CLINICAL STUDY PROTOCOL

A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of AMG 714 in Adult Patients with Type II Refractory Celiac Disease, an In Situ Small Bowel T Cell Lymphoma

Protocol Number:	CELIM-RCD-002
Version No:	3
Protocol Date:	11 July 2016
US IND Number **EudraCT Number**	126657 2015-004063-36
Investigational Product:	AMG 714
Phase:	Phase 2a
Sponsor:	Celimmune, LLC 8501 River Rock Terrace, Bethesda, MD 20817, USA

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for purposes of posting on clinicaltrials.gov

SPONSOR APPROVAL

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I, on behalf of Celimmune, LLC, approve this protocol and agree to comply with all requirements regarding the obligations of the Sponsor and all other pertinent requirements of the International Conference on Harmonization (ICH), Guidance on Good Clinical Practice (GCP), the Declaration of Helsinki, 21CFR parts 50, 56, 312 and 320, and applicable United States Food and Drug Administration (FDA) Guidelines for Industry

PPD [redacted], MD, PhD

CEO & Chief Medical Officer

Celimmune, LLC

PPD [redacted]

Date

INVESTIGATOR AGREEMENT

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By signing below, I certify that I have read and understand the protocol. I agree to personally conduct or supervise the described investigation, in accordance with Good Clinical Practice (GCP) requirements, the International Conference on Harmonization (ICH) guidelines, the Declaration of Helsinki and complying with the requirements and obligations of Clinical Investigators listed in 21 CFR parts 50, 54, 56, 312 and 320 in accordance with the study procedures provided by Celimmune, LLC and with all applicable local regulations.

I agree not to implement any changes to the protocol without prior agreement from Celimmune LLC or its appropriate agents and prior review/written approval from the IRB/Ethics Committee or equivalent, except as would be necessary to eliminate an immediate hazard to study subject(s).

I will ensure that all persons assisting me with the study are qualified to do so and are adequately informed about the investigational product(s) and of their study-related duties as described in the protocol.

I agree to completely inform all subjects in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with GCP and regulatory authority requirements.

I agree I am responsible for maintaining each subject's consent form in the study file and providing each subject with a signed copy of the consent form.

I certify that I will allow access to files for audit or inspection purposes by Celimmune LLC, its agents, or competent regulatory authorities.

I agree to the content of this protocol and the confidential nature of the documentation associated with this study.

_____ _____

Signature of Investigator *Date*

_____

Printed Name

STUDY PERSONNEL CONTACT INFORMATION

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LIST OF ABBREVIATIONS

ADA	Anti-drug antibodies
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ANCOVA	Analysis of variance
Anti-tTG	Anti-tissue transglutaminase
APC	Antigen-presenting cells
AUC	Area under concentration time curve
βhCG	Beta human chorionic gonadotropin
BP	Blood pressure
BMI	Body mass index
BMT	Bone marrow transplant
BSA	Body surface area
CCr	Creatinine clearance
CD	Cluster of Differentiation (when used preceding a numeral to indicate a marker on lymphocytes; e.g., CD3, CD45)
CeD-GSRS	Celiac Disease GSRS
CeD-PRO	Celiac Disease – Patient Reported Outcome
CFR	United States Code of Federal Regulation
cGCP	Current Good Clinical Practice
CL/F	Apparent clearance
C_{max}	Maximum serum concentration
CRF	Case Report Form
C_{trough}	Trough concentration
DGP	Deamidated gluten peptides
DH	Dermatitis herpetiformis
DSMB	Data Safety Monitoring Board
EATL	Enteropathy-associated T cell lymphoma
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture system
ePRO	Electronic patient reported outcome
EQ-5D	European Quality of Life 5 Dimensions questionnaire
FDA	Food and Drug Administration
FOCBP	Females of child bearing potential
FSH	Follicle stimulating hormone
GERD	Gastrointestinal Reflux Disease
GFD	Gluten-free diet
GI	Gastrointestinal
GIP	Gluten immunogenic peptides
g	Gram
GSRS	Gastrointestinal Symptom Rating Scale
Hb	Hemoglobin

HepB	Hepatitis B
HepC	Hepatitis C
HEENT	Head, eyes, ears, nose, throat
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICF	Informed consent form
ICH	International Conference on Harmonization
IEL	Intraepithelial lymphocytes
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGRA	Interferon gamma release assay
IHC	Immunohistochemistry
IRB	Institutional Review Board
ITT	Intent to treat
IUD	Intrauterine device
IV	Intravenous
kDa	Kilodalton
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
ml	Milliliter
MMRM	Linear mixed effects repeated measures model
NK	Natural killer
NRCD	Non-responsive celiac disease
PCR	Polymerase chain reaction
PGA	Physician Global Assessment of Disease
PK	Pharmacokinetics
PP	Per protocol
PT	Preferred Term
PtGA	Patient Global Assessment of Disease
Q2W	Every other week
RA	Rheumatoid arthritis
RBC	Red Blood Cell count
RCD	Refractory celiac disease
RCD-I	Type I refractory celiac disease
RCD-II	Type II refractory celiac disease
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SF-12	Short Form 12 questionnaire
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
SOC	System Organ Class
TcR	T cell receptor

TESAE	Treatment-emergent serious adverse events
$t_{½z}$	Terminal half-life
TB	Tuberculosis
TK	Toxicokinetics
t_{max}	Time present at maximum concentration in serum
Tregs	Regulatory T cells
tTG	Tissue transglutaminase
VH:CD	Villous height to crypt depth ratio
WBC	White Blood Cell
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

PROTOCOL SYNOPSIS

TITLE	**A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of AMG 714 in Adult Patients with Type II Refractory Celiac Disease, an In Situ Small Bowel T Cell Lymphoma**
INTENDED INDICATION	AMG 714 is a human anti IL-15 monoclonal antibody indicated for the treatment of Type II Refractory Celiac Disease (RCD-II), an in situ small bowel T cell lymphoma, in adult patients
STUDY OBJECTIVES	Primary Objective: To assess the efficacy of AMG 714 in treating RCD-II in adult patients Secondary Objective: To assess the safety and tolerability of AMG 714 when administered to adult patients with RCD-II Exploratory Objective: To assess the pharmacokinetics (PK), pharmacodynamics (PD), and PK/PD correlations of AMG 714

STUDY ENDPOINTS	Primary efficacy endpoint:
	• Immunological Response 1: Reduction from baseline in the % of aberrant intestinal intraepithelial lymphocytes (IELs) vs total IELs as assessed by flow-cytometry
	
	Secondary efficacy endpoints:
	• Immunological Response 2: Reduction from baseline in the % of aberrant IELs vs intestinal epithelial cells
	• Histological Response: Improvement from baseline in small intestinal villous height to crypt depth (VH:CD) ratio, Marsh score or total IEL counts
	• Clinical response: Change from baseline in clinical symptoms
	  ○ Bristol Stool Form Scale (BSFS)
	  ○ Gastrointestinal Symptom Rating Scale (GSRS), including the celiac disease GSRS (CeD-GSRS)
	
	Exploratory endpoints:
	• Reduction in aberrant and abnormal IELs by flow cytometry, immunohistochemistry and T cell receptor (TcR) clonality analyses
	• Physician Global Assessment of Disease (PGA) and Patient Global Assessment of Disease (PtGA)
	• Quality of Life Assessments:
	  ○ SF-12 v. 2

	○ EQ-5D • Biomarkers of disease activity • Pharmacokinetics (PK), Pharmacodynamics (PD) and Exposure/Response (PK/PD) • Celiac Disease Patient Reported Outcome (CeD PRO) <u>Safety endpoints</u>: • Adverse events • Clinical laboratory tests • Physical examination • Vital signs • Immunogenicity
STUDY DESIGN	Protocol CELIM-RCD-002 is designed to be a Phase 2a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of AMG 714 for the treatment of adult patients with RCD-II. After signing consent subjects will be screened for the study. All subjects who meet the study entry criteria will be randomized at a 2:1 ratio to receive either 8 mg/kg AMG 714 or placebo a total of 7 times over 10 weeks, with evaluation of the primary endpoint at Week 12. AMG 714 (N=16) or placebo (N=8) will be administered at the clinical site in a double-blind fashion via intravenous (IV) infusion over 120 minutes. Concomitant therapy with steroids at a maximum dose of 20 mg of prednisone, prednisolone or equivalent per day and/or oral budesonide at a maximum dose of 9 mg per day will be accepted. These doses will need to be stable for 4 weeks prior to randomization and remain stable for the duration of the study. Should AMG 714 show adequate efficacy and safety, as determined by the Sponsor, subjects in the study, including those in the placebo arm, may be offered participation in an open label extension study of AMG 714 in due course, but under no circumstances prior to study completion. In the interim, between the end of the study for an individual subject and the start of the possible open label extension, the Sponsor intends to provide a bridging program to allow objective study responders to have access to AMG 714 as determined by the site investigator or physician. The open label extension study and interim bridging program will be described in independent protocols.

	Subjects will be expected to maintain total adherence to a strict gluten-free diet (GFD) from 6 months before randomization through the final study visit (Visit 9, Week 16/Day 112). Subject's adherence to GFD will be assessed by an expert dietitian and monitored via stool sample testing using the iVYLISA gluten immunogenic peptide (GIP) stool gluten test. Subjects with known or suspected GFD transgressions will be counseled and allowed to continue in the study. A study staff member will contact the subject by phone one day after the first dose of study drug to assess for any new or worsening AEs. Subjects will return to the clinic for the next administration of study drug after 1 week (Visit 2, Week 1/Day 7). After Visit 2, subjects will return to the clinic for follow-up and study drug administration at Visit 3 (Week 2/Day 14) and every two weeks thereafter as indicated in the study schedule of events (Table 1). The final study dose will be administered at Visit 7 (Week 10/Day 70). An end-of-study efficacy visit will be conducted at Visit 8 (Week 12/Day 84). The final study visit will be conducted 6 weeks after the last dose of study drug at Visit 9 (Week 16/Day 112). All study subjects will undergo upper gastrointestinal endoscopy with mucosal biopsy prior to baseline (i.e., prior to Visit 1, Week 0/Day 0) and within 7 days of Visit 8 (Week 12/Day 84) in order to assess changes from baseline in aberrant and abnormal IELs, VH:CD ratio, TcR clonality, Marsh score and total IEL counts. Subjects enrolled in the study will complete the BSFS at the time of each bowel movement from baseline (Visit 1; Week 0/Day 0) up to the final study visit, Visit 9 (Week 16/Day 112). Subjects will complete the CeD PRO daily from baseline to the final study visit. Subjects will also complete the GSRS beginning at Visit 1 (Week 0/Day 0) and, thereafter, weekly from the time of randomization through the final study visit. The BSFS, GSRS and the daily CeD PRO will be completed using a handheld electronic diary. In addition, subjects will complete paper quality of life diaries (SF-12 v. 2, EQ-5D and PtGA). Diaries will be completed at the times specified in the Schedule of Events (Table 1). Randomization and initial dosing of the first ten subjects will be staggered, with no more than two subjects starting dosing per week, and avoiding the initiation of more than one patient on any single day. Safety will be monitored on an ongoing basis and subjects may undergo unscheduled visits for safety reasons, if needed. Safety will be assessed throughout the study by clinical laboratory tests, physical examination,

	vital sign and AE monitoring. In addition to the investigators and the Sponsor, an independent Data Safety Monitoring Board (DSMB) will monitor safety. An interim analysis for safety and PK will be conducted when the tenth patient reaches Week 4. The interim analysis will be performed by an independent DSMB, which will also monitor unblinded safety data throughout the study. In addition to safety and PK, any other information available at the time of the analysis will be considered and a recommendation to stop, continue or modify the study will be made by the DSMB to the Sponsor. The recommendation and decision will be shared with the sites and ethics committees.
STUDY SAMPLE SIZE	Approximately 24 subjects will be randomized into the study.
ANTICIPATED NUMBER OF CLINICAL SITES	The study will be conducted at approximately 5-6 clinical sites in the United States and Europe (e.g., France, Holland, Spain, and Finland).
INCLUSION CRITERIA	Subjects must fulfill all of the following inclusion criteria to be eligible for participation at screening and at Visit 1 (Week 0/Day 0): 1. Adult males or females 18 years of age or older. 2. Demonstrated willingness to participate in the study as documented by signed informed consent. 3. Females of non-childbearing potential defined as postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone [FSH] level >40 IU/L at Screening); or permanently sterilized (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, oophorectomy); or otherwise incapable of pregnancy **OR** Females of child bearing potential (FOCBP) or males who agree to practice two highly effective methods of birth control (as determined by the Investigator; one of the methods must be a barrier technique) from Screening through the end of study participation (Visit 9, Week 16/Day 112).

	4. Prior confirmed diagnosis of RCD-II defined by the following criteria: celiac disease confirmed by histology, endoscopy or serology; with persistent and recurrent symptoms (e.g., diarrhea, weight loss, abdominal pain); with abnormal small bowel histology; with aberrant intraepithelial lymphocytosis of > 20 aberrant intraepithelial lymphocytes (IEL) per 100 CD45+ cells as determined by flow cytometry (or >50% if determined by immunohistochemistry); despite adherence to a strict GFD for at least 6 months; and after exclusion of other potential causes of symptomatic non-response (e.g., microscopic colitis, bacterial overgrowth, lactose intolerance, exocrine pancreatic insufficiency, hyperthyroidism, etc.) and intestinal histological abnormality (autoimmune enteropathy, giardiasis, immunodeficiency, collagenous sprue, Whipple's disease, etc.). **NOTE:** Subjects who have been treated for RCD-II must continue to have increased aberrant IELs (>20% by flow cytometry or 50% by IHC) and abnormal small bowel histology (Marsh ≥1) and must have had prior history of symptoms, however symptoms are not required of previously treated subjects, or subjects being treated with steroids, at the time of study entry. 5. Total attempted adherence to a GFD for at least 6 consecutive months prior to screening. Subjects must also agree to make no changes to their current GFD for the duration of study participation. 6. Anti-tissue transglutaminase (IgA and IgG) at screening <2 x the diagnostic level for celiac disease (weak positive or negative). 7. Human leukocyte antigen DQ (HLA-DQ) typing compatible with celiac disease provided or obtained prior to baseline biopsy. 8. Life expectancy > 4 months. 9. Laboratory values: a) Estimated creatinine clearance (CCr) > 30 mL/min/1.73m^2 using the Cockcroft-Gault equation b) Serum alkaline phosphatase (AP), alanine transaminase (ALT/SGPT), and aspartate aminotransferase (AST/SGOT) less than 3x the upper limits of normal (ULN) c) Total bilirubin of less than 2.5 x ULN d) Total white blood cell count (WBC) ≥ 300/mm^3

	e) Platelet count $\geq$ 85,000/mm^3 f) INR less than 1.5 g) Albumin of more than 10 g/L (i.e., 1 g/dL or 1.45 µmol/L) 10. Subjects receiving systemic steroids must be on a stable dose for at least 4 weeks prior to randomization, the dose should not exceed 20 mg of prednisone, prednisolone or equivalent per day. Oral budesonide will be accepted at a maximum dose of 9 mg per day. 11. Willingness and ability to comply with study procedures and protocol stipulated concomitant medication guidelines. 12. Willingness to return for all scheduled follow-up visits.
EXCLUSION CRITERIA	Subjects will be excluded from participation in the study if there is evidence of any of the following, at screening or Visit 1: 1. Diagnosis of Type I Refractory Celiac Disease (RCD-I) or enteropathy-associated T cell lymphoma (EATL, excluded by the site's standard imaging techniques for this purpose). 2. Presence of any of the following related to infection: a) Active acute infection requiring systemic antibiotic, parenteral antifungal, or systemic antiviral treatments b) Severe infection within the 3 months prior to screening c) History of tuberculosis (TB) d) Positive Interferon Gamma Release Assay (IGRA) test at screening OR known recent exposure (within 6 months prior to screening) to a patient with active TB; the subject can be enrolled if he or she has been successfully treated with appropriate chemoprophylaxis. e) History within the 3 years prior to screening of an opportunistic infection typical of those seen in immunocompromised subjects (e.g., systemic candida infection, or systemic fungal infection). 3. Current diagnosis or history of cancer within the past 5 years, except RCD-II, successfully-treated basal cell or squamous cell carcinoma, cervical carcinoma-in-situ, or early stage prostate cancer. 4. History or presence of clinically significant disease that in the opinion of the Investigator would confound the subject's

	participation and follow-up in the clinical trial or put the subject at unnecessary risk including but not limited to: a) Cardiovascular disease [e.g., uncontrolled hypertension (defined as office systolic blood pressure [BP] equal to or greater than 180 mmHg or office diastolic BP equal or greater than 110 mm/Hg), unstable angina, congestive heart failure worse than the New York Heart Association Class II, coronary angioplasty or myocardial infarction within the last 6 months, uncontrolled atrial or ventricular cardiac arrhythmias clinically significant pleural or pericardial effusion or ascites) b) pulmonary disease (e.g., severe chronic pulmonary disease) c) renal, hematological, gastrointestinal, endocrine (e.g., poorly controlled diabetes), immunologic, dermatologic, neurological, or psychiatric disease 5. History of significant immune suppression: - Bone marrow transplant (BMT) or cladribine therapy less than 6 months prior to baseline. In other words, cladribine and bone marrow transplant naïve, primary non-responders (treatment resistant), secondary non-responders (relapse after response/remission) and incomplete responders may be enrolled in the study if cladribine therapy and/or BMT were not provided within the 6 months prior to randomization. - Potent systemic immune suppressants (e.g., azathioprine) in the 3 months prior to baseline. 6. History of alcohol or drug abuse that would interfere with the ability to comply with the study protocol. 7. History of clinically significant hypersensitivity to the study drug or any related drugs or to any of the excipients. 8. Positive hepatitis B (Hep B), hepatitis C (Hep C), or Human immunodeficiency virus (HIV) infection test results at the time of screening. 9. Females who are pregnant or are planning to become pregnant during the study participation period or 6 months after last dose, or are currently breastfeeding.

	10. Participation in another investigational drug or device study or treatment with an investigational drug within 30 days or 5 half-lives, whichever is longer, prior to randomization. 11. Any additional reason, which in the opinion of the Investigator, would prevent the subject from safely participating in the study or complying with protocol requirements.
STATISTICAL ANALYSIS	The primary endpoint is the Immunological Response 1: reduction at Week 12 in the % of aberrant IELs vs total IELs as assessed by flow-cytometry between the AMG 714 dose and the placebo arm. The primary endpoint of Immunological Response 1 will be tested as follows: $H_O: \mu_{AMG\,714} = \mu_{placebo}$ against the alternative $H_1: \mu_{AMG\,714} \neq \mu_{placebo}$ where $\mu_{AMG\,714}$ and $\mu_{placebo}$ denote the mean baseline to Week 12 reduction in % aberrant IELs vs total IELs as assessed by flow-cytometry in the AMG 714 and placebo arm respectively. The hypotheses will be tested using a two-sided type 1 error level of 10%. In gemeral, efficacy measures which require pre- and post-treatment biopsies will be based on the PP population (at least 2 biopsies, the second at least on Week 6 or later). Continuous variables will be analyzed based on the ITT population. The primary endpoint will be analyzed using analysis of covariance (ANCOVA) based on the Per Protocol population (PP), where baseline % aberrant IEL will be included as a covariate and treatment group as a fixed effect in the statistical model. Change from baseline of Immunological Response 2, VH:CD and of total IEL counts will be analyzed using the same method as for the primary endpoint. The Marsh scores will be analyzed using a multinomial logistic regression model, where treatment group, baseline Marsh score, and a treatment group-by-baseline Marsh score interaction term will be included in the model. The secondary variable BSFS will be analyzed by calculating daily and weekly number and type of bowel movements. The bowel movement counts will be analyzed using generalized linear mixed models with

	subject as random effect. The statistical model will also include treatment group, time (week) and their interaction. The change in the weekly BSFS scores will mainly be assessed with descriptive statistics, where change from the 'normal (mid-scale)' will be explored. The GSRS and the CeD-GSRS will be analyzed using a linear mixed effects repeated measures model (MMRM) with the baseline value, treatment group, time point, and a time point-by-treatment group interaction term as fixed effects with an underlying correlation structure between the time points that results in the best fit for the model. Subject will be included as a random effect. The exploratory variables, which include PK variables, PD variables, PK/PD variables, aberrant and abnormal IELs, TcR clonality analyses, PGA, quality of life assessments and biomarkers of disease activity will be tabulated by treatment group and time point (if feasible) using the ITT or PP populations as appropriate. The exploratory variable CeD PRO will be analyzed using the same method as for the GSRS and CeD-GSRS. Pharmacokinetics of AMG 714 in RCD-II patients will also be characterized using nonlinear mixed-effects modeling, including evaluation of effects of major covariates (e.g., weight or body mass index [BMI]), and body surface area [BSA], sex, biochemical parameters, and disease characteristics at baseline) on AMG 714 exposure. Exploratory exposure-response analysis will be performed for efficacy, safety, and biomarker measures. Change from baseline (by time point) will also be presented for reduction in aberrant and abnormal IELs by flow cytometry, immunochemistry and TcR clonality analyses, PGA and quality of life assessments (SF-12 v. 2 and EQ-5D). The safety variables, which include AEs (coded using the Medical Dictionary for Regulatory Activities [MedDRA]), clinical laboratory tests, physical examination findings, vital signs and immunogenicity will be tabulated by treatment group and time point (if feasible) using the intent to treat population.

Table 1. Schedule of Study Procedures

Study Procedures	Screening Visit	12-Week Double-Blind Randomized Period									Final Visit
	Up to Day -28	Visit 1	Follow-up Phone Call	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
		Week 0 (Day 0)	Week 0 (Day 1)	Week 1 (Day 7)	Week 2 (Day 14)	Week 4 (Day 28)	Week 6 (Day 42)	Week 8 (Day 56)	Week 10 (Day 70)	Week 12 (Day 84) or Early Termination	Week 16 (Day 112)
		Window	+1 Day	+0 Days[1]	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±7 Days
Informed Consent	X										
Demographics	X										
Medical History	X										
Physical Examination	X	X		X	X		X			X	X
Body Weight	X	X		X	X	X	X	X	X	X	X
Height	X										
Vital Signs	X	X		X	X	X	X	X	X	X	X
12-lead ECG	X										
Collection of blood and urine for clinical laboratory tests	X[2]	X		X	X	X		X		X	X
Serum Pregnancy test (all FOCBP)	X									X	
Urine pregnancy test (all FOCBP)		X		X	X	X	X	X	X		X
Blood cell pellet[12]		X									
Urine drug and alcohol screen	X										
Serum biomarkers[3]		X			X	X		X	X	X	X

Study Procedures	Screening Visit	12-Week Double-Blind Randomized Period									Final Visit
	Up to Day -28	Visit 1	Follow-up Phone Call	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
		Week 0 (Day 0)	Week 0 (Day 1)	Week 1 (Day 7)	Week 2 (Day 14)	Week 4 (Day 28)	Week 6 (Day 42)	Week 8 (Day 56)	Week 10 (Day 70)	Week 12 (Day 84) or Early Termination	Week 16 (Day 112)
		Window	+1 Day	+0 Days[1]	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±7 Days
Serum PK		X[8]		X[9]	X[9]	X[8]		X[9]	X[8]	X	X
Serum ADA		X			X	X		X		X	X
Serum tTG	X	X				X		X		X	X
Whole Blood for Flow Cytometry		X				X		X		X	X
Eligibility confirmation	X	X									
Randomization		X									
Study drug administration		X		X	X	X	X	X	X		
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Assessment of adverse events	X	X	X	X	X	X	X	X	X	X	X
iVYLISA GIP stool test[10]	X	X			X	X	X	X	X	X	X
Endoscopy and biopsy[4]	X									X[5]	
Bristol stool from scale (BSFS), CeD PRO[6]		X	→	→	→	→	→	→	→	→	X

Study Procedures	Screening Visit	12-Week Double-Blind Randomized Period									Final Visit
	Up to Day -28	Visit 1	Follow-up Phone Call	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
		Week 0 (Day 0)	Week 0 (Day 1)	Week 1 (Day 7)	Week 2 (Day 14)	Week 4 (Day 28)	Week 6 (Day 42)	Week 8 (Day 56)	Week 10 (Day 70)	Week 12 (Day 84) or Early Termination	Week 16 (Day 112)
		Window	+1 Day	+0 Days[1]	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±7 Days
Gastrointestinal symptom rating scale (GSRS)[7]		X									X
SF-12 v. 2 and EQ-5D		X				X				X	X
Physician and patient global assessments of disease/rating of change		X		X[11]	X[11]	X[11]		X[11]		X[11]	X[11]
Dietitian assessment of the GFD[13]		X				X		X		X	

Abbreviations: Abbreviations: ADA=anti-drug antibody, BSFS=Bristol Stool Form Scale, CeD-GSRS=Celiac Disease Gastrointestinal Symptom Rating Scale, CeD PRO=Celiac Disease Patient Reported Outcome, DGP=deamidated gliadin peptide antibody, ECG=electrocardiogram, GIP=gluten immunogenic peptide, GSRS=Gastrointestinal Symptom Rating Scale, PGA=Physician Global Assessment, PK=pharmacokinetics, PtGA = Patient Global Assessment, tTG=tissue transglutaminase.

1. All attempts should be made to conduct Visit 2 within 7 days from Visit 1 (Week 0/Day 0). This visit cannot be conducted early. If the visit is conducted late, the proceeding visit schedules must be readjusted based on the date of Visit 2.
2. Including HLA DQ typing if HLA DQ typing is not already part of the subject's available existing medical record..
3. Biomarker samples should be taken prior to study drug dosing. The time and date of these samples must be accurately recorded.
4. The screening biopsy can be collected any time prior to the day of randomization. The biopsy should preferably be collected after reasonable evidence is available that the subjects appear to meet most or all of the other entry criteria.

5. The Visit 8 endoscopy and biopsy can be collected within 7 days of Visit 8 (7 days before or after Visit 8). If conducting an Early Termination visit, an exit endoscopy will be collected unless indicated otherwise based on the subject's condition and at the PI's discretion.
6. The BSFS is collected episodically at the time of each bowel movement from Visit 1 to Visit 9. The CeD PRO is captured daily.
7. The GSRS is collected weekly from Visit 1 to Visit 9.
8. Two blood samples for PK should be collected: one sample should be collected BEFORE dosing starts, the other sample should be collected 1 hour after END of infusion.
9. One blood sample for PK should be collected BEFORE dosing starts.
10. The stool sample for iVYLISA GIP can be collected in the 3 days before or after the visits (i.e., window is ±3 days). At screening, the sample will be collected only after signing the consent form.
11. The Physician and Patient Rating of Change ("Part B" of the PGA and PtGA) should be administered beginning after Visit 1; Week 0/Day 0 as per the schedule of events.
12. Collected and stored for future testing. This sample can be collected at any time during the study.
13. Dietitian can contact the patient by phone within the allotted visit window.

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1 INTRODUCTION

1.1 BACKGROUND

The disease to be treated is Refractory Celiac Disease Type II (RCD-II), an in situ small bowel T cell lymphoma. RCD-II appears in ~0.5% of patients with celiac disease and has ~50% probability of progression to a systemic Enteropathy-Associated T cell Lymphoma (EATL). The treatment-resistant EATL has dismal prognosis with <20% survival at 5 years.

Celimmune is also investigating AMG 714 for the treatment of diet non-responsive celiac disease (NRCD). NRCD and RCD-II are different diseases, and RCD-II appears independent of gluten consumption. IL-15 plays an overlapping yet distinct pathophysiological role in each of these diseases, responsible for mucosal damage in NRCD and for aberrant IEL proliferation in RCD-II.

For the sake of providing a comprehensive background, we describe the presumed responsible mediator (IL-15), the precursor condition (celiac disease) and, finally, the specific disease to be treated (RCD-II, the in situ small bowel T cell lymphoma).

1.1.1 IL-15

Interleukin 15 (IL-15), a glycoprotein of approximately 14-15 kDa, is a proinflammatory cytokine with structural similarities to IL-2. IL-15 exerts biological effects on many immunologically relevant cells (Fehniger and Caligiuri, 2001). While important differences, discussed below, are present across species, IL-15 generally acts as a development, homeostasis and activation factor for NK cells and memory phenotype CD8+ T cells, and it induces the production of chemokines and cytokines by these cell types. IL-15 potently stimulates the production of proinflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) by monocytes/macrophages. IL-15 produced by follicular dendritic cells is reported to support germinal center B cell proliferation and immunoglobulin class switching (Park *et al*, 2004; Litinskiy *et al*, 2002). Targeted disruption of either the IL-15 or the IL-15 receptor alpha (IL-15Rα) genes in mice has been shown to result in the loss of NK, NK-T, TCRγδ+ intraepithelial lymphocytes, and memory CD8+ cells (Lodolce *et al*, 1998). In IL-15 knockout mice, these defects are reversible by the administration of exogenous IL-15 (Kennedy *et al*, 2000). In contrast, human NK cells are not entirely dependent on IL-15 (Lebrec *et al*, 2013).

IL-15 messenger RNA (mRNA) is expressed in a wide variety of tissues and cell types. However, expression of IL-15 protein is much more restricted and is subject to multiple post-transcriptional control mechanisms. Immunologically relevant sources of IL-15 protein include monocytes, macrophages, epithelial and fibroblastic cells, and bone marrow stromal cells (Fehniger and Caligiuri, 2001). IL-15 and its receptor are also expressed in some organs outside the immune system; the role of IL-15 in these systems is less well understood. The absence of any overt defects outside the immune system in IL-15 and IL-15Rα knockout mice suggests that IL-15 may not be essential in any other system.

IL-15 binds to a heterotrimeric receptor that consists of a β chain that is shared with the IL-2 receptor (CD122 or IL-2/IL-15Rβ), the common γ chain (γC), shared with the IL-2, -4, -7, -9, and -21 receptors, and a unique α chain. IL-15 binds with high affinity to the IL-15Rα chain, which then interacts with the IL-2/IL-15Rβ and the γC. The association of the IL-15/IL-15Rα complex with the other two components of the complete receptor complex can occur in a *cis* configuration where all three receptor components are present on the same cell, or in a *trans* configuration where the IL15/IL15Rα pair is on one cell and the receptor β and γC chains are on another (Schluns *et al*, 2005). IL-15 can also associate with IL-15Rα on the cell surface and then be cleaved into soluble cytokine/receptor complexes that have the potential to stimulate CD8+ T cells and NK cells (Anthony *et al*, 2015).

Increased expression of IL-15 has been demonstrated in a variety of inflammatory conditions, including rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease, graft-versus-host disease, solid organ transplant rejection (Blaser *et al*, 2005; Conti *et al*, 2003; Gianfrani *et al*, 2005; McInnes and Gracie, 2004) and celiac disease (reviewed in Gianfrani *et al*, 2005; Meresse *et al*, 2012).

1.2 CELIAC DISEASE

Celiac disease is a systemic autoimmune disease triggered by gluten consumption in genetically susceptible individuals (Green and Cellier, 2007). Currently approximately 1% of the western population is affected by celiac disease, albeit the vast majority of patients remain undiagnosed. The prevalence is twice that in countries with very high hygiene standards and/or very high gluten consumption. Presently it is estimated that 15-20 million patients are affected by celiac disease and approximately 1.0-1.5 million patients are diagnosed. This number has been reported to be doubling every 20 years (Riddle *et al*, 2012).

Gluten, the antigen responsible for celiac disease, is the main protein present in some of the most common cereals (wheat, barley, rye). Modern diets are increasingly enriched with gluten and it is also used as an additive in processed foods, cosmetics and oral medications. Gluten is the second most common food ingredient after sugar and, in some countries, is present in up to 80% of foodstuff. Gluten is also present in trace amounts in foods labeled as "gluten-free", as a tableting excipient, and in products such as toothpaste and lipstick. As little as 50 mg/day of gluten triggers the disease (Catassi *et al*, 2007). A normal diet contains >10 g/day, 200 times the amount that causes intestinal histological abnormalities. As such, celiac patients face an enormous challenge to follow a strict GFD.

The pathophysiology of celiac disease is characterized by an abnormal immune response to gluten. Gluten, which is normally a well-tolerated dietary component, elicits innate and adaptive immune responses in celiac patients (Green and Cellier, 2007). Humans lack enzymes to fully digest gluten, which against the right genetic background triggers inflammation and autoimmunity in the intestine and in other organs. An adaptive immune response is triggered when gluten peptides are deamidated in the extracellular space, by tissue transglutaminase (tTG), normally an intracellular enzyme that is released by damaged cells. This deamidation renders gluten peptides high-avidity binders to HLA-DQ2 and HLA-DQ8, which present these peptides to intestinal CD4+ T cells, thereby activating these T cells and initiating the inflammatory cascade. The innate immune system's intraepithelial lymphocytes (IELs),

primarily CD8+, are able to directly lyse and destroy intestinal epithelial cells, damaging the mucosal lining of the small intestine, in response to the IL-15 release, stimulated by gluten peptides (Abadie and Jabri, 2014). In healthy individuals, the activated T cells are controlled by regulatory T cells (Tregs), but this does not happen in celiac disease as IL-15 confers the effector CD4+ T cells resistance to suppression by Tregs (Abadie and Jabri, 2014). Anti-tTG auto-antibodies appear as a hallmark of the celiac autoimmune process and are used in accurately diagnosing the disease (Green and Cellier, 2007).

The only currently available strategy for the management of celiac disease patients is a lifelong total avoidance of gluten. While simple in theory, the ubiquity of gluten makes total avoidance of gluten very difficult – if not impossible in practice. As little as 50 mg/day (a normal diet contains >10 gr/day) triggers activation of the T cells of the small bowel and cause intestinal mucosal damage (Catassi *et al*, 2007). A study by Shah *et al* (2014) found the burden of celiac disease and a GFD on patient quality of life was ranked second only to end-stage renal disease – a debilitating and life-threatening condition that requires polypharmacy and multiple, weekly dialysis treatments. For these reasons, celiac patients are unable to comply with a zero gluten diet, and more than 50% of diagnosed patients on a GFD continue to present active disease and intestinal immune activation and mucosal atrophy (Lee *et al*, 2003; Cranney *et al*, 2007; Hopper *et al*, 2007; Midhagen *et al* 2003). Celiac patients who continue to have symptoms despite attempting to maintain a GFD are deemed to have diet "non-responsive celiac disease" or NRCD. NRCD has been defined as "persistent symptoms, signs or laboratory abnormalities typical of celiac disease despite 6–12 months of dietary gluten avoidance" (Rubio-Tapia *et al*, 2013). Mortality is increased in subjects with persistent intestinal mucosal damage (Ludvigsson et al, 2009).

1.2.1 Refractory Celiac Disease

A rare but specific complication of persistent diet non-responsive celiac disease is the development of Refractory Celiac Disease (RCD), which affects approximately 1% of celiac patients (Lebwohl *et al*, 2013) and is characterized by severe gastrointestinal symptoms in the absence of gluten consumption and in the presence of small bowel aberrant intraepithelial lymphocytes (IELs) (reviewed in Verbeek *et al* 2008, and in van Wanrooij *et al*, 2014).

Refractory Celiac Disease patients can be further classified according to the number of aberrant IELs. Patients with low numbers of aberrant IELs, defined as less than 20 % of total IELs, as determined by flow cytometry, are referred to as having **Type I RCD (RCD-I)**, and are not at increased risk of developing overt extra-epithelial lymphoma, otherwise referred to as enteropathy-associated T cell lymphoma, (EATL), and have a normal 5-year survival (van Wanrooij *et al*, 2014).

When the numbers of aberrant IELs exceed the 20% threshold, referred to as **Type II RCD (RCD-II)**, the risk of developing EATL is dramatically increased to >50% (Nijeboer *et al*, 2015a, 2015b). EATL has a very poor 5-year survival of <20% (Nijeboer *et al*, 2015a) and its prevalence is increasing (Sharaiha *et al*, 2012).

In RCD-II, aberrant IELs proliferate in what represents a slow-growing non-Hodgkin lymphoma localized (in situ) in the small bowel, primarily in the epithelial compartment. The aberrant IELs observed in RCD-II patients have been demonstrated to be precursors of the extra-epithelial lymphoma by observation that the TcR rearrangement repertoire is similar to that seen in sequential biopsies taken from RCD-II patients who developed EATL. Monoclonal IELs are demonstrated in most patients, which is why RCD-II is considered to be an in situ low-grade lymphoma. A thorough study of the low grade IEL proliferation in RCD-II has revealed a characteristic phenotype (presence of intracellular CD3without surface CD3 or TcR and generally no CD8 expression with expression of CD103), that is also shared by the high grade EATL proliferations. This phenotype is distinct from the normal phenotype of IELs in uncomplicated celiac disease and, together with the presence of a clonal TcR rearrangement in the intestinal biopsy, confirms the diagnosis of RCD-II and allows follow-up of the expansion.

Clinical guidelines (Rubio-Tapia *et al*, 2013) suggest 12 months of persistent disease activity while on a GFD as the timeframe that should trigger the suspicion and eventual diagnosis of NRCD and then RCD. However, the current study uses 6 months as the required time on GFD, since all patients are evaluated for aberrant IELs >20% by flow cytometry (or >50% by IHC), representing definitive evidence of RCD-II in the context of all other inclusion and exclusion criteria of the study (Nijeboer *et al*, 2015b). This definitive evidence obviates the need to evaluate the diet for a full year, a requirement only necessary when advanced diagnostic techniques are unavailable and diagnosis is made by clinical exclusion alone. This approach will reduce both the risk of complications and disease evolution if a patient was required to wait for 12 months before receiving a diagnosis. Nevertheless, it is expected that a majority of patients enrolled -if not all- will have been on a GFD for longer than a year. Spontaneous remission of RCD has not been documented in the literature, neither within the initial 6 months post-diagnosis, nor after this time.

For the purpose of this study, and in agreement with leading experts in RCD-II (Malamut *et al*, 2010; Nijeboer *et al*, 2015a, 2015b), aberrant IELs will be defined by flow cytometry as surface CD3-negative, intra-cellular CD3-positive IELs (sCD3-, icCD3+). The cut-off chosen for diagnosis of RCD-II is 20% in accordance with most recent studies (Nijeboer *et al*, 2015b). In IHC, these cells are identified as icCD3+ sCD8- and the cut-off is 50% (Nijeboer *et al*, 2015b).

Additionally, standard flow diagrams for the diagnosis of RCD-II (e.g., Rubio-Tapia *et al*, 2013) and exclusion of conditions that could simulate RCD-II clinically and histologically are considered in the inclusion/exclusion criteria.

Table 2. Characteristics of Celiac Disease, Refractory Celiac Disease and EATL

	Nature of the disease	Gluten dependence	Aberrant IELs	Clonality	Progression to overt systemic lymphoma
Celiac Disease	Autoimmune	Yes	No	Polyclonal	No
RCD-I	Unknown	Probably	Yes, <20%	Oligoclonal	No
RCD-II	Malignant, slow growing	Probably not	Yes, >20%	Monoclonal (in situ lymphoma)	>50%
EATL	Malignant, rapid progression	No	Yes, >20%	Monoclonal	N/A

1.2.2 Current Treatment of Refractory Celiac Disease

The treatment of RCD is difficult. Abnormal lymphocytes are scattered in the whole small intestinal epithelium and usually in the stomach and colon, thereby precluding surgery. Currently, there is no standard of care for RCD-I or RCD-II. In RCD-I, corticosteroid (local or systemic), azathioprine, purinethol, anti-TNF agents, or cladribine may be used with limited success (Brar *et al*, 2007; Goerres *et al*, 2003). In RCD-II, budesonide (Brar et al, 2007), cladribine (Tack *et al*, 2011a) and autologous bone marrow transplantation (Tack *et al*, 2011b) have also been used with different degrees of success, and better outcomes for autologous BMT (Nijeboer *et al*, 2015b). The prognosis of RCD-II is still poor with death occurring within 3-10 years due mainly to intractable diarrhea and/or development of high grade EATL lymphomas or, more rarely, to dissemination of the low grade proliferation to other tissues (e.g., skin, lungs). The treatment of the high grade lymphoma (EATL) relies on surgical resection and chemotherapy, but the prognosis is very poor.

An effective treatment for RCD-II that could reduce the presence of aberrant IELs and alleviate the histological abnormalities and/or the symptoms, remains the highest priority.

1.3 ROLE OF IL-15 IN CELIAC DISEASE

Substantial evidence suggests a pathophysiological role for IL-15 in celiac disease and RCD-II (reviewed in Abadie and Jabri *et al*, 2014):

- Innate immunity:

- IL-15 is an essential, non-redundant growth and activation factor for the IELs which destroy the intestinal mucosa;
- The expression of IL-15 in the intestinal epithelium is necessary for villous atrophy;
- In some patients, IL-15 drives progression towards lymphomagenesis and potentially fatal RCD-II (Malamut *et al*, 2010)

- Adaptive immunity:
  - IL-15 enhances the presentation of deamidated gluten peptides (DGP) by antigen-presenting cells (APCs);
  - IL-15 renders the activated CD4+ T cells resistant to inhibition by regulatory T cells;
  - IL-15 has been proven to be a key factor in the loss of tolerance to food antigens (DePaolo *et al*, 2011; Korneychuk, *et al*, 2014)

By activating the intraepithelial lymphocytes (IELs), IL-15 is believed to be the main mediator in the mucosal damage that ensues in response to gluten exposure in celiac disease (Korneychuk *et al*, 2014). The expression of IL-15 in the intestinal epithelium is necessary for villous atrophy in animal models of celiac disease and circumstantial evidence suggests this to be the case in humans, as well. In addition, IL-15 renders effector T cells resistant to inhibition by regulatory T cells (Tregs) (Abadie and Jabri, 2014), promoting loss of tolerance to food antigens (DePaolo *et al*, 2011, Korneychuk *et al*, 2014).

One of the studied mouse models of celiac disease is an IL-15-transgenic mouse, in which IL-15 overexpression by gut epithelial cells leads to celiac-like disease, including T and B cell-mediated pathology (Yokoyama *et al*, 2009 and 2011). IEL apoptosis has been observed in this animal model after treatment with anti-IL-15 (Malamut *et al* 2010) or anti-IL-15-receptor mAbs (Yokoyama *et al* 2009).

In RCD-II, the role of IL-15 appears even clearer, and IL-15 is believed to be the main driver of transformation and maintenance of the aberrant IELs (Meresse *et al*, 2012). IL-15 is up-regulated in the intestinal mucosa of patients with RCD-II and, more importantly, incubation of RCD-II patient duodenal biopsies with the anti-IL-15 monoclonal antibody, AMG 714, blocked anti-apoptotic signaling via JAK3 and STAT5, leading to apoptosis of the clonal aberrant IELs (Malamut *et al*, 2010, reviewed in Meresse *et al* 2012).

1.4 AMG 714

AMG 714, a fully human immunoglobulin (IgG1κ) monoclonal antibody (formerly HuMax-IL15, Genmab), binds to and inhibits the function of IL-15 in all its forms (cis, trans, soluble IL-15 bound to IL-15Rα). AMG 714 inhibits IL-15-induced T cell proliferation and shows a dose-dependent inhibition of IL-15-induced TNF-α production. AMG 714 was originally produced in a hybridoma cell line. The hybridoma-derived material (referred to in this document as AMG 714-HYB) underwent preclinical testing and was subsequently evaluated in a Phase 1 and Phase 2 study in subjects with rheumatoid arthritis (Baslund *et al*, 2005). [redacted] AMG 714 is now produced by

a Chinese hamster ovary (CHO) cell line (referred to in this document as AMG 714-CHO). [redacted] AMG 714-CHO has been tested in two studies in healthy volunteers and in patients with psoriasis. All future clinical studies will be performed with AMG 714-CHO.

1.5 SUMMARY OF PRE-CLINICAL STUDIES

The nonclinical development of AMG 714 consisted of a series of in vitro studies demonstrating the binding properties of AMG 714 against hIL-15; in vitro and vivo studies providing proof-of-concept for the benefit of blocking the IL-15 pathway in celiac disease; and a series of GLP studies evaluating the nonclinical safety profile of Hu714MuXHu, the AMG 714 surrogate molecule active in macaques. The full description of the pre-clinical studies can be found in the Investigator's Brochure.

1.5.1 Pharmacology

In nonclinical experiments conducted with the original hybridoma-derived antibody, AMG 714-HYB was found to recognize an epitope that is essential for the interaction between human IL-15 (hIL-15) and its receptor complex. AMG 714-HYB showed a dose-dependent inhibition of IL-15-induced proliferation of peripheral blood T cells, and cell lines expressing IL-15 receptors, as well as a dose-dependent inhibition of hIL-15-induced TNF-α production. Specificity for IL-15 was demonstrated by lack of inhibitory effects on human IL-2 (hIL-2)-mediated proliferation of peripheral blood T cells, on hIL-2-mediated TNF-α production, or on IL-2 induced cytotoxic T cell line (CTLL2) cell proliferation.

[redacted]

AMG 714-CHO was found to be efficacious in a mouse model of celiac disease triggered by the transgenic expression of human IL-15 in the gut epithelium (Malamut *et al*, 2010). In this model, AMG 714-CHO prevented IEL activation and proliferation, as well as histological abnormalities. In addition, AMG 714-CHO was able to induce apoptosis of human IELs in *ex vivo* culture of small intestinal explants from active celiac disease and RCD-II patients (Malamut *et al*, 2010). In this culture experiment, AMG 714-CHO resulted in a suppression of IL-15-driven anti-apoptotic signaling via JAK3 and STAT5.

In vitro studies demonstrated that AMG 714-CHO had high binding affinity for hIL-15, but lower affinity for macaque IL-15. Additionally, AMG 714-CHO neutralized hIL-15 but did not efficiently neutralize macaque IL-15. To enable preclinical studies in macaques, a surrogate antibody, Hu714MuXHu, was developed by fusing the F(ab) portion of a mouse anti-hIL-15 monoclonal antibody known to neutralize macaque IL-15, M111, with human IgG1 Fc. Hu714MuXHu was shown to neutralize macaque IL-15 with approximately the same potency as AMG 714-CHO neutralizes hIL-15.

In a safety pharmacology study, cardiovascular, respiratory, and neurobehavioral endpoints were evaluated in cynomolgus monkeys that received a single intravenous (IV) bolus dose of ≤ 300 mg/kg Hu714MuXHu. In this study, the no-observed-effect level (NOEL) was 300 mg/kg, the highest dose tested.

1.5.2 Toxicology

Because of the low binding affinity of AMG 714 for macaque IL-15 and the very low inhibitory activity of AMG 714 against macaque IL-15, the safety profile of AMG 714-CHO has been evaluated in nonclinical studies in non-human primates (cynomolgus monkeys) using the surrogate molecule Hu714MuXHu in a single dose safety pharmacology study (described above) and in repeated-dose toxicology studies.

[redacted]

1.6 EFFECTS OF AMG 714 IN HUMANS

The original hybridoma-derived material produced by Genmab (AMG 714-HYB) was evaluated in subjects with RA in a Phase 1 study (Hx-IL15-001) and a Phase 2 study (20030210). [redacted] AMG 714 is now produced by a CHO cell line. [redacted] AMG 714-CHO was studied in a first-in-human trial to investigate safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy subjects (Phase 1 Study 20050193) and in a proof-of-concept study in patients with psoriasis (Phase 2 Study 20060349). To date, AMG 714 has been shown to have clinical effect in RA; tolerability comparable to placebo in ~200 subjects exposed (including ~140 exposed for 12 weeks of bi-weekly dosing); a favorable pharmacokinetic profile with 3 weeks half-life; and no significant immunogenicity signal.

All completed clinical studies of AMG 714-CHO and AMG 714-HYB are summarized in Table 3.

Table 3. Summary of AMG 714 Clinical Studies

Study Number (Phase)	Key Design Features	Dose Route, Duration	Study Population	Status
AMG 714-CHO				
20050193 (Phase 1; Amgen)	Double-blind, placebo-controlled, single SC or IV doses, dose-escalation study	SC doses: 0, 30, 100, 300 or 700 mg (cohorts 1 to 4) IV dose: 0 or 100mg IV infusion (cohort 5)[a] Single dose	40 healthy subjects	Completed
20060349 (Phase 1b/2a; Amgen)	Double-blind, placebo-controlled, multiple SC doses, dose-escalating study	0 or 150 mg SC (cohort 1) 0 or 300 mg SC (cohort 2) Dose every 2 weeks for 12 weeks	22 subjects with moderate to severe psoriasis	Completed[b]
AMG 714-HYB				
Hx-IL15-001 (Phase 1; Genmab)	Double-blind, placebo-controlled, single SC infusion, dose escalation, study with open-label, repeat-dose (4 weekly doses) follow-up	Initial single dose: 0 or 0.15 to 8 mg/kg SC infusion Repeated dose: 0.5 to 4 mg/kg SC infusion once weekly for 4 weeks 5 doses total over 8 weeks	30 subjects with RA[c]	Completed
20030210[d] (Phase 2; Genmab/Amgen)	Double-blind, placebo-controlled, multiple SC infusion, parallel-group, multicenter study	0 or 40 to 280 mg SC infusion dose every 2 weeks for 12 weeks with initial 200% loading dose	180 subjects with RA	Completed

[a] Dose escalation occurred approximately every 4 weeks ; dosing cohorts initiated sequentially.

[b] Terminated early due to lack of efficacy in psoriasis

[c] All 30 subjects received initial single dose (0 or 0.15 – 8 mg/kg AMG 714-HYB); 24 of the 30 subjects entered into the repeated dosing portion (0.15 – 4 mg/kg AMG 714-HYB)

[d] Genmab initiated study as Hx-IL15-002

IV = intravenous; RA = rheumatoid arthritis; SC = subcutaneous

1.6.1 Pharmacokinetics of AMG 714 in Humans

1.6.1.1 Pharmacokinetics of AMG 714-HYB

[redacted]

1.6.1.2 Pharmacokinetics of AMG 714-CHO

[redacted]

[redacted]

1.6.2 Pharmacodynamics of AMG 714 in Humans

The effects of AMG 714-HYB and AMG 714-CHO on NK cell counts were explored in three Phase 1 and 2 clinical studies (Hx-IL15-001, 20030210, 20060349) using immunophenotyping that included markers specific for NK cells. This analysis was based on the observed pharmacodynamic effects in preclinical species. No changes in absolute or relative numbers of NK cells were observed in either study at any of the dose levels tested. This result contrasts with observations in cynomolgus monkeys, where a marked reduction in NK cell counts was noted after administration of the surrogate antibody, Hu714MuXHu.

This difference between observations in preclinical and clinical studies appears related to a differential sensitivity of human versus cynomolgus monkey NK cells to IL-15 deprivation. Human NK cells are not dependent on IL-15 for their survival (Lebrec *et al*, 2013), possibly due to the redundant role of IL-2 on human NK cells.

1.7 EFFICACY OF AMG 714 IN HUMANS

1.7.1 Efficacy of AMG 714-HYB in Rheumatoid Arthritis

1.7.1.1 Study Hx-IL15-001

Phase 1 Study Hx-IL15-001 was executed in 2 stages in subjects with RA. The first stage was a randomized, double-blind, placebo-controlled, single escalating dose design (0.15, 0.5, 1.0, 2.0, 4.0, and 8.0 mg/kg AMG 714-HYB), followed by a second stage that was a repeat dose (0.5, 1.0, 2.0, and 4.0 mg/kg AMG 714-HYB; 5 doses over 8 weeks), open-label extension. Twenty-eight of 30 subjects completed the single dose stage of the study, and 20 of 24 subjects completed the repeat-dose stage.

Evaluations of efficacy included ACR response assessment. Following a single dose of investigational product, the ACR20 response rate was similar in the AMG 714-HYB groups compared with placebo. However, repeated doses of AMG 714-HYB led to greater ACR20 response rates, without a clear dose response (Baslund *et al*, 2005).

1.7.1.2 Study 20030210

In Phase 2 Study 20030210, subjects were enrolled in two cohorts, with 110 subjects in Cohort 1 randomized equally to placebo or AMG 714-HYB (40, 80, 160, or 280 mg) and an additional 70 subjects in Cohort 2 randomized equally to placebo or 280 mg AMG 714-HYB. The primary efficacy endpoint was the 14-week ACR20 response rate in the 280 mg group compared with placebo after 12 weeks of study treatment. Secondary endpoints included the 14-week ACR50 and ACR70 response rates (50%, and 70% improvement in the ACR criteria from baseline); ACR response rates throughout the study; the change from baseline in individual ACR components; and the disease activity score (DAS28).

The ACR20 response rate in the 280-mg group (Cohorts 1 and 2 combined) increased over placebo at 14 weeks (54% vs 38%), but the difference was not statistically significant ($p = 0.097$, Cochran-Mantel-Haenszel test). However, a statistically significant difference in ACR20 response in the 280 mg group compared with placebo was observed at weeks 12 (64% vs 34%; $p = 0.003$) and 16 (66% vs 38%; $p = 0.003$). The overall distribution of the DAS28 scores (nonresponder imputation) decreased significantly in the 280-mg group compared with placebo at weeks 8, 12, and 16 ($p = 0.02$, 0.005, and 0.01, respectively, Wilcoxon rank-sum test), with medians of 5.1 vs 6.1, 4.9 vs 5.8, and 4.9 vs 5.7 (280 mg vs placebo). For observed data, a similar trend was observed. The mean score in the 280 mg group decreased from 6.8 at baseline to a low of 4.9 at week 16. Additionally, all of the intermediate-range dose groups showed an improvement over placebo. Additionally, improvements were evident in ACR components and especially in acute phase reactants. Beginning at week 4, concentrations of acute phase reactants decreased significantly in the 280 mg AMG 714-HYB group compared with placebo (C-reactive protein [CRP], $p < 0.0001$; erythrocyte sedimentation rate [ESR], $p = 0.005$), and remained significantly decreased throughout the study. Of note, CRP concentrations in the 280 mg AMG 714-HYB group decreased by 60% at week 4 and remained 50% to 67% lower than CRP concentrations in the placebo group for the remainder of the study. Significant improvements also were seen in other ACR components (weeks 12 and 16) and in DAS28 (weeks 8, 12, and 16).

Although the primary efficacy endpoint (significant difference in ACR20 responses at week 14 for subjects who received 280 mg AMG 714-HYB compared with placebo) was not met, the overall clinical results suggested AMG 714-HYB pharmacological activity, as indicated by the reduction of acute phase reactant concentrations and the efficacy of AMG 714-HYB in the treatment of RA refractory to disease-modifying anti-rheumatic drugs (DMARDs).

1.8 SAFETY OF AMG 714 IN HUMANS

1.8.1 Safety in AMG 714-HYB Clinical Studies

1.8.1.1 Study Hx-IL15-001

The study results indicated that single doses of ≤ 8 mg/kg and multiple doses of 4 mg/kg AMG 714-HYB were well tolerated, and no serious adverse events or infections were observed at the

highest doses (8 mg/kg single dose, 4 mg/kg repeated dose). No deaths or serious infections occurred at any dose during the study.

All 30 subjects received the initial double-blind dose, and of the 24 subjects who entered the repeat dosing period, two subjects in the 0.5-mg/kg group withdrew from the study due to worsening of RA, and two subjects in the 4-mg/kg repeated-dose group (8 mg/kg single dose) withdrew consent for participation.

During the double-blind, single-dose period, adverse events were reported by 8 of 30 (27%) subjects, and rates were similar among dose cohorts. All reported adverse events were mild to moderate in severity. Two subjects reported infections during this period. One subject in the 0.15-mg/kg cohort reported herpes simplex, and 1 subject in the 4 mg/kg cohort reported nasopharyngitis. One serious adverse event occurred in a subject in the 0.15 mg/kg cohort. The subject was hospitalized because of RA flare and the disease flare was considered by the investigator to be unrelated to investigational product. One subject in the 0.5 mg/kg cohort reported mild pyrexia and rigors and subsequently withdrew from the study prior to continuing into the open-label, repeat-dose stage. Treatment is unknown, however, the subject fully recovered from the reported events.

During the open-label, repeat-dose period, 15 of 24 (63%) subjects reported adverse events, also with similar rates among cohorts. All reported adverse events were mild to moderate in severity. Five subjects reported infections during this period. One subject in the 0.5 mg/kg cohort had an upper respiratory tract infection, sinusitis, and a urinary tract infection; three subjects in the 1 mg/kg cohort had an upper respiratory tract infection, nasopharyngitis, and pneumonia, respectively; and one subject in the 2 mg/kg cohort had bronchitis and herpes simplex. One subject in the 0.5 mg/kg cohort withdrew from the study after 3 repeated doses due to an upper respiratory tract infection described as being moderate in severity.

No clinically significant changes in laboratory parameters were observed, no depletion of NK cells occurred, and no subject developed anti-AMG 714-HYB antibodies.

1.8.1.2 Study 20030210

AMG 714-HYB was well tolerated in this study at doses of up to 280 mg every other week, with a safety profile similar to that of placebo. There were few serious adverse events or serious infections and the rates were similar in the AMG 714-HYB and placebo groups; no dose-related trends were evident. No deaths occurred during the study.

Injection site reactions, the most common adverse event, were more frequent in the AMG 714-HYB groups than placebo (9% vs 2%) and appeared to increase with dose (1 of 21 subjects, 5% [40 mg]; 2 of 23 subjects, 9% [80 mg]; 3 of 22 subjects, 14% [160 mg]; 5 of 55 subjects, 9% [280 mg]); no injection site reaction was considered severe or serious or led to a study withdrawal. Serious adverse events were reported in two (3%) subjects in the placebo group and in two (9%) and three (5%) subjects in the 80 and 280 mg AMG 714-HYB groups, respectively. No single event occurred in > 1 subject in a treatment group. Serious adverse

events considered by the investigator as possibly related to investigational product were sepsis and deep vein thrombosis, with one (4%) event each in two subjects in the 80 mg group.

The overall incidence of infections was similar in the placebo and 280 mg groups (24% vs 25%, respectively). Reported events for > 1 subject in any treatment group were bronchitis, influenza, nasopharyngitis, pharyngitis, upper respiratory tract infection, and urinary tract infection. These events occurred with similar frequency in the placebo and AMG 714-HYB treatment groups. The most frequently occurring events in the 280 mg group were nasopharyngitis (5% vs 2% in placebo group) and pharyngitis (5% vs 2% in placebo group). Serious infectious events were reported by two subjects: one in the placebo group (viral bronchitis), and one in the 80 mg AMG 714-HYB group (sepsis); the serious adverse event of sepsis led to study withdrawal. Adverse events leading to withdrawal occurred in five subjects, all of whom were in the intermediate AMG 714-HYB dose groups (1 [40 mg], 2 [80 mg], and 2 [160 mg] subjects).

Clinical laboratory assessments showed only minor differences between placebo and AMG 714-HYB treatment groups and no depletion of NK cells. One serious event (sepsis), reported by a subject in the 80 mg cohort, was associated with Common Toxicity Criteria grade 4 neutropenia. Following treatment with IV antibiotics and a blood transfusion, the subject fully recovered. No subject developed antibodies to AMG 714-HYB.

1.8.2 Safety in AMG 714-CHO Clinical Studies

1.8.2.1 Study 20050193

Of the 43 subjects enrolled in the study, 40 subjects (93%) received one dose of AMG 714 or placebo and were analyzed for safety. Three subjects did not receive investigational product (two subjects due to assessment of ineligibility and one subject due to a change in eligibility status). Thirty-nine of 40 subjects (98%) completed the study; one subject who received 100 mg AMG 714 SC discontinued due to non-study related reasons.

AMG 714 was generally well tolerated at all doses administered during the study. No deaths, serious adverse events, or study discontinuations due to adverse events were reported. Treatment-emergent adverse events were reported across all dose levels by subjects who received investigational product. No relationship was apparent between the subject incidence of treatment-emergent adverse events and the dose of AMG 714, or between the subject incidence of treatment-emergent adverse events and the route of administration of AMG 714 (SC versus IV). Twenty of thirty subjects (67%) who received AMG 714 and seven of ten subjects (70%) who received placebo reported treatment-related adverse events. All but eight adverse events were reported as mild in severity; seven adverse events were moderate and one event was severe. The severe adverse event was a tooth infection (placebo), and was not considered by the investigator as related to investigational product. Four of the seven moderate adverse events were reported as related to investigational product: injection site pain (100 mg AMG 714 SC), upper respiratory tract infection (700 mg AMG 714 SC), headache (100 mg AMG 714 IV), and gastroenteritis (100 mg AMG 714 IV). Three of the seven moderate events

were reported as not related to investigational product: diarrhea (placebo), lower respiratory tract infection (placebo), and vessel puncture site bruise (700 mg AMG 714 SC). Among the forty subjects who received investigational product, the most commonly reported adverse event was injection site reaction in five subjects ([17%] (700 mg AMG 714 SC), and 2 subjects [20%] (placebo). All injection site reactions were considered by the investigator to be treatment related. Other commonly reported adverse events included headache (two in AMG 714 [7%], two in placebo [20%]), pharyngolaryngeal pain (four in AMG 714 [13%]), and upper respiratory tract infection (four in AMG 714 [13%]). No clinically important effects of AMG 714 on selected laboratory variables, ECGs, or other vital signs were evident. Additionally, treatment with AMG 714-CHO did not result in a specific reduction in NK-cells. One serum sample from Day 57 from 1 subject in cohort 5 (100 mg, IV) was positive for anti-AMG 714 binding and neutralizing antibodies, but with no noticeable reduction in serum AMG 714 concentration at any time during the study.

1.8.2.2 Study 20060349

Subject Disposition: In total, 22 subjects were enrolled into this study; of these, 20 (91%) subjects received at least one SC dose of investigational product and were included in the safety analysis set. Overall, 17 (77%) subjects received all six planned doses of investigational product; 16 (73%) subjects completed all study visits and completed the study.

Twenty subjects received ≥ 1 dose of investigational product and were included in the principal analysis of safety (six placebo, six AMG 714 150 mg, eight AMG 714 300 mg). There were no deaths, serious adverse events, or study withdrawals because of an adverse event reported during this study. One subject (AMG 714 300 mg) discontinued investigational product in response to an adverse event of worsening psoriasis, but completed all study assessments. Overall, most (90%) subjects had ≥ 1 adverse event. Adverse events were no more common in the AMG 714 groups than in the placebo group and were not dose-related (five [83%] AMG 714 150 mg, seven [88%] AMG 714 300 mg, and six [100%] placebo subjects). Across treatment groups, the most commonly reported adverse events were headache (six subjects, 30%), upper respiratory tract infection (four subjects, 20%), and nasopharyngitis (three subjects, 15%). The overall subject incidence of treatment-related adverse events was 45%, with headache being the most common among all subjects (occurring in 1, 2, and 2 subjects in the placebo, AMG 714 150 mg, and AMG 714 300 mg groups, respectively); no other treatment-related adverse event was experienced by more than one subject. Immunophenotyping findings revealed several notable differences between subjects in the placebo and AMG 714 groups; however, these differences were isolated, and appeared to be driven by chance due to the large number of comparisons. No depletion of NK cells occurred.

None of the treatment differences appeared to be clinically significant. Changes from baseline in hematology, chemistry, and urinalysis laboratory results were not clinically meaningful. Out-of-range values were generally intermittent and indiscriminate, as were the minor shifts in either direction that were evident for most hematology and chemistry parameters. No out-of-range laboratory result was reported as an adverse event. No subject developed binding, non-neutralizing antibodies, and none of the tested samples in the immunoassay were positive for

binding antibodies at any time point. No clinically important observations in ECG or vital signs were reported.

2 KNOWN AND ANTICIPATED RISKS

2.1 NATURAL KILLER (NK) CELL DEPLETION AND RISK OF INFECTION

NK cell counts and NK cell activity were significantly decreased by blocking IL-15 in cynomolgus monkeys. This effect is thought to be a consequence of a pharmacodynamic response, given the known role of IL-15 in NK cell biology in monkeys and other animal species. Episodes of diarrhea required treatment with enrofloxacin in several animals. These observations started approximately two to three weeks after initiation of treatment in some animals and as late as 10 weeks after initiation of treatment in one animal. *Shigella* infections were diagnosed via stool culture in most of the animals treated for diarrhea episodes. Given the described role of NK activity in the defense against *Shigella* species, the observed effect on NK cells is considered a possible adverse event in the cynomolgus monkey.

In contrast, no reduction of NK cells has been observed in humans, and gastroenteritis and enteric infections have not been reported as a frequent adverse event in human studies. Experimental work has concluded that human NK cells, unlike murine and non-human primate NK cells, are not dependent on IL-15 for their survival and function (Lebrec *et al*, 2013). The absence of NK cell depletion in humans reduces concerns, and the risk of enteric infections will be closely monitored in forthcoming clinical studies including the proposed CELIM-RCD-002 and CELIM-NRCD-001.

The sponsor interprets the lack of efficacy in psoriasis as suggestive of AMG 714's selective effect on specific immune pathways, rather than a broad systemic immune suppression (since most systemic immune suppressants are efficacious in psoriasis).

2.2 IMMUNOGENICITY

Immunogenicity (generation of anti-drug antibodies [ADA]) is a potential risk for any biologic therapeutic. Immunogenicity may lead to injection reactions and to loss of efficacy when the antibodies are neutralizing and high-titer.

[redacted]

AMG 714-HYB and AMG 714-CHO are fully human anti-IL-15 monoclonal antibodies. Only one of the approximately 200 subjects dosed with active drug in all four studies conducted with

AMG 714 developed anti-AMG 714 antibodies (single time point, neutralizing), with no impact on PK.

In summary, immunogenicity has been exceptionally reported with AMG 714, and the risk of immunogenicity will be closely monitored with robust and fully validated assays. Any positive ADA will be monitored, even after completion of the study and study database lock, until the ADA level returns to baseline, unless the subject is maintained on AMG 714 outside of the scope of the study (i.e., in case of an extension in dosing).

2.3 INJECTION SITE REACTION AND ANAPHYLAXIS

In AMG 714 studies, injection site reactions have been mild and have appeared with low frequency (typically below 10%). There have not been any reports of anaphylaxis to AMG 714. All administrations of study drug will be monitored for 1 hour to detect any possible injection site reaction and/or anaphylaxis.

3 RATIONALE

There is considerable unmet need in celiac disease, and especially in RCD-II, an in situ small bowel T cell lymphoma which has 50% frequency of progression to overt systemic lymphoma (EATL), the latter characterized by very poor prognosis (<20% survival at 5 years). There are no medications approved for RCD-II.

Interleukin 15 (IL-15) is considered to be a central regulator of celiac disease immunopathology and a non-redundant driver of lymphomagenesis in RCD-II. AMG 714 is a fully human monoclonal antibody which binds to bioactive IL-15 and has been well-tolerated with demonstrated clinical and biochemical effects in RA. AMG 714 has been studied in approximately 200 subjects to date, including approximately 140 subjects dosed for 12 weeks. Its selectivity, favorable safety and pharmacokinetic profile in conjunction with the proof-of-mechanism in RA support the testing of AMG 714 in RCD-II, an in situ small bowel T cell lymphoma.

4 OBJECTIVES

4.1 PRIMARY OBJECTIVE

The primary objective of this study is to assess the efficacy of AMG 714 in treating RCD-II, an in situ small bowel T cell lymphoma, in adult patients.

4.2 SECONDARY OBJECTIVE

The secondary objective of this study is to assess the safety and tolerability of AMG 714 when administered to adult patients with RCD-II.

4.3 EXPLORATORY OBJECTIVES

The exploratory objective of this study is to assess the PK, PD, and PK/PD correlations of AMG 714.

5 ENDPOINTS

5.1 PRIMARY EFFICACY ENDPOINT

- Immunological response 1 as measured by reduction from baseline in the % of aberrant IELs vs total IELs as assessed by flow cytometry.

5.2 SECONDARY EFFICACY ENDPOINTS

- Immunological Response 2: Reduction from baseline in the % of aberrant IELs vs intestinal epithelial cells
- Histological response as measured by an improvement from baseline in small intestinal VH:CD ratio, Marsh score or total IEL counts.
- Clinical response as measured by change from baseline in clinical symptoms captured using:
    - Bristol Stool Form Scale (BSFS)
    - Gastrointestinal Symptom Rating Scale (GSRS) and celiac disease GSRS (CeD-GSRS)

5.3 EXPLORATORY ENDPOINTS

- Reduction in aberrant and abnormal IELs by flow cytometry, immunohistochemistry and TcR clonality analyses
- Physician Global Assessment of Disease (PGA) and Patient Global Assessment of Disease (PtGA)
- Quality of Life questionnaires: SF-12 v. 2 and EQ-5D
- Biomarkers of disease activity
- Pharmacokinetics (PK), Pharmacodynamics (PD), and Exposure/Response (PK/PK)
- Celiac Disease Patient reported Outcome (CeD PRO)

5.4 SAFETY ENDPOINTS

- AEs
- Clinical laboratory tests
- Physical examination
- Vital signs
- Immunogenicity

6 STUDY DESIGN

Protocol CELIM-RCD-002 is designed to be a Phase 2a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of AMG 714 for the treatment of adult patients with RDC-II, an in situ small bowel T cell lymphoma.

After signing consent, subjects will be screened for the study. All subjects who meet the study entry criteria will be randomized 2:1 ratio to receive either 8 mg/kg AMG 714 or placebo a total of 7 times over 10 weeks, with evaluation of the primary endpoint at Visit 8 (Week 12/Day 84).

AMG 714 (N=16) or placebo (N=8) will be administered at the clinical site in a double-blind fashion via intravenous (IV) infusion of approximately 120 minutes (2 hours) duration.

Subjects will remain confined to the study site for a minimum of 1 hour after the administration of study medication. During this time the Investigator and study site staff will assess the subject for AEs. As per Table 1, PK samples are to be collected prior to the infusion and 1 hour after the infusion, at the end of this observation period. The beginning and end of the infusion, as well as the PK sample collection times, will be recorded.

In addition to receiving study medication (AMG 714 or placebo), concomitant therapy with steroids at a maximum dose of 20 mg of prednisone, prednisolone or equivalent per day and/or oral budesonide at a maximum dose of 9 mg per day will be accepted. Steroid doses must be stable for 4 weeks prior to randomization and remain stable for the duration of the study. Budesonide has been used in RCD-II with improvement of symptoms and is considered adequate background therapy for RCD-II (Brar *et al*, 2007).

Should AMG 714 show adequate efficacy and safety, as determined by the Sponsor, subjects in the study, including those in the placebo arm, may be offered participation in an open label extension study of AMG 714 in due course, but under no circumstances prior to study completion. In the interim, between the end of the study for an individual subject and the start of the possible open label extension, the Sponsor intends to provide a bridging program to allow objective study responders to have access to AMG 714 as determined by their site investigator or physician. The open label extension study and interim bridging program will be described in independent protocols.

Subjects will be expected to maintain total adherence to a GFD from 6 months before randomization through the final study visit (Visit 9; Week 16/Day 112). Subject's adherence to the GFD will be assessed by an expert dietitian and monitored via stool sample testing using the iVYLISA GIP stool gluten test. Subjects with known or suspected GFD transgressions will be counseled and allowed to continue in the study.

A study site staff member will contact each subject by telephone one day after the first study drug administration to assess for AEs. Subjects will return to the clinic for the next administration of study drug after 1 week (Visit 2; Week 1/Day 7). After Visit 2, subjects will return to the clinic for follow-up and study drug administration at Visit 3 (Week 2/Day 14) and

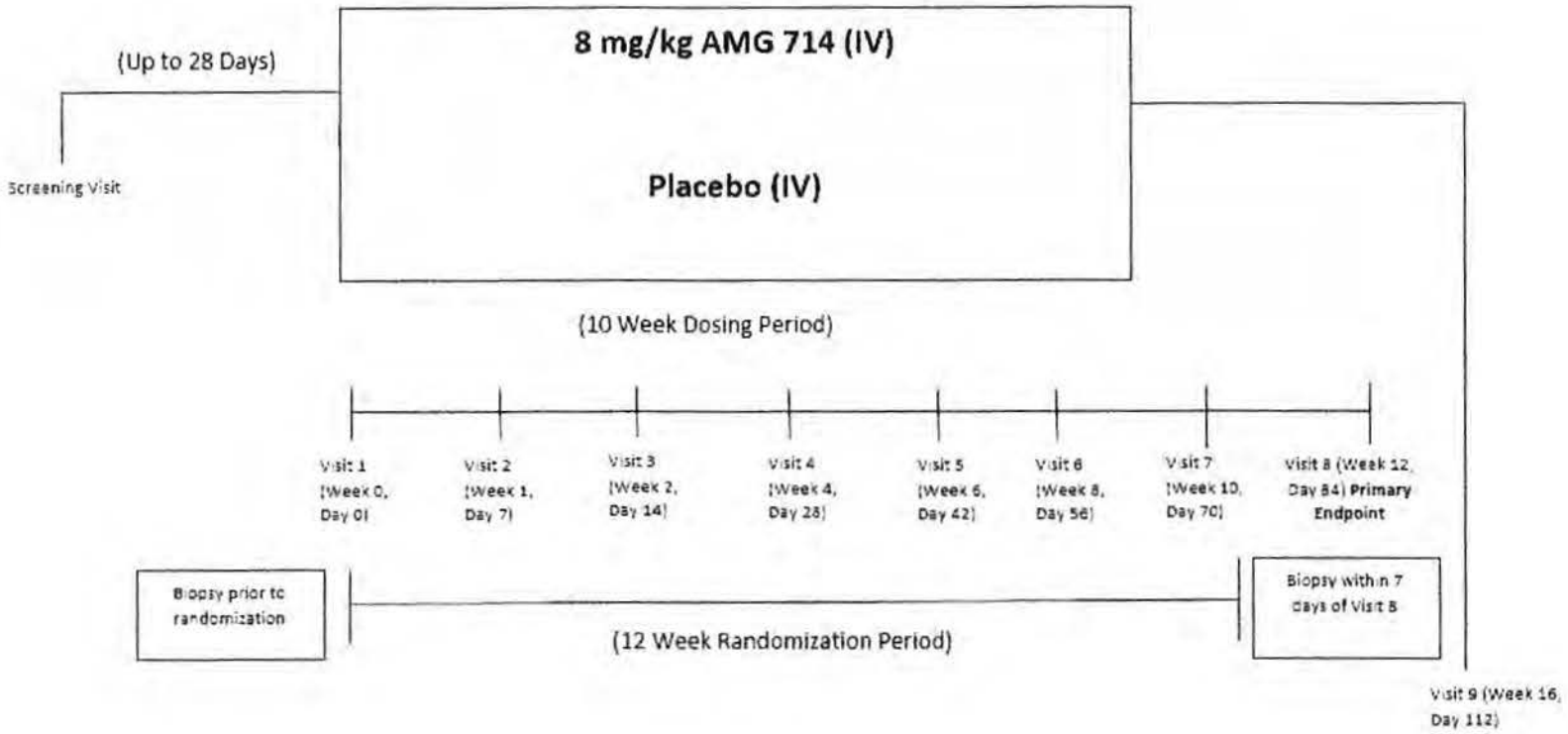
every two weeks thereafter as indicated in the study schedule of events (Table 1). The final dose of study drug will be administered at Visit 7 (Week 10/Day 70). An end-of-study efficacy visit will be conducted at Visit 8 (Week 12/Day 84). The final study visit will be conducted 6 weeks after the last dose of study drug at Visit 9 (Week 16/Day 112).

Subjects who meet all other study entry criteria will undergo upper gastrointestinal endoscopy with biopsy collection prior to baseline (i.e., prior to Visit 1, Week 0/Day 0) and within 7 days of Visit 8 (Week 12/Day 84) in order to assess changes from baseline to end of treatment in aberrant and abnormal IELs, VH:CD ratio, TcR clonality and Marsh score.

Subjects enrolled in the study will complete the BSFS at the time of each bowel movement from baseline (Visit 1; Week 0/Day 0) up to the final study visit, Visit 9 (Week 16/Day 112). Subjects will complete the CeD PRO daily from baseline up to the final study visit. Subjects will also complete the GSRS beginning at Visit 1 (Week 0/Day 0) and, thereafter, weekly from the time of randomization through the final study visit. The BSFS, GSRS and the daily CeD-PRO will be completed using a handheld electronic diary. In addition, subjects will complete paper quality of life diaries (SF-12 v. 2, EQ5D and PtGA). Diaries will be completed at the times specified in the Schedule of Events (Table 1). Safety will be monitored on an ongoing basis and subjects may undergo unscheduled visits if needed for safety reasons. Safety will be assessed throughout the study by clinical laboratory tests, physical examination, vital signs and AE monitoring. Immunogenicity will also be monitored.

Figure 1 represents a schematic drawing of the study periods and visits.

Figure 1. CELIM-RCD-002 Study Schematic



An interim analysis for safety and PK will be conducted when the tenth subject reaches Visit 4 (Week 4/Day 28). The interim analysis, to be pre-specified in the DSMB charter, will be performed by an independent DSMB which will also monitor unblinded safety data throughout the study. In addition to safety and PK, any other information available at the time of the analysis will be considered and a recommendation to stop, continue or modify the study will be made by the DSMB to the Sponsor. Should the exposure of AMG 714 be below the anticipated range, a root analysis will be done, which could result in a protocol amendment. The recommendation and decision will be shared with the investigational sites and ethics committees.

7 RANDOMIZATION AND TREATMENT ASSIGNMENT

Subjects will be randomized at a 2:1 allocation to receive 8 mg/kg AMG 714 or placebo for a total of 7 administrations over 10 weeks.

Randomization and initial dosing of the first ten (10) subjects will be staggered to allow observation in the initial subjects for any possible unanticipated side effect in the RCD-II population. To this effect, the first dosing of the first ten subjects will adhere to the following rules:

- No more than one subject per day.
- No more than two subjects per week.
- These rules will be implemented via randomization. The sites will obtain written approval from the Sponsor before dosing subjects by means of a Randomization Approval Form.

8 DURATION OF STUDY

Screening Visit: Up to 4 weeks (28 days)
Double-blind randomized period: 12 weeks
Final Visit: 4 weeks after last double-blind randomization visit
Duration of study per subject: Up to 20 weeks
Duration of entire study: Approximately 1.5 years

9 SUBJECT POPULATION

Approximately 24 males and females 18 years of age or older will be randomized into the study. Non-evaluable subjects will be replaced, if possible, at the discretion of the Sponsor.

Subjects will undergo screening procedures within 28 days of Visit 1; Week 0/Day 0. Those subjects who meet the study entry criteria will be invited to participate in the study.

9.1 INCLUSION CRITERIA

Subjects must fulfill all of the following inclusion criteria to be eligible for participation at screening and at Visit 1; Week 0/Day 0:

1. Adult males or females, 18 years of age or older.
2. Demonstrated willingness to participate in the study as documented by signed informed consent.
3. Females of non-childbearing potential defined as postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone [FSH] level >40 IU/L at Screening); or permanently sterilized (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, oophorectomy); or otherwise incapable of pregnancy

OR

Females of child bearing potential (FOCBP) or males who agree to practice two highly effective methods of birth control (as determined by the Investigator; one of the methods must be a barrier technique) from Screening through the end of study participation (Visit 9, Week 16/Day 112).

4. Prior confirmed diagnosis of RCD-II defined by the following criteria: celiac disease confirmed by histology, endoscopy or serology; with persistent and recurrent symptoms (e.g., diarrhea, weight loss, abdominal pain); with abnormal small bowel histology; with aberrant intraepithelial lymphocytosis of > 20% aberrant IELs vs total IELs (as determined by flow cytometry (or >50% if determined by immunohistochemistry); despite adherence to a strict GFD for at least 6 months and after exclusion of other potential causes of symptomatic non-response (e.g., microscopic colitis, bacterial overgrowth, lactose intolerance, exocrine pancreatic insufficiency, hyperthyroidism, etc.) and intestinal histological abnormality (autoimmune enteropathy, giardiasis, immunodeficiency, collagenous sprue, Whipple's disease, etc.).

   NOTE: Subjects who have been treated for RCD-II must continue to have increased aberrant IELs (>20% vs total IELs vs total IEL by flow cytometry or >50% by IHC) and abnormal small bowel histology (Marsh ≥1) and must have had prior history of symptoms; however, symptoms are not required of previously treated subjects, or subjects being treated with steroids, at the time of study entry.

5. Total attempted adherence to a GFD for at least 6 consecutive months prior to screening. Subjects must also agree to make no changes to their current GFD for the duration of study participation.
6. Anti-tissue transglutaminase (IgA and IgG) at screening <2 x the diagnostic level for celiac disease (weak positive or negative).
7. HLA-DQ typing compatible with celiac disease, provided or obtained prior to baseline biopsy.

8. Life expectancy > 4 months.
9. Laboratory values:
    a) Estimated CCr > 30 mL/min/1.73m^2 using the Cockcroft-Gault equation
    b) Serum AP, ALT/SGPT, and AST/SGOT less than 3x the ULN
    c) Total bilirubin of less than 2.5 x ULN
    d) Total WBC > 300/mm^3
    e) Platelet count > 85,000/mm^3
    f) INR less than 1.5
    g) Albumin of more than 10 g/L (i.e., 1 g/dL or 1.45 µmol/L)
10. Subjects receiving systemic steroids must be on a stable dose for at least 4 weeks prior to randomization; the dose should not exceed 20 mg of prednisone, prednisolone or equivalent per day. Oral budesonide will be accepted at a maximum dose of 9 mg per day.
11. Willingness and ability to comply with study procedures and protocol stipulated concomitant medication guidelines.
12. Willingness to return for all scheduled follow-up visits.

9.2 EXCLUSION CRITERIA

Subjects will be excluded from participation in the study if there is evidence of any of the following, at screening and Visit 1:

1. Diagnosis of RCD-I or EATL (excluded by the site's standard imaging techniques for this purpose).
2. Presence of any of the following related to infection:
    a) Active acute infection requiring systemic antibiotic, parenteral antifungal, or systemic antiviral treatments
    b) Severe infection within the 3 months prior to screening
    c) History of tuberculosis (TB)
    d) Positive IGRA test at screening OR known recent exposure (within 6 months prior to screening) to a patient with active TB (subject can be enrolled if he or she has been successfully treated with appropriate chemoprophylaxis).
    e) History within the 3 years prior to screening of an opportunistic infection typical of those seen in immunocompromised subjects (e.g., systemic candida infection, or systemic fungal infection).
3. Current diagnosis or history of cancer in the past 5 years, except RCD-II, successfully treated basal cell or squamous cell carcinoma, cervical carcinoma-in-situ, or early stage prostate cancer.
4. History or presence of clinically significant disease that in the opinion of the Investigator, would confound the subject's participation and follow-up in the clinical trial or put the subject at unnecessary risk including but not limited to:

a) Cardiovascular disease [e.g., uncontrolled hypertension (office systolic blood pressure [BP] equal to or greater than 180 mmHg or office diastolic BP equal or greater than 110 mm/Hg), unstable angina, congestive heart failure worse than NYHA Class II, coronary angioplasty or myocardial infarction within the last 6 months, uncontrolled atrial or ventricular cardiac arrhythmias clinically significant pleural or pericardial effusion or ascites)

b) Pulmonary disease (e.g., severe chronic pulmonary disease)

c) Renal, hematological, gastrointestinal, endocrine (e.g., poorly controlled diabetes), immunologic, dermatologic, neurological, or psychiatric disease

5. History of significant immune suppression:
   a) BMT or cladribine therapy less than 6 months prior to baseline.
   b) Potent systemic immune suppressants (e.g., azathioprine) within the 3 months prior to baseline.
6. History of alcohol or drug abuse that would interfere with the ability to comply with the study protocol.
7. History of clinically significant hypersensitivity to the study drug or any related drugs or to any of the excipients.
8. Positive Hep B, Hep C, or HIV test results at the time of screening.
9. Females who are pregnant or planning to become pregnant during the study participation period of 6 months after last dose, or are currently breastfeeding.
10. Participation in another investigational drug or device study or treatment with an investigational drug within 30 days or 5 half-lives, whichever is longer, prior to randomization.
11. Any additional reason, which in the opinion of the Investigator, would prevent the subject from safely participating in the study or complying with protocol requirements.

10 CONCOMITANT MEDICATIONS

10.1 PROHIBITED MEDICATIONS

The following medications are not allowed at the time of randomization (Visit 1, Week 0/Day 0) or throughout the study:

- Systemic or intestinal immune suppressants, excluding steroids at a maximum dose of 20 mg of prednisone, prednisolone or equivalent per day and/or oral budesonide at a maximum dose of 9 mg/day. Systemic immune suppressants should not be used within the 3 months prior to randomization. Inhaled steroids for respiratory diseases such as asthma, and topical steroids are permitted.
- Chronic or continuous oral and IV antibiotics (>2 weeks use). Topical antibiotic use is allowed.

- Systemic antivirals
- Parenteral antifungals
- Anticoagulants in the week prior to the protocol-indicated biopsies (alternatively, local guidelines for the prevention of bleeding during endoscopy can be followed).
- Live vaccines.
- Investigational drugs or devices.

Note: After randomization, use of any of these medications is permitted if required for treatment of an AE. These medications may be started following discussion with and approval of the medical monitor. If discussion is not possible and approval has not been obtained prior to starting these medications, the situation should be discussed with the medical monitor promptly after treatment has been instituted to avoid classification as a protocol deviation. In the absence of discussion with the medical monitor, as described, starting these medications following randomization will be classified as a protocol deviation. If the prohibited concomitant medication is determined to interfere with the results of the study, withdrawal of the subject shall occur at the discretion of the Investigator or the sponsor.

Note: It is permitted to administer albumin if needed for the purpose of correcting excessive hypoalbuminemia in the context of protein-losing enteropathy, at the Investigator's discretion.

11 STUDY ASSESSMENTS AND PROCEDURES

All study procedures and their timing are summarized in the Schedule of Events (Table 1).

All visits, except the Follow-up Phone Call, Visit 2 (Week 1/Day 7) and Visit 9 (Week 16/Day 112) should be conducted within +/-3 days from the scheduled visit day relative to the randomization visit (unless otherwise indicated). The Follow-up Phone Call should be conducted within +1 day from the randomization (Visit 1; Week 0/Day 0) visit date. The Visit 2 (Week 1/Day 7) study drug administration must be conducted on the scheduled visit date relative to the date of randomization. This visit cannot be conducted early and, should it be conducted late, the visit schedule must be adjusted based on the actual date of Visit 2 (Week 1/Day 7). The Visit 8 endoscopy and biopsy (not the visit, but the endoscopy and biopsy only) can be conducted within +/- 7 days of Visit 8, and Visit 9 (Week 16/Day 112) should be within +/-7 days from the original or adjusted scheduled visit date.

All study visits occurring after randomization (Visit 1, Week 0/Day 0) should be based on the Visit 1 study visit date, or the adjusted visit schedule in the event of a delayed Visit 2 (Week 1/Day 7). During the 12-week randomization period, subsequent to Visit 2 (Week 1/Day 7), if a study visit occurs no more than a maximum of 4 days outside of the visit window (±7) the study drug can be administered and the next visit scheduled in accordance with the original or adjusted visit calendar. If a late study visit should occur more than 4 days outside of the study visit window the study drug should not be administered and a protocol deviation recorded. Under no circumstances should any 2 doses of study drug be administered within fewer than 7 days of each other.

If a subject misses 2 consecutive doses of study drug the subject should be terminated from the study after consultation with the Sponsor and should complete the Early Termination visit. The Final Study Visit should be conducted at least 6 weeks (+/- 7 days) after the last study administration of study drug. The Final Study Visit is not required if the last administration of study drug occurred 6 or more weeks prior to the Early Termination visit.

11.1 ASSESSMENTS AT EACH VISIT

All subjects who sign an Informed Consent Form will be assigned a unique subject number. This number will be used for identification purposes for all study visits.

All subjects who sign an Informed Consent but do not enter the study must have a reason recorded as to why randomization into the study did not occur. This information will be input into the Electronic Case Report form (eCRF).

Retesting of screening evaluations is permitted once for each test without prior approval from the Sponsor. Additional retesting may be permitted on a case by case basis after consultation with the study Sponsor.

Rescreening of subjects is permitted at the discretion of the Investigator.

11.1.1 Screening Visit

- Obtain informed consent.
- Register the visit in the electronic data capture (EDC) system.
- Review inclusion/exclusion criteria. For interpretation of hepatitis testing results, see Appendix F.
- Document demographics and medical history.
- Collect vital signs.
- Measure height and weight.

  NOTE: Height will be measured at the Screening Visit only. Subjects will not wear shoes during height measurement. Body weight is measured at all visits. Body weight should be obtained while the subject is wearing light weight clothing. Shoes will not be worn during body weight measurement.

- Document prior and concomitant medications (including prescription and over-the-counter medications, nutritional supplements, and herbal preparations taken within 30 days of screening).
- Perform physical examination to include an examination of general appearance; head, eyes, ears, nose, throat (HEENT); lymph nodes; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological, psychological and dermatological systems.
- Perform 12-lead electrocardiogram (ECG).

NOTE: A 12-lead resting ECG will be obtained from all subjects at the time of screening. ECGs will be recorded after the subject has been supine for approximately 5 minutes. Each 12-lead ECG will be evaluated by an appropriately qualified physician at the study site. ECG data will be evaluated using the following categories:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

Any suspected cardiovascular AE should be followed with an additional ECG at the discretion of the Investigator.

- Collect stool sample for iVYLISA GIP testing.
- Collect blood and urine specimens for clinical laboratory testing (see Appendix B and/or Central Laboratory manual for the parameters).

NOTE: HLA DQ typing is only required when this information is not already part of the subject's available existing medical record.

- Collect blood for serum pregnancy test for FOCBP.
- Begin assessment of AEs.
- Schedule subject for endoscopy procedure.

When the screening clinical laboratory test results are received, they must be reviewed by the Investigator or appropriate qualified designee for clinically significant abnormalities.

If no clinically significant abnormalities or exclusions are found, the site should proceed with the scheduled endoscopy and biopsy (or proceed directly to the endoscopy and biopsy without having lab results if required due to logistical or clinical considerations). If clinically significant abnormalities are found, retesting of the subject shall occur at the discretion of the Investigator or designee physician. Retesting is permitted one time for each laboratory parameter. Additional testing may be permitted after consultation with the Sponsor's appropriate qualified designee. If the clinically significant abnormalities resolve, the subject can proceed with the scheduled endoscopy and biopsy.

11.2 12-WEEK RANDOMIZATION PERIOD

11.2.1 Randomization and Dosing preparation

The unblinded pharmacist or unblinded study staff member assigned to the receipt and preparation of study drug materials (see Section 18 for guidance on study drug blinding) should register medication dispensing in the EDC system at least 24 hours before the first dosing visit to obtain a randomized treatment assignment for the subject and subsequent vial distribution.

Study drug must be thawed overnight and prepared in advance of the study visit as per the guidance in Section 18 of this protocol.

11.2.2 Visit 1 (Week 0/Day 0)

- Review inclusion/exclusion criteria.
- Document visit in the EDC system.
- Allow subject to complete SF-12 v. 2 and EQ-5D.
- Assign e-diary and allow subject to complete the first weekly GSRS and daily CeD PRO.
- Collect vital signs.
- Measure body weight.
- Perform physical examination to include an examination of general appearance; HEENT; lymph nodes; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological, psychological and dermatological systems.
- Complete Physician Global Assessment (PGA), BEFORE study drug administration.
- Allow the subject to complete the Patient Global Assessment of Disease (PtGA) BEFORE study drug administration.
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK, ADA and biomarkers BEFORE start of study drug administration. Record date and actual time of sampling.
- Collect Whole Blood for Flow Cytometry.
- Collect blood cell pellet.
- Collect iVYLISA GIP stool sample. The stool sample will be produced within 3 days prior to, or after, the scheduled study visit (±3 day window).
- Perform urine pregnancy test on FOCBP.
- Administer study medication. See section 18 for administration procedures.

  NOTE: Subject should remain in the clinic for a minimum of 1 hour after the end of study drug administration to monitor for new AEs and collect the second PK sample.

- Assess AEs.
- Monitor for changes to concomitant medications.
- Dietitian assessment of the GFD. This assessment can be conducted by phone provided it is conducted within the allotted visit window.
- Collect blood sample for PK 1 hour after END of infusion of study medication. Record date and actual time of infusion beginning, end and sampling.
- Remind subjects to complete the BSFS at each occurrence of a bowel movement and the CeD PRO daily.
- Remind subject to complete the weekly GSRS.
-

11.2.3 Safety Phone Call (Week 0/Day 1)

- Assess AEs.
- Monitor for changes to concomitant medications.
- Remind subjects to complete the BSFS at each occurrence of a bowel movement and the CeD PRO daily.
- Remind subject to complete the weekly GSRS.

11.2.4 Visit 2 (Week 1/Day 7)

- Document visit in the EDC system.
- Collect vital signs.
- Measure body weight.
- Perform physical examination to include an examination of general appearance; HEENT; lymph nodes; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological, psychological and dermatological systems.
- Complete PGA BEFORE study drug administration.
- Allow the subject to complete the Patient Global Assessment of Disease (PtGA), BEFORE study drug administration.
- Perform urine pregnancy test on FOCBP.
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK and biomarkers BEFORE start of study drug administration. Record date and actual time of sampling.
- Administer study medication. See section 18 for administration procedures.

  NOTE: Subject should remain in the clinic for a minimum of 1 hour after the end of study drug administration to monitor for new AEs.

- Assess AEs.
- Monitor for changes to concomitant medications.
- Remind subjects to complete the BSFS at each occurrence of a bowel movement and the CeD PRO daily.
- Remind subject to complete the weekly GSRS.
- Provide subject with iVYLISA GIP test kit and instructions for home collection.

11.2.5 Visit 3 (Week 2/Day 14)

- Document visit in the EDC system.
- Collect vital signs.
- Measure body weight.
- Perform physical examination to include an examination of general appearance; HEENT; lymph nodes; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological, psychological and dermatological systems.

- Complete PGA BEFORE study drug administration.
- Allow the subject to complete the Patient Global Assessment of Disease (PtGA) BEFORE study drug administration.
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK, ADA and biomarkers BEFORE start of study drug administration. Record date and actual time of sampling.
- Collect stool for iVYLISA GIP test. The stool sample will be produced within 3 days prior to, or after, the scheduled study visit.
- Perform urine pregnancy test on FOCBP.
- Administer study medication. See section 18 for administration procedures.

  NOTE: Subject should remain in the clinic for a minimum of 1 hour after the end of study drug administration to monitor for new adverse events.

- Assess AEs.
- Monitor for changes to concomitant medications.
- Remind subjects to complete the BSFS at each occurrence of a bowel movement and the CeD PRO daily.
- Remind subject to complete the weekly GSRS.
- Provide subject with iVYLISA GIP test kit and instructions for home collection.

11.2.6 Visit 4 (Week 4/Day 28)

- Document visit the EDC system.
- Allow subject to complete SF-12 v. 2 and EQ-5D.
- Collect vital signs.
- Measure body weight.
- Collect vital signs.
- Complete PGA BEFORE study drug administration.
- Allow the subject to complete the Patient Global Assessment of Disease (PtGA) BEFORE study drug administration.
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK, ADA and biomarkers BEFORE start of study drug administration. Record date and actual time of sampling.
- Collect Whole Blood for Flow Cytometry.
- Collect stool for iVYLISA GIP test. The stool sample will be produced within 3 days prior to, or after, the scheduled study visit.
- Perform urine pregnancy test on FOCBP.
- Administer study medication. See section 18 for administration procedures.

  NOTE: Subject should remain in the clinic for a minimum of 1 hour after the end of study drug administration to monitor for new adverse events and to

collect the second PK sample. Collect blood sample for PK 1 hour after END of infusion of study medication.

- Assess AEs.
- Monitor for changes to concomitant medication.
- Dietitian assessment of the GFD. This assessment can be conducted by phone, provided it is conducted within the allotted visit window.
- Remind subjects to complete the BSFS at each occurrence of a bowel movement and the CeD PRO daily.
- Remind subject to complete the weekly GSRS.
- Provide subject with iVYLISA GIP test kit and instructions from home collection.

11.2.7 Visit 5 (Week 6/Day 42)

- Document visit in the EDC system.
- Collect vital signs.
- Measure body weight.
- Perform physical examination to include an examination of general appearance; HEENT; lymph nodes; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological, psychological and dermatological systems.
- Perform urine pregnancy test on FOCBP.
- Collect stool for iVYLISA GIP test. The stool sample will be produced within 3 days prior to, or after, the scheduled study visit.
- Administer study medication. See section 18 for administration procedures.

  NOTE: Subject should remain in the clinic for a minimum of 1 hour after the end of study drug administration to monitor for new adverse events.

- Assess AEs.
- Monitor for changes to concomitant medications.
- Remind subjects to complete the BSFS at each occurrence of a bowel movement and the CeD PRO daily.
- Remind subject to complete the weekly GSRS.
- Provide subject with iVYLISA GIP test kits and instructions from home collection.

11.2.8 Visit 6 (Week 8/Day 56)

- Document visit in the EDC system.
- Collect vital signs.
- Measure body weight.
- Collect blood sample for PK, ADA and biomarkers BEFORE start of study drug administration. Record date and actual time of sampling.
- Complete PGA BEFORE study drug administration.

- Allow the subject to complete the Patient Global Assessment of Disease (PtGA), BEFORE study drug administration.
- Collect blood and urine for clinical laboratory testing; including sample for biomarkers BEFORE study drug administration.
- Collect Whole Blood for Flow Cytometry.
- Perform urine pregnancy test on FOCBP.
- Collect stool for iVYLISA GIP test. The stool sample will be produced within 3 days prior to, or after, the scheduled study visit.
- Administer study medication. See section 18 for administration procedures.

  NOTE: Subject should remain in the clinic for a minimum of 1 hour after the end of study drug administration to monitor for new adverse events. Collect blood sample for PK 1 hour after END of infusion of study medication. Record date and actual time of infusion beginning, end and sampling.

- Assess AEs.
- Monitor for changes to concomitant medications.
- Dietitian assessment of the GFD. This assessment can be conducted by phone, provided it is conducted within the allotted visit window.
- Remind subjects to complete the BSFS at each occurrence of a bowel movement and the CeD PRO daily.
- Remind subject to complete the weekly GSRS.
- Provide subjects with iVYLISA GIP test kit and instructions for home collection.

11.2.9 Visit 7 (Week 10/Day 70)

- Document visit in the EDC system.
- Collect vital signs.
- Measure body weight.
- Collect blood sample for PK and biomarkers BEFORE start of study drug administration. Record date and actual time of sampling.
- Perform urine pregnancy test on FOCBP.
- Collect stool for iVYLISA GIP test. The stool sample will be produced within 3 days prior to, or after, the scheduled visit.
- Administer study medication. See section 18 for administration procedures.

  NOTE: Subject should remain in the clinic for a minimum of 1 hour after the end of study drug administration to monitor for new adverse events and to collect the second PK sample.

- Assess AEs.
- Monitor for changes to concomitant medications.
- Remind subjects to complete the BSFS at each occurrence of a bowel movement and the CeD PRO daily.

- Remind subject to complete weekly GSRS.
- Provide subject with iVYLISA GIP test kit and instructions for home collections.

11.2.10 Visit 8 (Week 12/Day 84)

NOTE: DO NOT ADMINISTER STUDY MEDICATION AT THIS VISIT

- Document visit in the EDC system.
- Allow subject to complete SF-12 v. 2 and EQ-5D.
- Collect vital signs.
- Measure body weight.
- Perform physical examination to include an examination of general appearance; HEENT; lymph nodes; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological, psychological and dermatological systems.
- Complete PGA BEFORE study drug administration.
- Allow the subject to complete the Patient Global Assessment of Disease (PtGA), BEFORE study drug administration.
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK, ADA and biomarkers. Record date and actual time of sampling.
- Collect Whole Blood for Flow Cytometry.
- Perform serum pregnancy test on FOCBP.
- Collect stool for iVYLISA GIP testing. The stool sample will be produced within 3 days prior to, or after, the scheduled visit.
- Assess AEs.
- Monitor for changes to concomitant medications.
- Dietitian assessment of the GFD. This assessment can be conducted by phone, provided it is conducted within the allotted visit window.
- Remind subjects to complete the BSFS at each occurrence of a bowel movement and the CeD PRO daily.
- Remind subject to complete the weekly GSRS.
- Provide subject with iVYLISA GIP test kit and instructions for home collection.
- Perform endoscopy and collect biopsy specimens within 7 days of Visit 8.

11.3 FINAL STUDY VISIT

11.3.1 Visit 9 (Week 16/Day 112) or 6 Weeks After Last Study Drug Administration

- Document visit in the EDC system.
- Allow subject to complete SF-12 v. 2 and EQ-5D.
- Collect vital signs.
- Measure body weight.

- Complete PGA.
- Allow the subject to complete the Patient Global Assessment of Disease (PtGA) BEFORE study drug administration.
- Perform physical examination to include an examination of general appearance; HEENT; lymph nodes; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological, psychological and dermatological systems.
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK, ADA and biomarkers. Record date and actual time of sampling.
- Collect Whole Blood for Flow Cytometry.
- Perform urine pregnancy test on FOCBP.
- Collect stool for iVYLISA GIP testing. The stool sample will be produced within 3 days prior to, or after, the scheduled visit.
- Assess new our ongoing AEs.
- Monitor for changes to concomitant medications.
- Collect eDiary and assure that any outstanding diaries have been entered.

11.4 EARLY TERMINATION (ET)

Early Termination visits should be conducted for randomized subjects (subjects who received double-blind treatment) who discontinue participation in the study. Early termination visit procedures are not required for subjects who do not receive study drug and are therefore considered screen failures.

- Document visit in EDC system.
- Collect vital signs.
- Measure body weight.
- Perform physical examination to include an examination of general appearance; HEENT; lymph nodes; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological, psychological and dermatological systems.
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK, ADA and biomarkers. Record date and actual time of sampling.
- Perform serum pregnancy test on FOCBP.
- All attempts should be made to collect a final iVYLISA GIP stool sample, if the sample was not collected within 3 days prior to the scheduled Early Termination visit.
- Assess AEs.
- Monitor for changes to concomitant medications.
- Allow subject to complete SF-12 v. 2 and EQ-5D.
- Complete PGA.
- Allow the subject to complete the Patient Global Assessment of Disease (PtGA), BEFORE study drug administration.

- Perform endoscopy and collect biopsy specimens within 7 days of the Early Termination visit unless not indicated based on the subject's condition, at the PI's discretion.
- Schedule the Final Study Visit. The Final Study Visit is not required if the Early Termination visit occurs 6 or more weeks after the last study drug administration.

12 DEFINITION OF END OF STUDY

The end of study is defined as the last study visit (Visit 9; Week 16/Day 112, Final Study Visit) for the last subject randomized.

13 EFFICACY ASSESSMENTS

13.1 IMMUNOLOGICAL RESPONSE: ASSESSMENT OF ABERRANT INTRAEPITHELIAL LYMPHOCYTES

The primary endpoint in this trial is the reduction in the % of aberrant intestinal IELs with respect to total IELs as assessed by flow-cytometry (Immunological Response 1). The first secondary endpoint is Immunological Response 2, the reduction in the % of aberrant intestinal IELs with respect to intestinal epithelial cells, a composite endpoint calculated by multiplying the % of aberrant IEL vs total IELs (determined by flow cytometry) by the % of total IEL vs intestinal epithelial cells, as assessed by immunohistochemistry. The secondary endpoint could be more representative of a benefit driven by functional impact rather than simple reduction in IEL numbers.

Both endpoints address the core abnormality in RCD-II, an in situ small bowel T cell lymphoma in which aberrant lymphocytes are responsible for mucosal damage and symptoms and for the progression to EATL. Aberrant IELs are described as surface CD3-negative, intracellular CD3-positive. The reduction in the proportion and number of aberrant lymphocytes is specific to RCD-II, is analogous to a reduction in tumor size in a solid tumor cancer, and has been proposed as the most direct measurement of efficacy in RCD-II (as reviewed in van Wanrooij *et al*, 2014).

This exploratory study, first industry-sponsored trial in RCD-II, will be considered positive for the purposes of Go-No decision-making if at least one of the two calculations of Immunological Response is found to be positive.

Flow cytometry is the most accurate tool available to quantify aberrant IELs (van Wanrooij *et al*, 2014), and it is preferred over IHC, (less sensitive) and TcR rearrangement or clonality by polymerase chain reaction (PCR, less specific) (van Wanrooij *et al*, 2014). Enumeration of total IELs will be done by IHC to calculate the secondary endpoint of % of aberrant IELs vs intestinal epithelial cells. Enumeration of aberrant (intracellular CD3) and abnormal (altered phenotype, such as overexpression of NKG2D) IELs by IHC and PCR will be performed as well, as exploratory endpoints.

Flow cytometry of IELs requires the acquisition of fragment(s) of small bowel tissue by endoscopy and biopsy, and the method to disperse, stain and analyze the IELs is described elsewhere (Leon, 2011).

Flow cytometry is the clinical-grade technique employed and validated in the routine phenotyping of hematological cancers such as leukemias and lymphomas. It is exquisitely quantitative (>10,000 single cells are quantified by laser beams per second based on multiple specific surface markers) (Leon 2011, van Wanrooij *et al*, 2014). The large number of cells stained and analyzed, estimated to be between 0.5 million and 5 million per time point per patient, ensures low variability and reproducibility. All sites will use the same procedure and experimental protocol, and technical validation will be performed prior to study start.

13.2 HISTOLOGIC RESPONSE: SMALL BOWELL ENDOSCOPY, BIOPSY AND HISTOLOGY

At each time point specified in Table 1, small-bowel biopsies will be collected in order to perform the aberrant IEL analysis and the histological assessment of mucosal inflammation. The latter will provide the secondary endpoint of Histological Response, as measured by improvement from baseline in small intestinal VH:CD ratio assessed with a validated morphometric analysis (Taavela *et al*, 2013). Lack of Histological Response has been shown to correlate with long term outcomes including progression to EATL (Nijeboer *et al*, 2015 a, b), albeit the current Phase 2a study may be of insufficient duration to fully assess histological recovery (slower than immunologic resolution). In addition to the VH:CD ratio, the second commonly used histological score, the Marsh-Oberhuber classification (Marsh, 1992, Oberhuber 2000), as well as the total IEL count (all IEL, not just aberrant) will also be calculated as a secondary endpoint.

At each time point specified in Table 1, approximately eleven to thirteen (11-13) fragments or specimens of small-bowel tissue will be taken from the second part of the duodenum distal to the ampulla by trans-oral upper endoscopy and forceps biopsy. Biopsies should be collected from the D2 segment of the duodenum. Ulcerative lesions should be avoided. The location and macroscopic appearance of the tissue will be noted in the source documents. The potential presence of any observable lesion such as ulcerative jejunitis will be captured in the eCRF. When necessary, samples will be re-oriented and sectioned again until they are of good quality. The procedures will be described in a Study or Laboratory Manual or similar document, and the IEL/LPL preparation method will be based on published methods by the Paris site. The fragments or specimens will be prioritized as follows:

i. First five specimens collected, for flow cytometry: Approximately 5 biopsy specimens will be used for flow cytometry, done locally at each site with fresh tissue.
ii. Second three specimens collected, for histology and immunohistochemistry: Approximately three (3) biopsy specimens will be fixed in 10% formalin or other fixative, with one (1) of them used for standard pathology at the site and two (2) of them embedded in paraffin wax after orientation for analysis

at the histology central laboratory. The Central Pathologist, blinded to treatment assignment, will assess villus height (VH, in micrometers) and crypt depth (CD, in micrometers) and their ratio, VH:CD ratio. Further, the Marsh-Oberhuber score will be given (M0, M1, M2, M3a, M3b, or M3c) and the density of CD3-positive IELs (cells/100 epithelial cells) will be assessed. Histology and immunohistochemistry (IHC, e.g., the determination of NKG2D on IEL) analysis will be performed following standard operating procedures for fixed biopsy specimen orientation, paraffin embedding, cutting, staining and scanning for whole slide virtual microscopy. Standard operating procedures will also be followed for biopsy morphometry readings using validated methods (Taavela *et al*, 2013). If it is not feasible to measure at least 3 villus-crypt units for a subject's given biopsies, even after re-cutting, the results will be considered not evaluable.

iii. Three specimens collected for experimental biomarkers: Approximately three (3) specimens will be used for biomarker research. Two fragments will be placed in mRNA preservative for future mRNA analysis and one will be used for TcR clonality (fresh, frozen or embedded in paraffin).

iv. Optionally, two fragments for functional experiments: Two specimens, if available, may be used fresh in select sites for analysis of IL-15 related functional biomarkers. Measurement of AMG 714 in the biopsies may be attempted. In Finland one or both optional specimens will be used in some patients for crypt cell "mini-gut" *in vitro* culture at baseline and post-treatment to study biomarkers of epithelial cell differentiation in the crypt-villous axis.

Every effort will be made to collect all 11 to 13 specimens, but should this number not be reached, the specimens will be allocated in the order indicated.

13.3 CLINICAL RESPONSE: BRISTOL STOOL FORM SCALE (BSFS) AND GASTROINTESTINAL SYMPTOMS RATING SCALE (GSRS)

Clinical Response, based on symptoms recorded with patient reported outcome (PRO) questionnaires, will be considered secondary endpoints.

13.3.1 Bristol Stool Form Test

The Bristol Stool Form Scale (BSFS, Appendix C) is a pictorial aid to help subjects identify the shape and consistency of their bowel movements during the study (Riegler *et al* 2001).

Subjects will be asked to complete this form daily using an electronic diary at the time of each bowel movement from randomization through the Final Study Visit (Visit 9; Week 16/Day 112). If no bowel movements were experienced by the subject on any given day, the subject should document this using the electronic diary.

13.3.2 Gastrointestinal Symptom Rating Scale (GSRS)

The GSRS (Appendix D) is a 15-question 7 scale questionnaire used to assess five dimensions of gastrointestinal syndromes: diarrhea, indigestion, constipation, abdominal pain and reflux (Svedlund *et al* 1988). While not specific for celiac disease, the GSRS is widely used in gastroenterology and has been used in several clinical trials of experimental medications in celiac disease, thus becoming a very useful tool with abundant existing reference data (Kelly *et al* 2013; Lähdeaho *et al*, 2011; Leffler *et al*, 2015).

Subjects will be asked to complete this questionnaire weekly, using an electronic diary, from the day of randomization through the Final Study Visit.

The analysis will include the full GSRS questionnaire as well as the subset of questions most closely related to celiac disease (termed "Celiac GSRS" or CeD-GSRS") (Leffler *et al*, 2015).

14 EXPLORATORY ASSESSMENTS

14.1 PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetics of AMG 714 in RCD-II patients will be characterized using nonlinear mixed-effects modeling, including evaluation of effects of major covariates (weight or body mass index [BMI] and body surface area [BSA], sex, biochemical parameters and disease characteristics at baseline) on AMG 714 exposure.

Exploratory exposure-response analysis will be performed for efficacy, safety, and biomarker measures.

The time and date of each PK sample must be carefully recorded and reported in the eCRFs, as well as the beginning and end of each investigational product infusion.

14.2 ASSESSMENT OF THE GLUTEN-FREE-DIET: IVYLISA GIP STOOL TEST AND DIETITIAN CONSULTATION

In celiac disease, identification of gluten contamination is essential for the management of the disease and for the successful conduct of clinical trials. Contaminating gluten is a confounding factor in both diagnosis of RCD-II and in the evaluation of a potential therapeutic effect of any experimental medication. Histologic and clinical endpoints are heavily influenced by the presence of gluten in the diet.

In addition to measuring symptoms through patient reported diaries, Celimmune plans to use the iVYLISA GIP-S gluten stool test, a gluten assay developed to detect inadvertent gluten consumption by measuring gluten immunogenic peptides (GIP) in feces (Comino *et al*, 2012). The iVYLISA GIP-S test has a CE mark and is commercially available in Europe from Biomedal SL (as a research test) and, at the time of this writing, from LABCO (as a laboratory-developed test). iVYLISA GIP-S measures GIP in stools by immunoassay, a sandwich ELISA with antibody G12, specific for an immunodominant epitope of gluten that is resistant to degradation in the intestine. The lower quantification limit of the assay is 0.16 µg of GIP/g of

feces and the upper quantification limit is 5 µg GIP/g of feces. In unpublished results from Biomedal (Deliac clinical trial; manuscript submitted), gluten in feces is highly correlated with mucosal atrophy in celiac patients on a purported GFD. The sensitivity and specificity have been 96.3% and 100%, respectively, with positive and negative predictive values of 100% and 96.1%, respectively, in the aforementioned celiac study.

This assay will be used in the CELIM-RCD-002 trial to assist with data interpretation by assessing if the subjects are compliant with the GFD before enrollment and during the study. Non-compliance information will aid understanding outliers and will be used in pre-specified subgroup analyses.

The test detects gluten for up to four days after consumption, and testing will be done every two weeks – subjects should provide a stool sample collected up to 3 days before, or after, the visit to the sites, in order to have a good probability of identifying dietary transgressors to enable correct data interpretation. Testing will be done at a central lab. Stools may also be used for microbiome analysis, known to affect gluten composition and the biology of IL-15.

In addition to the gluten stool test, adherence to the GFD will be assessed periodically (Table 1) by an expert dietitian who will counsel the subjects. The dietitian will fill out a questionnaire, provided by the Sponsor, to document the conversation and any detected dietary transgressions. This assessment can be conducted by phone, provided it is conducted within the allotted visit window. This information may be analyzed in an exploratory fashion.

The questionnaire will address the following items:

- Did the subject have nutritional counseling with an expert dietitian during the visit? Yes/No
- Was a dietary transgression detected since the last visit? Yes/No
- If Yes, please indicate the number of transgressions since the last visit.

Patients will be provided a calendar or similar tool to note their dietary transgressions between visits.

14.3 PHYSICIAN GLOBAL ASSESSMENT OF DISEASE (PGA) AND PATIENT GLOBAL ASSESSMENT OF DISEASE (PTGA)/RATING OF CHANGE

The PGA (Appendix E) is designed to be used by the Investigator or qualified designee to assess the subjects' disease activity at the time points specified in the study schedule of events (Table 1). An attempt should be made to use the same assessor at each specified time point. Part B of the PGA is designed to assess physician perception of change in disease activity. Part B should be completed as per the schedule of events (Table 1) beginning after Visit 1, Week 0/Day 0.

Assessments should be made prior to study drug administration using all tools available to the assessor including laboratory test results.

The PtGA (Appendix L) is deigned to be used by the subject to assess perception of disease activity that the time points listed in the Table 1. Part B of the PtGA, is designed to assess subject perception of change in disease activity and should be administered as per the schedule of events (Table 1) beginning after Visit 1, Week 0/Day 0.

The PtGA should be completed by the subject prior to study drug administration.

14.4 QUALITY OF LIFE QUESTIONNAIRES: SF-12 V. 2 AND EQ-5D

The SF-12v2 Health Survey is a shorter version of the SF-36v2 Health Survey uses just 12 questions to measure functional health and well-being from the patient's point of view.

The SF-12v2 covers the same eight health domains as the SF-36v2 with one or two questions per domain (Ware, *et al.* 2009).

The EQ-5D is a simple, brief and standardized instrument for use as a measure of health outcome (http://www.euroqol.org/about-eq-5d.html). The 5L version, available since 2009, will be used in the study.

14.5 BIOMARKERS OF DISEASE ACTIVITY

Several biomarkers of disease activity will be analyzed in serum (e.g., CRP, IL-15, sIL-15R), as exploratory indicators of disease activity and potential predictors of response to AMG 714.

Flow cytometry will be performed with fresh whole blood and with intestinal mucosal cells (IEL and *lamina propria* cells). Blood flow cytometry may be conducted on isolated peripheral blood mononuclear cells and/or directly in whole blood. Flow cytometry will be used to describe the phenotype of blood (including NK cells) and intestinal cells, including markers relevant to the enumeration (e.g., CD3, CD103) and function (e.g., NKG2D) of aberrant IELs.

Immunohistochemistry (IHC) will be performed in biopsy tissue to assess markers on IELs (e.g., NKG2D) and epithelial cells.

Biomarkers of IL-15 biology may also be analyzed in fresh biopsies, if available at sites with the relevant experimental capabilities.

In addition, other exploratory biomarkers may be analyzed at a later time in stored samples, including serum (for proteins, RNA), blood cell pellet (for future biomarkers using gene expression profiling and possibly lymphoma mutational analysis), biopsy fragments (for mRNA, protein, and possibly lymphoma mutational analysis), stool (gluten, microbiome), urine (gluten, metabolites). Future biomarker analysis will solely be for the purpose of celiac disease or AMG 714 research and will be reported separately and not in the clinical study report. The sample retention timelines will be described in the informed consent.

The DNA sample for HLA testing at screening, in subjects without pre-existing available HLA typing information, will be used solely for that purpose and will be destroyed after the result is obtained.

Blood samples for biomarkers must be obtained PRIOR to study drug administration at each time point listed in the schedule of events (Table 1). The time and date of sampling must be carefully recorded and reported in the eCRFs.

Select safety biomarkers will be evaluated as well as exploratory indicators of possible clinical efficacy, such as BMI (derived from the weight measures at every visit), serum albumin (patient with albumin being provided exogenously will be excluded from this analysis), hemoglobin, hematocrit.

14.6. IMMUNOGENICITY

A two tiered immunogenicity testing approach will be used in order to determine if a sample contains ADAs. Samples will be initially tested in an immunoassay (ELISA). Samples that test positive for binding antibodies will then be tested in a bioassay (CTLL-2 cell line that responds to recombinant human IL-15), to detect neutralizing antibodies (NAb).

The sensitivity of the ELISA assay is approximately 20 ng/mL and the lower limit of reliable detection (LLRD), even in the presence of serum levels of drug, is approximately 250 ng/mL. The LLRD of the bioassay is approximately 1.5 µg/mL.

In addition to these existing validated methods, the sponsor will develop and validate a bridging immunoassay (for binding ADA) and a target binding method (for neutralizing ADA) in the Meso Scale Discovery (MSD) platform to potentially improve performance. The final method chosen will be described in the study manual and regulatory submissions

14.7 CELIAC DISEASE PATIENT REPORTED OUTCOME (CED PRO)

Subjects will be asked to maintain a daily e-diary for the CeD PRO instrument (Appendix K) at times indicated on the Schedule of Events (Table 1). This questionnaire was developed to assess symptom severity in clinical trials in subjects with celiac disease.

Items in the questionnaire were formulated based on one-on-one interviews with patients with celiac disease, thus they reflect the symptoms that patients consider part of their celiac disease experience. The questionnaire is designed as a self-administered daily diary, to be completed at the same time each day, and requires less than 10 minutes to complete. It includes 9-items asking participants about the severity of celiac disease symptoms they may experience each day. Participants are asked to rate their symptom severity on an 11-point, 0 to 10 scale; from "not experiencing the symptom" to "the worst possible symptom experience". Symptoms include abdominal cramping, abdominal pain, bloating, gas, diarrhea, loose stool, nausea, headache and tiredness.

15 SAFETY ASSESSMENTS

In addition to AE monitoring (Section 21), the procedures listed in this section of the protocol must be performed at the required time points to monitor subject safety during the study.

In addition to the investigators and the Sponsor, an independent Data Safety Monitoring Board (DSMB) will monitor safety (Section 22.10).

The conduct of imaging tests is acceptable if required to evaluate the status of the lymphoma at any time during the conduct of the study, including during screening for the purpose of assessing eligibility criteria (e.g., exclusion of EATL, which requires the use of the site's standard imaging techniques). These tests may include enteroscopy (videocapsule and double balloon enteroscopy), entero CT scan, MRI (for size of mesenteric lymph nodes; thickness of bowel wall) and ^{18}FDG-PETscan. The nature of the test and the results will be captured in the eCRF.

15.1 VITAL SIGNS

The Investigator or qualified designee will obtain vital signs including temperature, blood pressure (sitting), pulse rate, and respiratory rate at screening and all study visits. BMI and BSA will be obtained from measurements of body weight and height. The calculation for BSA will be outlined in the study SAP.

15.2 PHYSICAL EXAM

The Investigator or qualified designee will perform a complete physical exam at times indicated on the Schedule of Events (Table 1). The physical exam should include at a minimum the assessment of general appearance, HEENT, lymph nodes, respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system (including extremities), neurological, psychological and dermatological systems.

15.3 CLINICAL LABORATORY RESULTS

Laboratory parameters, as listed in Appendix B and the Central Laboratory Manual or equivalent document, will be obtained at times indicated on the Study Schedule of Study Procedures (Table 1). Blood and urine samples collected at the Screening Visit will require a minimum 8-hour fast.

A subject with a clinically significant laboratory finding identified at the Screening Visit should not participate in the study.

All clinically significant findings during the study should be followed until resolution or until the finding is clinically stable. Subjects may be withdrawn from the study if the Investigator or Sponsor deems the clinically significant finding compromising to the subject's safety.

Detailed information regarding the collection and handling of clinical laboratory specimens, including blood draw totals for each visit and instructions for re-testing of missing or compromised specimens, can be found in a separate Central Laboratory Manual or equivalent document supplied by the central clinical laboratory.

15.3.1 Pregnancy Testing

All females of child bearing potential (FOCBP) will have urine or serum pregnancy tests throughout the study as outlined in Schedule of Study Procedures (Table 1). Subjects who become pregnant during the study will be withdrawn from participation and the outcome of the pregnancy followed.

16 CENTRAL LABORATORIES

Detailed information about local and central laboratory activities will be provided in a separate Central Laboratory Manual or equivalent document.

17 LIFESTYLE AND DIETARY RESTRICTIONS

Subjects must adhere to the following lifestyle and dietary restrictions:

- Subjects must maintain a diet totally free of gluten.
- Subjects must be willing to return for all scheduled study visits and complete required study diaries
- Subjects must refrain from illicit drug use and alcohol abuse throughout the duration of the study.

18 INVESTIGATIONAL PRODUCTS

18.1 DESCRIPTION OF INVESTIGATIONAL PRODUCT

AMG 714 is a sterile solution for IV infusion will be administered at the study site by a qualified staff member in a double-blind fashion, via a 120 minute IV infusion a total of 7 times for a maximum of 10 weeks.

Active clinical supply will be provided in glass vials as a frozen, clear, sterile protein solution, with a light yellow color. Prolonged exposure to light should be avoided.

The characteristics and properties of AMG 714 as well as the exact volume and concentration of the supplied vials will be described in the Investigator's Brochure (IB), Investigational Product Manual, or equivalent document. The vials are intended for single-dose use only.

18.2 PLACEBO

Placebo will be administered at the study site by a qualified staff member in a double-blind fashion via a 120 minute IV infusion a total of 7 times for a maximum of 10 weeks (+/- 3 days).

Placebo clinical supply will be provided in glass vials as a frozen, clear, colorless, sterile protein-free solution. Sufficient volume will be provided to match the active drug volume to preserve the blind. The vials are intended for single-dose use only.

18.3 DOSE RATIONALE

The selection of dosing level for the CELIM-RCD-002 study is based on a desire to strike the appropriate benefit/risk balance, striving for efficacy by testing an adequately high dose of AMG 714 in an attempt to quickly alleviate the presumed effects of IL-15 on aberrant IELs and on RCD-II symptoms while using a dose that is similar to doses used in prior studies with tolerability comparable to placebo. The highest clinical dose of AMG 714 used chronically IV has been 8 mg/kg IV single dose followed by 4 mg/kg IV q2w for 8 weeks. The proposed dose of 8 mg/kg IV for 10 weeks, q2w with an extra dose at week 1, is modestly higher in order to account for the presumed protein-losing enteropathy typical of RCD-II (up to 40% protein loss can be expected based on albumin levels in RCD-II patients) and for the larger target organ area (small bowel as compared to more localized joints).

While exposure data at relevant IV doses are only available in healthy volunteers, the high bioavailability of 86.6% observed in healthy volunteers and the expected protein-losing enteropathy in RCD-II suggest that it is unlikely RCD-II patients will present with meaningfully higher exposures than those studied in healthy volunteers.

Human studies to date, as well as modeling, support the dosing regimen of an IV infusion of 8 mg/kg AMG 714 a total of 7 times over 10 weeks, over 120 minutes. The highest doses of AMG 714 studied in clinical trials are a single SC dose of 700 mg, SC doses of 300 mg every two weeks for 12 weeks, and the aforementioned 8 mg/kg IV single dose followed by 4 mg/kg q2w for 8 weeks, all regimens with no safety signals identified to date. In addition, the proposed study regimen has adequate safety margins based on toxicology. [redacted]

The expected ranges provided by the dosing regimen are not only presumed to be tolerable, but also expected to be efficacious based on available mechanistic data. While there is no clinical experience with AMG 714 in RCD-II nor any understanding of the potential PK/PD relationships in this disease, incubation of duodenal biopsies from RCD-II patients with 10 µg/mL of AMG 714 for 48 hours effectively inhibited endogenous activation of JAK3 and STAT5 (Malamut *et al*, 2010). Serum concentrations in this study are predicted to always exceed 59 µg/mL, and following a dose at 1 week to exceed 96 µg/mL, even after accounting for possible leakage of protein in the intestine. Even if local mucosal tissue levels were lower

than serum levels, these serum values are several times higher than the 10 µg/mL concentrations that were effective in the *ex-vivo* setting, and provide a reasonable expectation that the tissue levels achieved will be efficacious.

Serum exposure will be monitored with frequent PK sampling and with an unblinded interim analysis to be conducted by the DSMB, when the tenth patient reaches Week 4. Tissue effects will be monitored with experimental biomarkers to be measured in the biopsies to be obtained in the study.

18.4 BLINDING

This is a double-blind, placebo-controlled study. To maintain blinding, an assigned unblinded study staff member will be required to receive and prepare the study drug at each site. Due to the difference in appearance between active study drug and placebo, only the unblinded study staff member should prepare the study medication for dosing.

18.5 UNBLINDING

If there is a need to unblind a subject's treatment assignment for emergency medical management, the Investigator will contact the Medical Monitor. The Medical Monitor, in consultation with Sponsor, will make a decision to unblind. If the decision has been made to unblind, a prompt written or electronic notification will be provided to the Investigator.

If reporting of an AE is to be performed unblinded as per any regulatory authority's guidelines, study-unrelated Sponsor personnel will unblind the individual subject's treatment group and will perform the unblinded reporting. No treatment group information would be shared with blinded study personnel.

18.6 RANDOMIZATION AND TREATMENT ASSIGNMENT

Subjects will be randomized at a 2:1 allocation ratio to receive AMG 714 8 mg/kg or placebo a total of 7 times over 10 weeks. The randomization will not be stratified as type II RCD is rare and the number of subjects in the study is small. For dosing times see the study Schedule of Events (Table 1).

The unblinded pharmacist, or unblinded study staff designee, will be responsible for dispensing the study medication according to the treatment assignment provided by EDC.

18.7 DRUG SUPPLIES, DISPENSING, STORAGE AND ACCOUNTING

In addition to the information contained in this section of the study protocol, detailed information regarding the study drug will be provided in a separate IB, Investigational Product Manual, or equivalent document.

18.7.1 Packaging and Formulation

AMG 714 will be manufactured and packaged by Amgen and distributed using the Sponsor or Sponsor representative's clinical study drug distribution procedures.

Active clinical supply will be provided in glass vials as a frozen, clear, sterile protein solution, with a light yellow color. The vials supplied are for single-dose use only. Volume and concentration will be provided in the IB, Investigational Product Manual, or equivalent document.

18.7.2 Storage

AMG 714 must be stored in a secured -30°C+/-10°C freezer, protected from light in its original packaging. Prolonged exposure to light should be avoided.

Efforts should be made to ensure that the preparation procedures and conditions are consistent.

Records of the actual storage conditions for AMG 714 and placebo during the period of the study must be maintained and recorded (e.g., daily and continuous freezer temperatures, date, time, and initials of person checking). A temperature alarm should be maintained and be used to alert site personnel of significant changes in freezer temperature. Study site staff must notify the Sponsor immediately if any clinical supply is exposed to excessive or uncontrolled temperatures so that possible replacement clinical supplies can be provided if necessary.

18.7.3 Preparation and Administration

The unblinded study staff member responsible for receiving and preparing the study medication must obtain the treatment assignment via the EDC system a minimum of 24 hours prior to the scheduled randomization visit (Visit 1; Week 0/Day 0). This will allow for proper thawing and preparation of the study drug. Each subsequent visit should be documented in the EDC system in order to assure proper drug accountability.

On the day before investigational product administration, AMG 714 must thaw overnight at 2 to 8° C. Vials must continue to be protected from light during the thawing process. Once thawed, vials should be transferred to room temperature and gently swirled to ensure mixing. Avoid vigorous shaking or vortexing. Mixing may result in the formation of small bubbles, which is normal. Preparation of the clinical supplies should be performed using aseptic techniques, under sterile conditions. Prolonged exposure to light should be avoided.

Please note that certain routine supplies and equipment will be provided by the study site, including but not limited to:

1) IV bags (5% dextrose)
2) Infusion pump
3) IV line

The investigational product must be diluted using the following instructions:

1) Withdraw the volume of the thawed investigational product needed for the weight of the patient (8 mg per kg, calculating the volume needed given the concentration of investigational product of 100 mg/ml) and inject this volume directly into a 100 mL 5% dextrose IV bag using the injection port at the base of the bag.

2) Gently inverse the IV bag a couple of times to ensure mixing and also ensure that there are no air bubbles remaining in the injection port.

After thawing, the product may be stored for up to 72 hours at 5 ± 3°C, and no longer than 12 hours at room temperature. The prepared product (i.e., the diluted product in the IV bag) should be used immediately, and can be kept for a maximum of 12 hours at room temperature, including the administration time of 2 hours.

All prepared IV bags must be labeled prior to administration with the following information:

- Study number
- Subject identification number (001-###-###)
- Date and time of preparation
- Initials of pharmacist
- Initials of subject (if permitted by regulations)

Once mixed with the investigational product prepared IV bags will not differ in color from the IV bags containing placebo. The product must continue to be protected from light using either foil or other light protective material.

An experienced and qualified blinded study staff member must perform the placement of the IV catheter and subsequent IV administration.

On any given day, if more than one subject is scheduled to receive study drug administration at the same research facility (which can only happen after the 10th patient has been dosed, see Section 7), each dose administration must be given at least 15 minutes apart.

18.7.4 Supply and Return of Drug

At study initiation, and as needed thereafter, AMG 714 will be shipped to the assigned unblinded pharmacist or unblinded study staff member at the Investigator's institution. To maintain blinding only the assigned unblinded pharmacist or unblinded study staff member should check the amount and condition of the drug and enter these data into the drug accountability form or equivalent document. At the end of the study, or as directed by the Sponsor, all unused investigational product will be destroyed or returned. Used vials of study drug may be destroyed on site at the time of study drug preparation with preapproval from the study sponsor. Please reference the Investigational Product Manual for additional information regarding study drug destruction and return.

18.7.5 Investigational Product Accountability

An Investigational Product Accountability Record for AMG 714 must be kept current and should contain:

- The dates and quantities of investigational product received
- Manufacturing batch numbers for product received
- Subject's identification
- Date and quantity of investigational product dispensed
- The initials of the dispenser
- Dose preparation records
- Date and quantity of drug destroyed

At the end of the study, the Final Investigational Product Disposition Statement must be completed and provided to the Sponsor.

18.8 TREATMENT OF INVESTIGATIONAL PRODUCT OVERDOSE

There is no information available on the effects of an overdose of AMG 714. Given the known safety profile, no specific recommendations can be issued at this time and Investigators shall use clinical judgment to treat this potential event.

19 STOPPING CRITERIA

19.1 INTERRUPTION OF DOSING IN AN INDIVIDUAL SUBJECT

Due to the current safety profile, no specific stopping rules have been identified for individual subjects. Investigators will exercise clinical judgment to assess whether an adverse event merits discontinuation of dosing in any given subject.

Dose escalation or reduction is not allowed.

19.2 INTERRUPTION OF DOSING FOR ALL SUBJECTS IN THE ENTIRE TRIAL

If any of the following occur:

- Death of any subject
- Anaphylactic reaction in any subject
- A life-threatening adverse event in any subject

The Sponsor will ask the DSMB to review the case. The committee and Sponsor will determine if a study wide interruption in dosing is required.

20 SUBJECT COMPLETION AND WITHDRAWAL

20.1 SUBJECT COMPLETION

Subjects will be considered study completers at Visit 8 (Week 12/Day 84), regardless of whether or not the Final Study Visit (Visit 9; Week 16/Day 112) is attended.

Randomized subjects who withdraw and are not lost to follow-up will complete the study at the ET Visit.

Randomized subjects who withdraw and are considered to be lost to follow-up will complete the study at the last attended visit.

20.2 SUBJECT WITHDRAWAL

All subjects are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, without prejudice.

Reasons for withdrawal (subjects refuse to return for any remaining study visits) or discontinuation (subjects who prematurely stop the active treatment) at any time during the study may include but are not limited to the following:

- Safety reasons, either at the discretion of the Investigator or at the subject's request. In particular, subjects will be discontinued from the study if they develop severe complications of celiac disease that require intensive treatment (EATL, perforation, etc.).
- Protocol violations at the discretion of the Sponsor.
- Subject noncompliance to study procedures or schedule
- Concomitant therapy that could interfere with the results of the study (the Investigator will report all such information on the eCRFs and decide, in accordance with the Sponsor, whether the subject is to be withdrawn).
- Subject's decision to withdraw at any time.

Subjects who withdraw prior to receiving the study drug are considered screen failures.

20.2.1 Withdrawal Procedures

If for any reason a subject is withdrawn or discontinues before completing the final visit, the reason for termination must be recorded in the source documents and reported on the appropriate eCRF. All data gathered on the subject prior to termination will be made available to the Sponsor.

Subjects discontinuing study drug should continue to be fully evaluated per the protocol event schedule, when possible, for safety purposes. However, if the subject discontinues before

Week 6, the second biopsy will not be collected. If a discontinuation occurs on or after Week 6, the second biopsy will be obtained.

21 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

21.1 REPORTING RESPONSIBILITY

The Investigator and study staff are responsible for detecting and recording AEs and SAEs, during scheduled safety evaluations and whenever such information is brought to their attention. This section of the protocol provides definitions and detailed procedures to be followed.

During each visit, the Investigator or qualified designee will assess adverse events using an open question that does not to influence the subject's answers, e.g., "have you noticed any change in your health?"

All AEs occurring after signing of the Informed Consent, and at or before the final visit must be reported regardless of suspected relationship to study drug.

All AEs will be evaluated by the Investigator and intensity (severity) and relationships to study drug will be assessed and recorded.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits as necessary. If these have resolved, the resolution date should be documented. Changes in intensity or frequency of AEs should be recorded as separate events (i.e., a new record started).

AEs and SAEs in possible subjects traveling to study sites from countries other than the study site country will be assessed and managed in the same fashion as those appearing in subjects from the study site countries.

21.2 DEFINITION OF AN AE

An AE is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness) that occurs in a study subject, following the signing of informed consent, regardless of the suspected cause. Only subjects who have been exposed to study drug (active drug or placebo) can experience treatment emergent AEs. Untoward experiences occurring prior to initiation of first administration of study drug are considered non-treatment emergent AEs.

21.3 SEVERITY

The term of severity is used to describe the intensity of a specific event. The event itself, however, may be of minor medical significance. This is not the same as serious, which is based

on outcome of the event. Seriousness, not intensity, serves as a guide for defining regulatory reporting obligations.

For all AEs, severity will be recorded in the source documents and reported on the appropriate AE eCRF page. There are 3 levels of severity, defined as follows:

Mild: Noticeable, but does not disrupt normal daily activity

Moderate: Sufficient to reduce or disturb normal daily activity

Severe: Incapacitating, significantly interferes with or prevents normal daily activity

21.4 RELATIONSHIP

For all AEs, relationship to study drug will be recorded in the source documents and reported on the appropriate AE eCRF page. The Investigator must judge whether the study drug caused or contributed to the AE, and report it as either:

- Related (definitely, possibly or probably): when there is a reasonable possibility that the study drug caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for a determination of related:

  a) There is a plausible time sequence between onset of the AE and study drug administration;

  b) There is a plausible biological mechanism through which study drug may have caused or contributed to the AE;

or

- Not related: when it is highly unlikely or impossible that the study drug caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for a determination of not related:

  a) Another cause of the AE is evident and most plausible;

  b) The temporal sequence is inconsistent between the onset of the AE and study drug administration;

  c) A causal relationship is considered biologically implausible.

21.5 SERIOUS ADVERSE EVENTS

An AE is serious if:

- it was fatal (i.e., the AE caused or led to death)
- it was life threatening (i.e., the AE placed the subject at immediate risk of death; an AE that hypothetically might have caused death if it were more severe is not an SAE by this criterion)
- it required or prolonged hospitalization (i.e., the AE resulted in a minimum 24 hour hospitalization or prolonged a hospitalization beyond the expected length of stay; hospital admissions for elective medical/surgical procedures, or scheduled treatments are not SAEs by this criterion)
- it resulted in permanent or significant disability/incapacity (i.e., the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions)
- it resulted in a congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the study drug prior to conception or during pregnancy)
- it required significant medical or surgical intervention to prevent permanent impairment or damage (e.g., hypotension requiring pressers to prevent ischemia, replacement of broken or malfunctioning device).

21.6 SPECIAL REPORTING SITUATIONS

21.6.1 Death

Death is an outcome of an event. The AE that resulted in the death should be recorded and reported as the SAE. If an autopsy is performed, efforts should be made to obtain the results.

21.6.2 Hospitalizations for Surgical or Diagnostic Procedures

The AE leading to the surgical or diagnostic procedure should be recorded and reported as the SAE. The procedure should be reported as an action in response to or treatment for the medical condition.

21.6.3 Pregnancy

Any pregnancy that occurs during the study or within 6 months of the last dose of study drug should be recorded on a Pregnancy Report Form to facilitate outcome follow-up. Pregnancy should be reported whether occurring in a female subject or the partner of a male subject. Spontaneous abortion should be reported as an SAE.

Regardless of subject sex, the Investigator should counsel the subject (and partner, if appropriate) regarding possible effects on the fetus and risks of continuing with the pregnancy. Monitoring should continue until conclusion of the pregnancy.

21.6.4 Inadvertent Exposure or Overdose

Any inadvertent exposure or overdose of study medication should be recorded in the source documents and reported immediately to the Sponsor by phone and email. The exposure and any AEs should be reported of the appropriate eCRF forms.

21.6.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs shall be reported by the Sponsor to the regulatory authorities as applicable and to the relevant ethics committee to fulfill EU regulations ("Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use").

Expedited reporting is required electronically to the regulatory authority and EudraVigilance database as soon as possible, however no later than within seven (7) days of the Sponsor being informed of fatal or life-threatening adverse reaction.

Serious unexpected adverse reactions which are not life-threatening or fatal must be reported to the regulatory authority and EudraVigilance database as soon as possible and in any case within fifteen (15) days of the sponsor first being informed.

Once a year, the Sponsor shall provide a list of all suspected serious adverse reactions which have occurred during the period in question (Annual Safety Report) to regulatory authorities as applicable or required.

21.7 PROCEDURES FOR REPORTING ADVERSE EVENTS

Adverse events occurring after the subject has signed informed consent will be reported in the source documents and recorded on the appropriate AE eCRF pages.

It is not necessary to complete an AE eCRF page for chronic medical conditions present at enrollment that remain stable during the trial. However, if a medical condition present at enrollment worsens in intensity or frequency, it should be reported as an AE. It is not necessary to complete an AE eCRF for fluctuations in the disease under study if: these fluctuations are adequately captured by the efficacy assessments, and the degree of variation in frequency or severity is typical of the disease under study. An AE eCRF must be completed if the disease course is atypical or there is development of new signs or symptoms related to the disease under study.

Investigators should observe the following guidelines when recording AEs on the AE eCRF pages: use recognized medical terms; do not use jargon, colloquialisms or abbreviations; record a diagnosis (i.e., disease or syndrome) rather than component signs and symptoms (e.g., migraine rather than headache, nausea, transient visual loss); if a diagnosis is not feasible, record component signs and symptoms; AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause.

21.8 PROCEDURES FOR REPORTING SERIOUS ADVERSE EVENTS

SAEs and other specified special reporting situations require expedited reporting to the Sponsor regardless of relationship to study drug. **The Investigator must report all SAEs to sponsor by phone AND by email as soon as possible but within no longer than 24 hours of observing or learning of the event.** The initial SAE report should include all case details that can be gathered within 24 hours of the event. Additional SAE pages may be submitted later as the case evolves or additional information becomes available.

The SAE should be reported immediately to Sponsor at:

+1 301 798 4988

Or

+40 723 676 900

The completed SAE Report should be emailed immediately to the sponsor at:

Email: GlobalSAEInbox@chiltern.com

Additional relevant information or clinical follow-up should be emailed to the same contact as soon as it becomes available.

21.9 FOLLOW-UP FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All AEs will be followed until resolution or until the subject's participation in the study ends. However, SAEs and non-serious AEs assessed by the PI and the medical monitor as related to AMG 714 will be followed until resolution or until the PI and the medical monitor assess them as "chronic" or "stable," even if this requires extending follow-up beyond the usual duration of study participation. The Sponsor should be contacted regarding subjects who require follow up beyond the usual study duration.

AE and SAE care and follow-up will be similar for subjects traveling to the study site from countries other than the study site country.

21.10 SAFETY REVIEW COMMITTEE

Safety will be monitored throughout the study by the Sponsor and by a panel of independent experts, the DSMB. The DSMB is enabled and is expected to review any or all available study data on an ongoing basis in an unblinded fashion, as deemed appropriate for protection of subject safety. The DSMB will be formed before the start of study enrollment. The members of the DSMB will not be members of the AMG 714 study team, and will include at least one physician and one statistician.

If any of the stopping rules are met, an ad-hoc meeting of the DSMB will occur to assess the adverse events or findings. Safety findings will be reported to the investigators, the IRBs/IECs, and any other appropriate regulatory authorities.

After determination of the cause and significance of safety events, the DSMB is empowered to recommend continuing enrollment, pausing of enrollment, ceasing dosing, changing the protocol and study assessments to enhance subject safety, or terminating the study, as appropriate. If the investigation indicates with a high probability that the observed safety event was due to an identifiable cause other than the study drug, the DSMB may recommend continuation of study enrollment.

A separate DSMB Charter, finalized prior to the first DSMB meeting, outlines the specific guidelines for all DSMB activities. DSMB decisions will be communicated to the Investigators by the clinical study team.

22 DATA ANALYSIS AND STATISTICS

In addition to this section of the study protocol, a statistical analysis plan (SAP) and a PK analysis plan will be developed and finalized prior to the final database lock and unblinded data analysis. The SAP will provide a detailed description for the handling of missing data, subject eligibility criteria for the analysis, and statistical methodology for the data summary and between-group comparisons.

In addition to the main analyses, pre-specified subgroup analyses may include:

- Previous treatment for RCD-II
- Dietary transgressions (gluten consumption) based on serial iVYLISA GIP testing and on the dietitian's assessment
- Sex
- Duration of disease
- Age of onset
- Site

Non-evaluable subjects will include subjects missing one of the two biopsies and subjects dropping out of the study before Week 6. If a discontinuation occurs on or after Week 6 the subject is considered evaluable. The non-evaluable subjects will be excluded from the PP population.

The primary analyses will be based on the PP population. The PPpopulation is defined in Section 22.2.

22.1 SAMPLE SIZE DETERMINATION

The CELIM-RCD-002 study is an exploratory proof-of-concept (POC) study of an experimental medication, AMG 714, in RCD-II patients. While it will be the first such study sponsored by a pharmaceutical company, the straightforward design is based on several academic studies (Goerres *et al*, 2003; Brar *et al*, 2007; Tack *et al*, 2011a, 2011b) as well as on the nonclinical proof-of-principle signal obtained with AMG 714 in intestinal explants from patients with RCD-II (Malamut *et al*, 2010).

The sample size is based on the size of previous academic studies. Published prospective academic studies have ranged from 13 to 18 patients total (Tack *et al*, 2011a, 2011b) and CELIM-RCD-002 will be the largest prospective trial ever conducted in RCD-II, a very rare malignant disease.

The sample size of approximately 24 subjects (16 subjects in AMG 714 arm and 8 subjects in placebo arm) has been calculated to achieve at least ~ 80% power to detect a 20 percentage point difference in the primary endpoint, the difference in the baseline-to-Week 12 reduction of % aberrant IELs vs total IELs between the AMG 714 arm and placebo arm.

This sample size calculation was based on the following assumptions:

- Two-sided type one error rate $\alpha = 0.1$
- Power $1-\beta = 0.8$
- Analysis method: one-way ANOVA by SAS® (proc power)
- 2:1 allocation ratio between the AMG 714 and placebo arms
- Common SD = 17.4 for the baseline to Week 12 reduction in % aberrant IELs as assessed by low-cytometry
- Mean change of 20 percentage points and 0 percentage points in the baseline to Week 12 reduction in % aberrant IELs in the AMG 714 and placebo arms, respectively
- No drop-outs accounted (efforts will be made to replace drop-outs before Week 6 and/or subjects who do not provide the second biopsy)

The standard deviation used for the sample size calculation is computed from the % aberrant IEL (obtained by flow cytometry) data from 13 subjects treated with cladribine (subset of the patients reported in Tack et al, 2011).

22.2 POPULATIONS FOR ANALYSIS

The populations for analysis will be intention to treat (ITT, safety population who at least received one dose of investigational product) and the per protocol population (PP, efficacy, i.e., available and evaluable pre- and post-biopsy information).

PP Population: The PP population will exclude non-evaluable subjects and subjects with major protocol deviations thought to impact the ability to assess the effect of treatment. Exclusion of subjects from the PP set will be reviewed, documented and approved before the study is unblinded to the study Sponsor. The criteria for excluding subjects from the PP population will be specified in the SAP.

ITT (Safety) Population: This population consists of all randomized subjects who have received at least one dose of the study drug. Subjects will be analyzed in the treatment group they were randomized to. Subjects with only one measurement available will be excluded from the ITT population for all endpoints defined as change from baseline. The safety population is by definition the same as the ITT population.

Main efficacy measures which require pre- and post-treatment biopsies will be based on the PP population (at least 2 biopsies, the second at least on Week 6 or later). Continuous variables will be analyzed based on the ITT population. Demographics and safety parameters will be analyzed using the ITT population.

22.3 MISSING DATA

Subjects withdrawing from study drug administration before Week 6 will be excluded from the PP analysis and the second biopsy will not be collected. Subjects withdrawing on or after Week 6 will be included and the second biopsy will be collected. Missing data after Week 6 will be imputed and the imputation rules will be described in the SAP.

No other data imputation will be done.

22.4 STATISTICAL ANALYSES

22.4.1 Subject Disposition

The number of subjects randomized, completed, or discontinued from the study and the reason for study discontinuation will be tabulated by treatment group as appropriate. Subject count by analysis population will be tabulated.

22.4.2 Protocol Deviations

Major protocol deviations will be summarized by treatment group. Subjects with major protocol deviations affecting the efficacy evaluation will be excluded from the PP population.

22.4.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and will be based on the ITT population, except for baseline variables based on biopsy data where the PP population may be appropriate in addition to ITT.

22.5 EFFICACY ANALYSES

22.5.1 PRIMARY ENDPOINT

The primary endpoint is the Immunological Response 1: reduction at Week 12 in % aberrant IELs vs total IEL as assessed by flow-cytometry between the AMG 714 and placebo arms.

The primary endpoint will be tested as follows:

$$H_0: \mu_{AMG\ 714} = \mu_{placebo}$$

against the alternative

$$H_1: \mu_{AMG\ 714} \neq \mu_{placebo}$$

where $\mu_{AMG\ 714}$ and $\mu_{placebo}$denote the mean baseline to Week 12 reduction in % aberrant IELs vs total IELs as assessed by flow-cytometry in the AMG 714 and placebo arm respectively. The hypotheses will be tested using a two-sided type 1 error level of 10%.

The primary endpoint will be analyzed using analysis of covariance (ANCOVA) based on the per protocol population (PP), where baseline % aberrant IEL will be included as a covariate and treatment group as a fixed effect in the statistical model. The analysis will also include the percentage of patients with normalization of IEL counts by flow cytometry (aberrant IELs < 20% of total IEL).

22.6 SECONDARY ENDPOINTS

Secondary endpoints will be described in the SAP and will include:

- Immunological Response 2: Reduction from baseline in the % of aberrant IELs vs intestinal epithelial cells
- Histological Response: improvement from baseline in small intestinal VH:CD ratio score, Marsh score and total IEL counts
    - VH:CD ratio by validated morphometry. Includes the % of patients with histological remission (VH:CD > 2).
    - Marsh-Oberhuber classes, Marsh 0, 1, 2, 3a-c. Grouping by converting the morphometric results into Marsh classes (Mäki-Jilab converter). Includes the % of patients with histological remission (Marsh 0-1).
    - IEL: for mucosal inflammation the density of IELs/100 epithelial cells will be calculated. The analysis will also include the percentage of patients with normalization of IEL counts vs. epithelial cells (% IELs <50%).

- Clinical response: change from baseline in symptoms,
    - BSFS and number bowel movements by day and week
    - GSRS and CeD-GSRS, by week

In gemeral, efficacy measures which require pre- and post-treatment biopsies will be based on the PP population (at least 2 biopsies, the second at least on Week 6 or later). Continuous variables will be analyzed based on the ITT population.

Change from baseline of Immunological Response 2, VH:CD and of total IEL counts will be analyzed using the same method as for the primary endpoint.

The Marsh scores will be analyzed using a multinomial logistic regression model, where treatment group, baseline Marsh score, and a treatment group-by-baseline Marsh score interaction term will be included in the model.

The secondary variable BSFS will be analyzed by calculating daily and weekly number and type of bowel movements. The bowel movement counts will be analyzed using generalized linear mixed models with subject as random effect. The statistical model will also include treatment group, time (week) and their interaction. The change in the weekly BSFS scores will mainly be assessed with descriptive statistics, where change from the 'normal (mid-scale)' will be explored. The GSRS and the CeD-GSRS will be analyzed using a linear mixed effects repeated measures model (MMRM) with the baseline value, treatment group, time point and a time point-by-treatment group interaction term as fixed effects with an underlying correlation structure between the time points that results in the best fit for the model. Subject will be included as a random effect.

22.7 EXPLORATORY ENDPOINTS

Exploratory endpoints will be described in the SAP and will include:

- Reduction in aberrant and abnormal IELs by flow cytometry, immunohistochemistry and TcR clonality analyses (including % patients with normalization in IELs)
- PGA and PtGA
- Quality of Life Assessments:
    - SF-12 v. 2
    - EQ-5D
- Biomarkers of disease activity
- PK, PD, and PK/PD correlations
- CeD PRO

The exploratory variables will be tabulated by treatment group and time point (if feasible) using the ITT or PP populations as appropriate.

The exploratory variable CeD PRO will be analyzed using the same method as for the GSRS and CeD-GSRS.

Pharmacokinetics of AMG 714 in RCD-II patients will also be characterized using nonlinear mixed-effects modeling, including evaluation of effects of major covariates (e.g., weight or BMI, BSA, sex, biochemical parameters and disease characteristics at baseline) on AMG 714 exposure.

For PK/PD correlations, individual patients' exposure measures obtained from the PK analysis will be graphically assessed with select PD endpoints and if associations are observed will be further elucidated with modeling and/or summaries by quartiles of exposure.

Exploratory exposure-response analysis will be performed for efficacy, safety, and biomarker measures. These exploratory analyses will be assessed with appropriate descriptive statistics and graphical displays.

Change from baseline (by time point) will also be presented for reduction in aberrant IELs by immunochemistry and TcR clonality analyses, PGA and quality of life assessments (SF-12 v. 2 and EQ-5D).

22.8 SAFETY ANALYSES

22.8.1 Adverse Events

All AEs will be coded using MedDRA. The AEs will be summarized by system organ class (SOC), preferred term and separately by causality and severity.

22.8.2 Other Safety Assessments

The following safety parameters will be assessed:

- Clinical laboratory tests
- Physical examination
- Vital signs

All safety variables will be summarized by treatment group. Some of these variables will be tabulated by treatment and by visit.

For the assessment of immunogenicity, the number and percent of subjects who developed binding antibodies and who developed neutralizing antibodies will be determined.

In addition to the abovementioned safety assessments, all females will have urine or serum pregnancy tests throughout the study.

All safety variables will be tabulated by treatment group and time point (if feasible) using the ITT population.

22.8.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD).

23 INTERIM ANALYSIS

An interim analysis for safety and PK will be done when the tenth patient randomized reaches Visit 4 (Week 4/Day 28; subjects not replaced if dropped out). The interim analysis, to be pre-specified in the DSMB charter, will be unblinded and conducted by an independent DSMB, which will also monitor unblinded safety data throughout the study. In addition to safety (including immunogenicity data if available) and PK, any other information available at the time of the analysis will be considered and a recommendation to stop, continue or modify the study will be made by the DSMB to the Sponsor. The recommendation and decision will be shared with the clinical sites and ethics committees.

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APPENDIX A. ADMINISTRATIVE, ETHICAL AND REGULATORY POLICIES

Celimmune is the Sponsor responsible for the entire conduct of the study.

Study Initiation

The Investigator is responsible for supplying at a minimum all of the required regulatory documentation specified below to Celimmune or its designees prior to the start of the trial. The Investigator must complete all regulatory documentation as required by local and national regulations as appropriate; current signed and dated curricula vitae of the Investigator and all sub-investigators; complete financial disclosure forms for the Investigator and all sub-investigators, if required by local regulatory authorities; Human Research Ethics Committee (HREC)/Independent Ethics Committee (IEC) membership list and/or registration number by appropriate regulatory authority; written documentation of HREC/IEC approval of protocol; written documentation of the HREC/IEC approval of the informed consent document; a copy of the HREC/IEC-approved informed consent form (ICF); the ICF must be reviewed and approved by Celimmune or its designees as outline in the Section labeled 'Informed Consent' in Appendix A of this study protocol. Written documentation of HREC/IEC review and approval of any recruitment materials to be used for study recruitment, if applicable; any recruitment materials must be reviewed and approved by Celimmune or its designees prior to submission to the HREC/IEC; current laboratory certification and analyte normal ranges for any local laboratory performing analyses to be recorded in the clinical trial database; a signed Clinical Research Agreement; a signed and dated protocol acceptance form; qualified translations of approved informed consent document or other documents to be read or completed by subjects (when applicable). Any additional contents or essential regulatory documents required in the trial master file by regional or local regulatory authorities must be filed at the investigator and Sponsor sites before the start of the trial.

Informed Consent Form

An Informed Consent Form will be prepared and provided to Celimmune or its designees to review prior to HREC/IEC submission. The final HREC/IEC-approved informed ICF must be provided to Celimmune for filing.

The ICF must be signed and dated by the subject or the subject's legally authorized representative before participation in the study. A copy of the signed ICF must be provided to the subject or the subject's legally authorized representative. The source documentation and e CRFs will document for each subject that informed consent was obtained prior to participation in the study. The signed ICF must remain in each subject's study file and must be available for verification by study monitors at any time.

If necessary, informed consent will be obtained in the subject's primary language using a qualified translation of the ICF into that language.

Human Research Ethics Committee (HREC)/Independent Ethics Committee (IEC) Approval

This protocol, the ICF, any anticipated recruitment materials and relevant supporting information must be submitted to the HREC/IEC, by the Investigator or sponsor appointed designee, prior to study initiation. Investigator, or sponsor appointed designee, must obtain HREC/EC's written approval before being allowed to conduct and participate in the study.

The Investigator, or sponsor appointed designee, is responsible for keeping the HREC/IEC informed of amendments or changes to the protocol, and the progress of the study, as appropriate. Investigator is responsible for fulfilling any conditions of approval imposed by the HREC/IEC. The Investigatora, or sponsor appointed designee, is responsible for keeping the HREC/IEC informed of safety events. The Investigator, or sponsor appointed designee, must promptly forward to the HREC/IEC, as required, any written safety report or update provided by Celimmune (e.g., expedited safety report, IB safety amendment). The Investigator, or sponsor appointed designee, is are required to promptly notify the HREC/IEC, as required, of all AEs occurring at the site which are both serious and unexpected. This generally means SAEs that are not already identified in the IB or protocol, and that are considered related to the study drug by the Investigator. Some HREC/IECs may have additional safety reporting requirements to which Investigators are expected to adhere.

Case Report Forms

Electronic CRFs as well as access to an eCRF system (including user names a passwords) will be supplied by Celimmune or its designee.

Instructions for eCRF completion will be provided in a separate eCRF Completion Guideline or equivalent document.

The completed eCRF should be reviewed and the case book electronically signed, and dated by the Investigator. Instructions regarding e CRF completion should be followed by site personnel. Data recording, verification and corrections to eCRFs should be made according to the instructions.

Source documentation for subjects should be the physician/investigator's patient records, and as such, will be maintained at the study site. The information on the eCRFs must match the source documents.

Study Monitoring Requirements

All aspects of the study will be carefully and periodically monitored by Celimmune or its designee for conformance to protocol, and compliance to good clinical practices (GCPs), standard operating procedures (SOPs), and applicable government regulations.

One or more authorized representatives of the Celimmune will periodically inspect study data, subjects' medical records, and eCRFs in accordance with current US and European community GCPs (ICH E6).

The Investigator will permit authorized representatives of relevant national and local health authorities, as appropriate, to inspect facilities and records pertaining to this study.

Study Completion

The following data and materials are required before a study can be considered complete or terminated. This includes but is not limited to clinical data, laboratory test results and any special test results from Screening through the end of study for all enrolled subjects, eCRFs (including correction forms) properly completed by appropriate study personnel and signed and dated by the Investigator, complete drug accountability records; a summary of the study prepared by the Investigator, all regulatory documents (e.g., curriculum vitae for Investigator and sub investigators); a signed and dated protocol amendment acceptance form and HREC/IEC approval/notification (if applicable); updated financial disclosure forms for the Investigator and all sub-investigators (if required by local regulatory authorities).

Study Medication Accountability

All study drugs will be provided by Amgen, Inc. The Investigator, with the help of an unblinded pharmacist or unblinded study staff member, is responsible for ensuring adequate accountability of all used and unused study drug. This includes the acknowledgment of receipt of each shipment of study product (quantity and condition) and subject dispensing records. Damaged supplies will be replaced.

Accurate records of all study drug dispensed by the study site should be recorded on the appropriate form.

All drug supplies and associated documentation will be reviewed and verified by the study monitor.

Disclosure of data

Subject Confidentiality

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Data generated by this study must be available for inspection upon request by representatives of the Therapeutic Goods Administration (TGA), European Agency for the Evaluation of Medicinal Products (EMEA), FDA, other national or local health authorities, and the HREC/IEC, if appropriate.

With the subject's permission, medical information may be shared with his or her personal physician or with other medical personnel responsible for the subject's welfare.

If the data from this study are published, the presentation format will not include names, recognizable photos, personal information or other data which compromises the anonymity of participating subjects.

The PI is responsible for compliance with other federal, local or institutional legislation and regulations related to subject privacy and confidentiality.

Nondisclosure of Confidential Proprietary Information

All investigators have completed Non-Disclosure Agreements with Celimmune. Any confidential proprietary information, including but not limited to, information on the study design, IB, efficacy or AE data, study doses, or method of administration should be disclosed on a need to know basis for the sole purpose of conducting the study. If any

outside parties contact the study site regarding confidential information the study personnel are obligated to inform Investigator and Celimmune.

Retention of Records

Following the ICH E6 Guidance on GCP, the records and documents pertaining to this study must be retained by the Investigator for 2 years after approval of the last marketing application for the study drug in an ICH region and until there are no pending or contemplated marketing applications. If no application is filed, these records must be kept 2 years after discontinuation of the study and notification to appropriate regulatory authorities. Celimmune will notify the Investigator in writing of these events.

Records to be retained include, but are not limited to, consent forms, source documentation, laboratory test results, medication inventory records, and regulatory documents.

Quality Assurance

The e CRFs will be reviewed for completeness by a clinical monitor or other representative of Celimmune. Electronic Case Report Forms (eCRFs) will be used for data management and analysis. A clinical monitor will contact Investigator for corrections and/or clarifications of discrepant data. All data will be entered into a study database for analysis and reporting. A Clinical Monitoring and Data Management/Quality Plan that describes the quality checking to be performed on the data will be produced. Upon completion of data entry, the database will be checked to ensure acceptable accuracy and completeness.

Investigators and other individuals involved in study evaluations will be trained to perform the safety evaluations and activity measurements described in the protocol. Site staff will be trained on performance of study procedures. The training will be performed at an Investigator Meeting or Site Initiation Visit according to a written training plan.

Financing and Insurance Information

Financing and insurance issues are addressed in the ICF and in the site contracts.

Publication Policy

All data generated from this study are the property of Celimmune, and shall be held in strict confidence along with all information furnished by Celimmune. Independent analyses and/or publication of these data by the Investigator or any member of his/her staff are not permitted without the prior written consent of Celimmune.

Should the results of this study be published the draft of the publication and the lead authors will be determined by a Publication Committee.

Any formal presentation or publication of data from this trial will be considered as a joint publication by the Investigator(s) and appropriate Sponsor personnel. Authorship will be determined by mutual agreement. For multicenter studies it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol and not by individual Investigators. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full publication, unless formally agreed to in writing. Written permission to the Investigator will be contingent on the review by the Sponsor of the methodology and statistical analysis and any publication or

presentation will provide for nondisclosure of Celimmune confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties at least 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties. Authorship of the results of this study will be designated by the Sponsor. All participating Investigators will be appropriately acknowledged.

APPENDIX B. LABORATORY PARAMETERS

1) Screening Visit (within 28 Days of Visit 1)

- Comprehensive Metabolic Panel (Albumin, Alkaline Phosphatase, LDH, ALT, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total bilirubin, Total protein)
- Complete Blood Count (Hemoglobin, Hematocrit, Red Blood Cell (RBC) count, Platelet Count, WBC with Differential)
- Anti-tissue transglutaminase antibodies (IgA and IgG)
- HLA-DQ (as needed)
- HCV Antibodies
- HBsAg
- HIV Antibodies
- Interferon Gamma Release Assay (IGRA)
- Urinalysis (Protein, Glucose, Ketones, Blood Cells)
- Urine drug screen
- Urine Pregnancy (all FOCBP)
- IELs
- VH:CD
- Biopsy flow-cytometry
- Biopsy mRNA
- Biopsy DNA for TCR clonality
- iVYLISA GIP Stool Test
- Serum Pregnancy (all FOCBP)

2) Visit 1 (Randomization – Week 0/Day 0)

- Comprehensive Metabolic Panel (Albumin, Alkaline Phosphatase, LDH, ALT, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total bilirubin, Total protein)
- Complete Blood Count (Hemoglobin, Hematocrit, RBC, Platelet Count, WBC with Differential)
- Anti-tissue transglutaminase antibodies (IgA and IgG)
- PK/PD/Biomarkers (including CRP)
- Whole Blood flow cytometry
- Anti-drug antibodies
- Urinalysis (Protein, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test
- Urine Pregnancy (all FOCBP)

3) Visit 2 (Week 1/Day 7)

- Comprehensive Metabolic Panel (Albumin, Alkaline Phosphatase, LDH, ALT, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total bilirubin, Total protein)
- Complete Blood Count (Hemoglobin, Hematocrit, RBC, Platelet Count, WBC with Differential)
- Urinalysis (Protein, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test
- Urine Pregnancy (all FOCBP)

4) Visit 3 (Week 2/Day 14)

- Comprehensive Metabolic Panel (Albumin, Alkaline Phosphatase, LDH, ALT, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total bilirubin, Total protein)
- Complete Blood Count (Hemoglobin, Hematocrit, RBC, Platelet Count, WBC with Differential)
- PK/PD/Biomarkers (including CRP)
- Anti-drug antibodies
- Urinalysis (Protein, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test
- Urine Pregnancy (all FOCBP)

5) Visit 4 (Week 4/Day 28)

- Comprehensive Metabolic Panel (Albumin, Alkaline Phosphatase, LDH, ALT, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total bilirubin, Total protein)
- Complete Blood Count (Hemoglobin, Hematocrit, RBC, Platelet Count, WBC with Differential)
- Anti-tissue transglutaminase antibodies (IgA and IgG)
- PK/PD/Biomarkers (including CRP)
- Whole Blood flow cytometry
- Anti-drug antibodies
- Urinalysis (Protein, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test
- Urine Pregnancy (all FOCBP)

6) Visit 5 (Week 6/Day 42)

- iVYLISA GIP Stool Test
- Urine Pregnancy (all FOCBP)

7) Visit 6 (Week 8/Day 56)

- Comprehensive Metabolic Panel (Albumin, Alkaline Phosphatase, LDH, ALT, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total bilirubin, Total protein)
- Complete Blood Count (Hemoglobin, Hematocrit, RBC, Platelet Count, WBC with Differential)
- Anti-tissue transglutaminase antibodies (IgA and IgG)
- PK/PD/Biomarkers (including CRP)
- Whole Blood flow cytometry
- Anti-drug antibodies
- Urinalysis (Protein, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test
- Urine Pregnancy (all FOCBP)

8) Visit 7 (Week 10/Day 70)

- iVYLISA GIP Stool Test
- PK
- Urine Pregnancy (all FOCBP)

9) Visit 8 (Week 12/Day 84) OR Early Termination Visit

- Comprehensive Metabolic Panel (Albumin, Alkaline Phosphatase, LDH, ALT, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total bilirubin, Total protein)
- Complete Blood Count (Hemoglobin, Hematocrit, RBC, Platelet Count, WBC with Differential)
- Anti-tissue transglutaminase antibodies (IgA and IgG)
- PK/PD/Biomarkers (including CRP)
- Whole Blood flow cytometry
- Anti-drug antibodies
- Urinalysis (Protein, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test
- IELs
- VH:CD
- Biopsy flow-cytometry
- Biopsy mRNA
- Biopsy DNA for TCR clonality

- Serum Pregnancy (all FOCBP)

NOTE: If conducting an Early Termination visit, an exit endoscopy will be collected unless indicated otherwise based on the subject's condition and at the PI's discretion.

10) Visit 9 (Final Visit, Week 16/Day 112

- Comprehensive Metabolic Panel (Albumin, Alkaline Phosphatase, LDH, ALT, AST, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total bilirubin, Total protein)
- Complete Blood Count (Hemoglobin, Hematocrit, RBC, Platelet Count, WBC with Differential)
- Anti-tissue transglutaminase antibodies (IgA and IgG)
- PK/PD/Biomarkers (including CRP)
- Anti-drug antibodies
- Urinalysis (Protein, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test
- Urine Pregnancy (all FOCBP)

APPENDIX C. BRISTOL STOOL FORM SCALE (BSFS)

Type 1 Separate hard lumps, like nuts

Type 2 Sausage-like but lumpy

Type 3 Like a sausage but with cracks in the surface

Type 4 Like a sausage or snake, smooth and soft

Type 5 Soft blobs with clear-cut edges

Type 6 Fluffy pieces with ragged edges, a mushy stool

Type 7 Watery, no solid pieces

APPENDIX D. SAMPLE GASTROINTESTINAL SYMPTOM RATING SCALE (GSRS)

Please read this first:

This survey contains questions about how you have been feeling and what it has been like DURING THE PAST WEEK. Mark the choice that best applies to you and your situation with an "X" in the box

1. Have you been bothered by PAIN OR DISCOMFORT IN YOUR UPPER ABDOMEN OR THE PIT OF YOUR STOMACH during the past week?

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

2. Have you been bothered by HEARTBURN during the past week? (By heartburn we mean an unpleasant stinging or burning sensation in the chest.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

3. Have you been bothered by ACID REFLUX during the past week? (By acid reflux we mean the sensation of regurgitating small quantities of acid or flow of sour or bitter fluid from the stomach up to the throat.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

4. Have you been bothered by HUNGER PAINS in the stomach during the past week? (This hollow feeling in the stomach is associated with the need to eat between meals.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

5. Have you been bothered by NAUSEA during the past week? (By nausea we mean a feeling of wanting to throw up or vomit.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

6. Have you been bothered by RUMBLING in your stomach during the past week? (Rumbling refers to vibrations or noise in the stomach.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

7. Has your stomach felt BLOATED during the past week? (Feeling bloated refers to swelling often associated with a sensation of gas or air in the stomach.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

8. Have you been bothered by BURPING during the past week? (Burping refers to bringing up air or gas from the stomach via the mouth, often associated with easing a bloated feeling.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

9. Have you been bothered by PASSING GAS OR FLATUS during the past week? (Passing gas or flatus refers to the need to release air or gas from the bowel, often associated with easing a bloated feeling.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

10. Have you been bothered by CONSTIPATION during the past week? (Constipation refers to a reduced ability to empty the bowels.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

11. Have you been bothered by DIARRHEA during the past week? (Diarrhea refers to a too frequent emptying of the bowels.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

12. Have you been bothered by LOOSE STOOLS during the past week? (If your stools (motions) have been alternately hard and loose, this question only refers to the extent you have been bothered by the stools being loose.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

13. Have you been bothered by HARD STOOLS during the past week? (If your stools (motions) have been alternately hard and loose, this question only refers to the extent you have been bothered by the stools being hard.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

14. Have you been bothered by an URGENT NEED TO HAVE A BOWEL MOVEMENT during the past week? (This urgent need to go to the toilet is often associated with a feeling that you are not in full control.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

15. When going to the toilet during the past week, have you had the SENSATION OF NOT COMPLETELY EMPTYING THE BOWELS? (This feeling of incomplete emptying means that you still feel a need to pass more stool despite having exerted yourself to do so.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

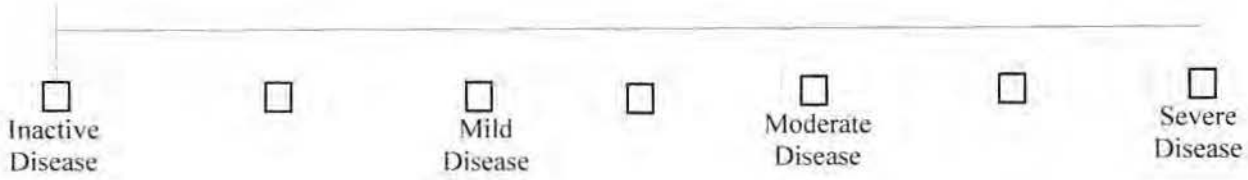
PLEASE CHECK THAT ALL QUESTIONS HAVE BEEN ANSWERED!

THANK YOU FOR YOUR COOPERATION.

APPENDIX E. SAMPLE PHYSICAN GLOBAL ASSESSMENT OF DISEASE/RATING OF CHANGE

Part A: To be completed by the physician at all required visits.

Based on the information available, chose the box that best represents the subject's current overall disease activity:



	Symptoms & Signs				
Category	Abdominal Pain	Diarrhea	Fatigue	Activity	Lab Tests
Inactive Disease – Minimal or no symptoms thought to be related to RCD-II	Asymptomatic	One or two episodes that resolve spontaneously	Asymptomatic or symptoms felt to be due to another disorder (i.e., depression)	Asymptomatic or symptoms felt to be due to another disorder	Normal or minimal abnormalities
Mild Disease – Mild recurring or persistent symptoms thought to be secondary to RCD-II	Mild pain secondary to RDC-II occurring several times a week	Mild diarrhea thought to be secondary to RCD-II	Asymptomatic or mild symptoms that resolved spontaneously	Asymptomatic or symptoms felt to be due to another disorder	Persistent and significant laboratory abnormalities felt to be secondary to RCD-II with no or mild associated symptoms
Moderate Disease – Moderate or a combination of mild and moderate recurring or persistent symptoms thought to be due to RCD-II	Moderate abdominal pain thought to be secondary to RCD-II	Moderate diarrhea thought to be secondary to RCD-II	Significant fatigue thought to be due to RDC-II	In ability to maintain normal activities due to fatigue or other symptoms	Significant laboratory abnormalities felt to be secondary to RCD-II with mild or moderate associated symptoms
Severe Disease – Severe or a combination of moderate and severe recurring or persistent symptoms thought to be related to RCD-II	Severe abdominal pain thought to be secondary to RCD-II	Significant diarrhea thought to be secondary to RCD-II	Significant fatigue thought to be secondary to RCD-II	Severe impairment of normal activities due to fatigue or other symptoms	Significant laboratory abnormalities felt to be secondary to with moderate to severe associated symptoms

Part B: To be completed by the physician at all required visits after Visit 1; Week 0/Day 0.

Please choose one of the following options that best describes the patient's overall change in their celiac symptoms since their baseline study visit:

☐ VERY MUCH BETTER

☐ MODERATELY BETTER

☐ A LITTLE BETTER

☐ NO CHANGE

☐ A LITTLE WORSE

☐ MODERATELY WORSE

☐ VERY MUCH WORSE

APPENDIX F. INTERPRETATION OF HEPATITIS RESULTS

Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs) ***are eligible*** for this study.
- Subjects who test **positive** for surface antigen (HBsAg+) ***are not eligible*** for this study, regardless of the results of other hepatitis B tests.
- Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this study unless local guidelines require additional testing.
- Subjects who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study unless local guidelines require additional testing.
- Subjects who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the subject ***is not eligible*** for this study. If the HBV DNA test is **negative**, the subject ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the subject ***is not eligible*** for this study.

Eligibility based on Hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Exclude	+	— *or* +	— *or* +
Include	—	—	—
	—	+**	—
	—	+**	+
Require Hepatitis B viral DNA (HBV DNA) testing*	—	—	+
* If HBV DNA is detectable, exclude from clinical trial. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from clinical trial. ** Local guidelines may require additional testing to rule out the presence of HBV.			

APPENDIX G. PREDICTED EXPOSURE AND SAFETY MARGINS

Table 4 shows predictions of exposure and safety margins calculated for proposed 8 mg/kg IV q2w dosing with an additional dose at Week 1.

Two sets of assumptions were used: a) that AMG 714 PK in RCD-II patients is the same as in healthy subjects, and b) that AMG 714 clearance is higher in RCD-II patients due to protein leakage in the intestine, and that the extent of the leakage is reflected in the serum albumin values.

The data used in the calculations are described in Table 4. Calculations are described below the tables.

Table 4. Predicted Exposure and Safety Margins

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 5. Data used for calculation of safety margins

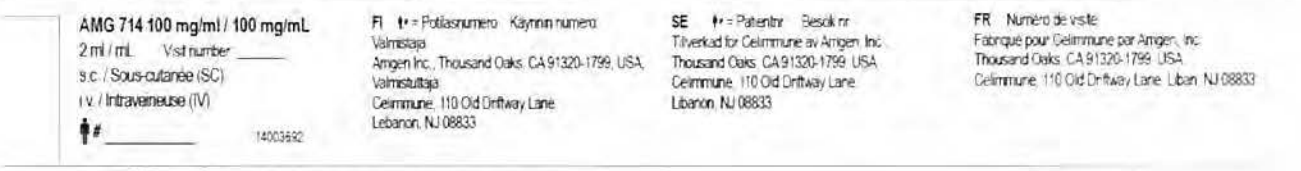
Parameter	Value	Comment
[redacted]	[redacted]	[redacted]

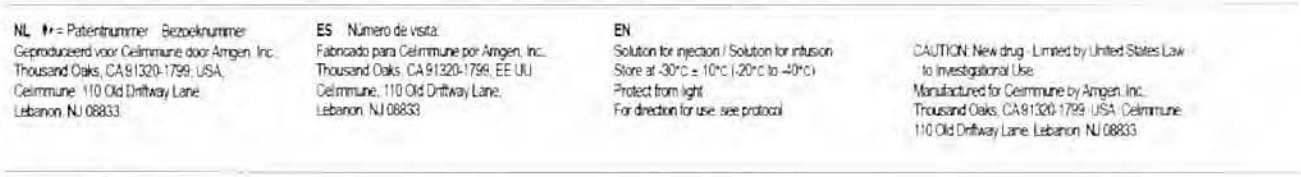
[redacted]

[redacted]

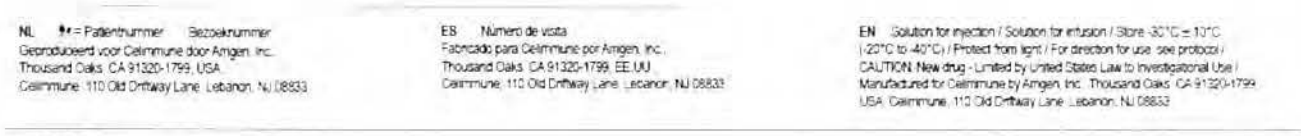
APPENDIX H. SAMPLE INVESTIGATIONAL PRODUCT LABEL

AMG 714:





PLACEBO:



Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

3. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

APPENDIX J. SAMPLE EQ-5D QUESTIONNAIRE (5L VERSION)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g., work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

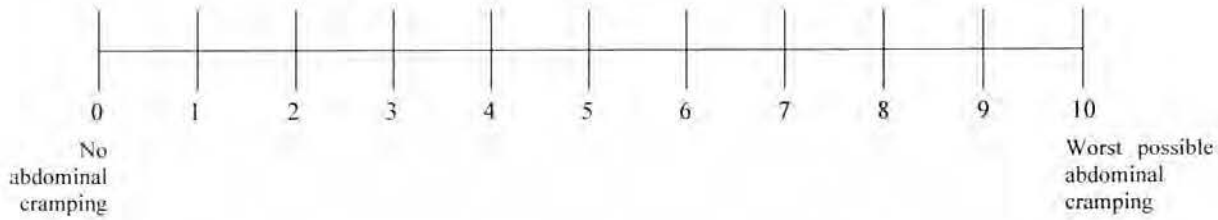
Your own health state today

APPENDIX K. SAMPLE CELIAC DISEASE PATIENT REPORTED OUTCOME (CED PRO)

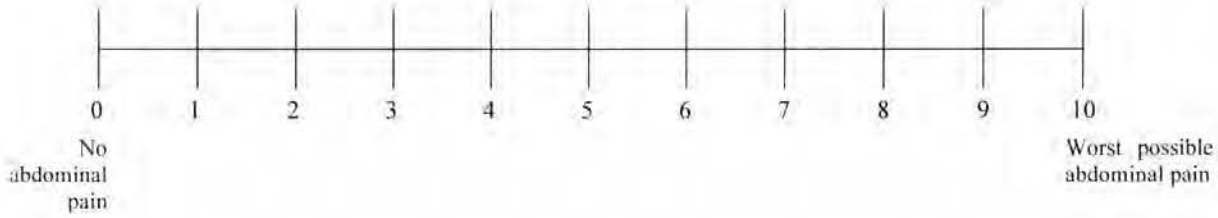
Instructions: These questions ask about how you feel each day. Please complete the daily diary every evening, at approximately the same time.

1. **Thinking about your worst experience in the past 24 hours, how severe was each of the following symptoms? On the following screens, please tap a number to indicate how you felt.**

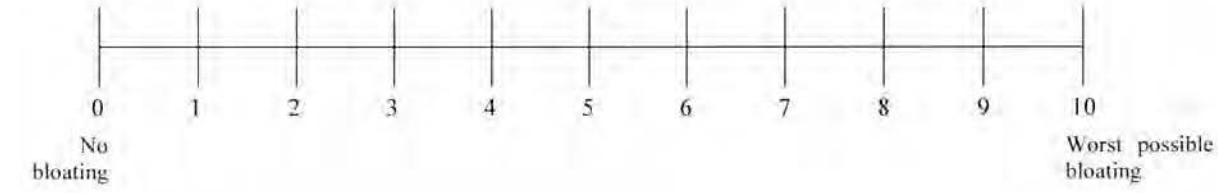
   a. How severe was your abdominal cramping?



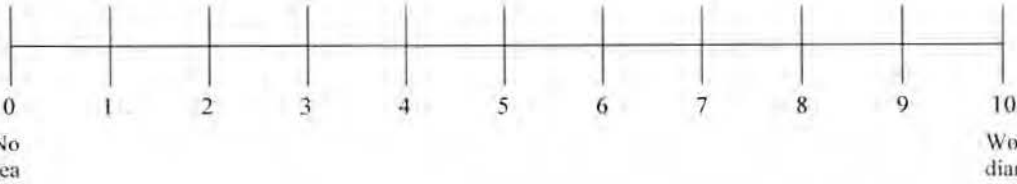
   b. How severe was your abdominal pain?



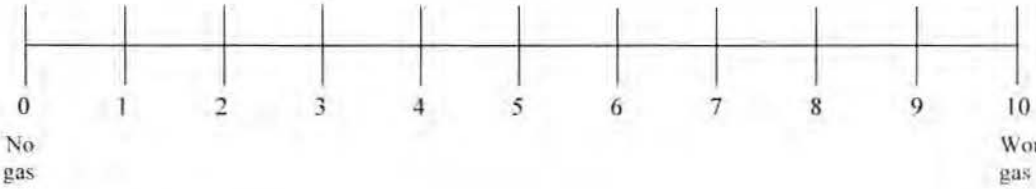
   c. How severe was your bloating?



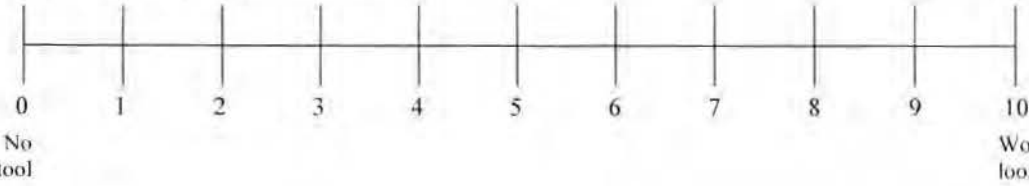
d. How severe was your diarrhea?



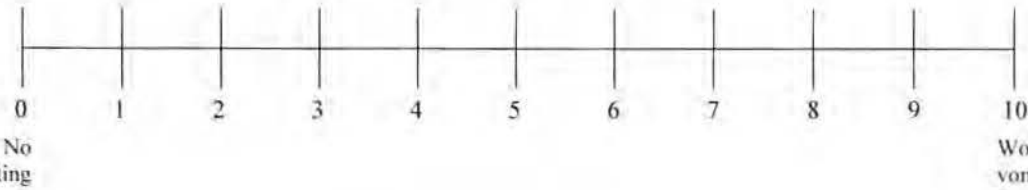
e. How severe was your gas (flatulence)?



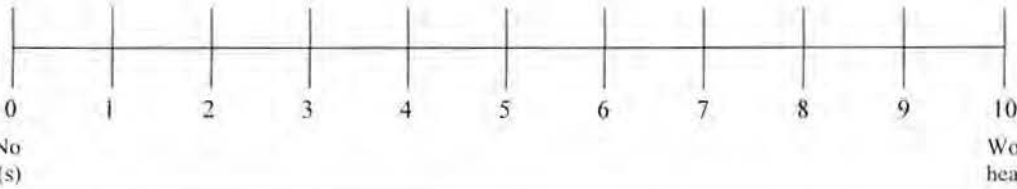
f. How severe was your loose stool?



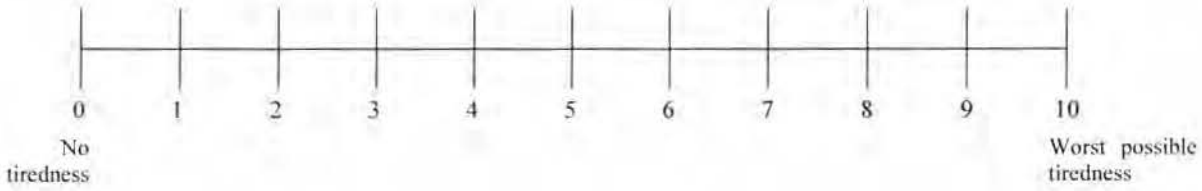
g. How severe was your nausea?



h. How severe was your headache(s)?



i. How severe was your tiredness?



APPENDIX L. SAMPLE PATIENT GLOBAL ASSESSMENT OF DISEASE/RATING OF CHANGE

Part A: (To be completed by the patient at all required visits)

Please indicate your overall assessment of the severity of your celiac symptoms:

☐ NO CELIAC SYMPTOMS

☐ VERY MILD

☐ MILD

☐ MODERATE

☐ SEVERE

☐ VERY SEVERE

Part B: (To be completed by the patient at all required visits after baseline Visit 1; Week 0/Day 0)

Please choose one of the following options that best describes the overall change in your celiac symptoms since you began treatment in this study:

☐ VERY MUCH BETTER

☐ MODERATELY BETTER

☐ A LITTLE BETTER

☐ NO CHANGE

☐ A LITTLE WORSE

☐ MODERATELY WORSE

☐ VERY MUCH WORSE

APPENDIX M. PROTOCOL AMENDMENTS

The protocol was modified to create version 3 on July 11th 2016. The following changes and clarifications were made in the sections specified:

1. To reduce burden on patients:
   (1) , the rules for collection of stool samples have been revised to allow a more flexible window of +/- 3 days and to allow any place of collection, not just the patient's home (Table 1, Footnote 10; Section 11; Section 14.2).
   (2) The time of collection of the blood cell pellet has been changed to allow collection at any time during study (Table 1, Footnote 12).
2. It has been clarified throughout the protocol that the DSMB is expected to review unblinded data, including during the interim analysis (Screening, Sections 6, 11, 18, 21.10, 22 and 23).
3. Clarification that simultaneous concomitant therapy with topical and systemic steroids is permissible, at or below the maximum doses indicated in the protocol. (Synopsis, Sections 6 and 10.1).
4. Clarification that, after thawing, the product may be stored for up to 72 hours at 5 ± 3°C, and no longer than 12 hours at room temperature. And after preparation (once injected in the IV bag), it should be used immediately and can only be kept at room temperature for a maximum of 12 hours including the 2 hrs. of the IV administration. These instructions are in line with the study manual and have been correctly followed by the sites (Section 18.7.3).
5. Clarification of the instructions to prepare the IV bag by withdrawing the volume of the thawed investigational product needed for the weight of the patient (8 mg per kg, calculating the volume needed given the concentration of investigational product of 100 mg/ml) and injecting this volume directly into a 100 mL 5% dextrose IV bag using the injection port at the base of the bag. These instructions are in line with the study manual and have been correctly followed by the sites (Section 18.7.3).
6. Clarification of the patient populations for analysis (Section 22.2 and throughout the protocol) and the statistical analysis method for the Marsh score (Synopsis and Section 22.6). The definitions and method are consistent with the Statistical Analysis Plan and will be used at completion of the study.

Additional editorial changes, corrections of typos and omissions, as well as minor clarifications were made throughout the protocol

This protocol was modified to create version 2 on 01 February 2016. The following changes and clarifications were made in the sections specified:

7. Addition of IND number (Page 1).

8. Update of contact information for protocol vendors and responsible staff.

9. Minor corrections to Schedule of Study Procedures (Table 1):

    - Addition of superscript to PK sample collection at Visit 6 (Week 8) to indicate that the sample for PK analysis at this visit should be collected before dosing starts.
    - Clarification that the Visit 8 endoscopy and biopsy can be collected 7 days before or after Visit 8.

3. Addition of rules to stagger the randomization and initial dosing of the first ten subjects (Synopsis and Section 7).

4. Correct provision of iVYLISA GIP test kit and instructions for home collection from Visit 1 to Visit 2 in the Assessments at Each Visit section (Section 11.2).

5. Removal of mandatory hood use for preparation of clinical supplies as long as preparation is performed using aseptic techniques, under sterile conditions (Section 18.7.3).

6. Corrections to the list of Laboratory Parameters (Appendix B) to match Schedule of Events (Table 1):

    - Clarification that "mRNA/DNA" at Screening and Visit 8 (Week 12) means "Biopsy mRNA" and "Biopsy DNA for TCR clonality."