[35] B. G. Feagan *et al.*, "Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study," *Gastroenterology*, vol. 135, no. 5, pp. 1493–1499, Nov. 2008.
[36] A. Amiot and L. Peyrin-Biroulet, "Current, new and future biological agents on the horizon for the treatment of inflammatory bowel diseases," *Ther. Adv. Gastroenterol.*, vol. 8, no. 2, pp. 66–82, Mar. 2015.
[37] I. Solovic *et al.*, "The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement," *Eur. Respir. J.*, vol. 36, no. 5, pp. 1185–1206, Nov. 2010.
[38] T. Ali, S. Kaitha, S. Mahmood, A. Ftesi, J. Stone, and M. S. Bronze, "Clinical use of anti-TNF therapy and increased risk of infections," *Drug Healthc. Patient Saf.*, vol. 5, pp. 79–99, 2013.
[39] P. Raaschou, J. F. Simard, M. Holmqvist, J. Askling, and ARTIS Study Group, "Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden," *BMJ*, vol. 346, p. f1939, Apr. 2013.
[40] J. A. Smith and C. A. Kauffman, "Endemic fungal infections in patients receiving tumour necrosis factor-alpha inhibitor therapy," *Drugs*, vol. 69, no. 11, pp. 1403–1415, Jul. 2009.
[41] R. Fayad, M. I. Brand, D. Stone, A. Keshavarzian, and L. Qiao, "Apoptosis resistance in ulcerative colitis: high expression of decoy receptors by lamina propria T cells," *Eur. J. Immunol.*, vol. 36, no. 8, pp. 2215–2222, Aug. 2006.
[42] M. Boirivant *et al.*, "Lamina propria T cells in Crohn's disease and other gastrointestinal inflammation show defective CD2 pathway-induced apoptosis," *Gastroenterology*, vol. 116, no. 3, pp. 557–565, Mar. 1999.
[43] S.-C. Chen *et al.*, "Cross-linking of P-selectin glycoprotein ligand-1 induces death of activated T cells," *Blood*, vol. 104, no. 10, pp. 3233–3242, Nov. 2004.
[44] C.-C. Huang *et al.*, "A novel apoptosis-inducing anti-PSGL-1 antibody for T cell-mediated diseases," *Eur. J. Immunol.*, vol. 35, no. 7, pp. 2239–2249, Jul. 2005.
[45] "Efficacy, safety, tolerability, and pharmacokinetics of multiple doses of AbGn-168H administered by intravenous infusion to patients with moderate to severe chronic plaque psoriasis (randomized, double-blind, placebo-controlled)," AbGenomics, Clinical Study Report Study 2012.005.01, 2012.
[46] "Efficacy, safety, tolerability, and pharmacokinetics of multiple doses of AbGn-168H administered by intravenous infusion to patients with moderate to severe chronic plaque psoriasis (randomized, double-blind, placebo-controlled)," AbGenomics, Clinical Study Report Study 2014.002.01, 2014.
[47] "Efficacy and safety of AbGn-168H in patients with active psoriatic arthritis: a 24-week, open-label, multi-center, phase II proof of principle trial," AbGenomics, Clinical Study Report, Study 2014.009.01.
[48] "A Phase 1b Treatment Trial using AbGn-168H to Treat Steroid-Refractory Acute Graft-vs-Host Disease (aGvHD) in Patients undergoing Allogeneic Hematopoietic Cell Transplantation," Clinical Study Report BMT-285, 2017.
[49] "Safety, tolerability and pharmacokinetics study of single rising doses of AbGn-168H administered by intravenous infusion (125 μg/kg, 500 μg/kg, 1 mg/kg, 2 mg/kg) or subcutaneous injection (125 μg/kg, 1 mg/kg) to healthy male volunteers (randomised,

double-blind, placebo-controlled within dose groups),” AbGenomics, Clinical Study Report Study 1304.1.

[50] “Investigator’s brochure.”

10. APPENDICES

10.1 PROCEDURES FOR PREPARING NEIHULIZUMAB FOR INTRAVENOUS ADMINISTRATION

All steps will be done at room temperature.

Have IV infusion set ready: IV tubing must be able to be used with appropriate infusion pump to precisely control flow rate (NOTE: flow rate for all groups will be fixed at 1.67 mL/min). Proximal end of IV infusion tubing is inserted into appropriate portion of 100 mL IV infusion bag of normal saline (0.9% NaCl). Distal end of IV infusion set is inserted into the tubing end of a 25G x ¾ inch butterfly infusion set. An infusion set of similar size can be used as long as the infusion rate can be controlled at 1.67 mL/min.

Note that throughout the following preparation procedures the maximum holding time at each step should not exceed 10 min except the time between preparation and administration to the patient which should not exceed 90 min. Preparation will be done under aseptic conditions.

Required items for preparation (refer to the respective dosing sections below for quantities):

- Vial(s) of AbGn-168H (concentration of antibody in stock solution is 40 mg/mL)
- Standard 10 mL syringe (BD 300912 or equivalent)
- #20 gauge needle (Braun 4657500 or equivalent)
- IV tubing (non-DEHP, 0.2 micron filter i.e Paclitaxel 2C7558 or equivalent)
- IV infusion bag of 100 mL normal saline (Braun S8004-5264 non-DEHP or equivalent).
- 25G x 3/4 inch butterfly infusion set (Exel International 26708 or equivalent/similar)

1. Use a 10 ml syringe with #20 gauge needle attached to remove appropriate amount of saline solution from the 100 mL 0.9% NaCl (normal saline) bag according in the patient's weight in kg, as shown in the following table. Discard the removed saline.
2. Inject the required volume of AbGn-168H, as shown in the table above into the reduced 100 mL saline bag and mix gently. Syringes to be used here are the same type as those for removing saline solution from the 0.9% saline.
3. Within 90 minutes of starting the preparation, start the infusion of the saline solution at 1.6-1.7 mL/min, for a total of approximately 100 mL over about 1 hr (60 minutes).

9 mg/kg Neihulizumab dosing table

Weight (Kg/lb)				Volume of saline to be withdrawn out of saline bag	Volume of Neihulizumab to be injected into saline bag
at least		and less than			
Kg	lb	Kg	lb	(mL)	(mL)
40	88.2	45	99.2	9	9
45	99.2	50	110.2	10.1	10.1
50	110.2	55	121.3	11.3	11.3
55	121.3	60	132.3	12.4	12.4
60	132.3	65	143.3	13.5	13.5
65	143.3	70	154.3	14.6	14.6
70	154.3	75	165.3	15.8	15.8
75	165.3	80	176.4	16.9	16.9
80	176.4	85	187.4	18	18
85	187.4	90	198.4	19.1	19.1

Weight (Kg/lb)				Volume of saline to be withdrawn out of saline bag	Volume of Neihulizumab to be injected into saline bag
at least		and less than			
Kg	lb	Kg	lb	(mL)	(mL)
90	198.4	95	209.4	20.3	20.3
95	209.4	100	220.5	21.4	21.4
100	220.5	105	231.5	22.5	22.5
105	231.5	110	242.5	23.6	23.6
110	242.5	115	253.5	24.8	24.8
115	253.5	120	264.6	25.9	25.9
120	264.6	125	275.6	27	27
125	275.6	130	286.6	28.1	28.1
130	286.6	135	297.6	29.3	29.3
135	297.6	140	308.6	30.4	30.4

11. CLINICAL STUDY PROTOCOL AGREEMENT FORM

PROTOCOL NUMBER: 2017.008.01

CLINICAL STUDY PROTOCOL DATE (NOVEMBER 2018) AND VERSION NO.: AMENDMENT 4

Each participating investigator must agree to the approved Clinical Study Protocol and any subsequent amendment(s). By signing this form, I acknowledge receipt of and confirm to have read the above clinical study protocol.

I shall implement all requirements specified in the clinical study protocol after approval/authorization by the regulatory authority and/or IRB (as appropriate) has been obtained.

I shall ensure to inform all my staff involved in the trial about the Clinical Study Protocol and any changes it may lead to for staff's trial related duties/responsibilities.

Investigator's Signature	Date of Signature (DD MMM YYYY)