

## 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 Celiac Disease**

<b>Protocol Number:</b>	CELIM-NRCD-001
<b>Version No:</b>	3
<b>Protocol Date:</b>	29 August 2016
<b>EudraCT Number:</b>	2015-003647-19
<b>Investigational Product:</b>	AMG 714
<b>Phase:</b>	Phase 2a
<b>Sponsor:</b>	Celimmune, LLC 8501 River Rock Terrace, Bethesda, MD 20817, USA

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NCT Number: 02637141

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## SPONSOR APPROVAL

**PROTOCOL NUMBER:** CELIM-NRCD-001  
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**PROTOCOL DATE:** 29 Aug 2016  
**PROTOCOL 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 Celiac Disease

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, and applicable laws and regulations.

August 29<sup>th</sup>, 2016

\_\_\_\_\_  
PPD [REDACTED] MD, PhD  
CEO & Chief Medical Officer  
Celimmune, LLC

\_\_\_\_\_  
Date

## COORDINATING INVESTIGATOR APPROVAL

**PROTOCOL NUMBER:** CELIM-NRCD-001

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**PROTOCOL 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 Celiac Disease

I certify that I have reviewed and 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, and applicable laws and regulations.

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PPD [REDACTED] MD, PhD  
University of Tampere  
School of Medicine

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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 any applicable laws and 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.

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Signature of Investigator

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Date

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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 covariance
Anti-tTG	Anti-tissue transglutaminase
APC	Antigen presenting cells
AUCU-t	Area under concentration time curve
βhCG	Beta human chorionic gonadotropin
BP	Blood pressure
BSFS	Bristol Stool Form Scale
CD	Cluster of Differentiation
CFR	United States Code of Federal Regulation
CeD-GSRS	Celiac Disease – Gastrointestinal Symptom Rating Scale
CeD-PRO	Celiac Disease – Patient-Reported Outcome
cGCP	Current Good Clinical Practice
CL/F	Apparent clearance
C <sub>max</sub>	Maximum observed concentration
CRF	Case report form
CRP	C Reactive Protein
C <sub>trough</sub>	Trough concentration
DH	Dermatitis herpetiformis
DGP	Deamidated gliadin peptide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture system
eCRF	Electronic case report form
ePRO	Electronic patient reported outcome
FDA	Food and Drug Administration
FOCBP	Females of child bearing potential
FSH	Follicle stimulating hormone
GERD	Gastroesophageal reflux disease
GFD	Gluten-free diet
eGFR	Estimated glomerular filtration rate
GI	Gastrointestinal
GIP	Gluten immunogenic peptide
g	Gram
GSRS	Gastrointestinal Symptom Rating Scale
Hb	Hemoglobin
HbA1C	Glycosylated hemoglobin
Hep B	Hepatitis B
Hep C	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
IEC	Independent ethics committee
IELs	Intraepithelial lymphocytes
INR	International normalized ratio
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	Mixed effects repeated measures model
NK	Natural killer
NYHA	New York Heart Association
PD	Pharmacodynamics
PGA	Physician Global Assessment of Disease
PK	Pharmacokinetics
PP	Per protocol
POC	Proof of concept
PT	Preferred Term
RBC	Red Blood Cell
RCD	Refractory celiac disease
RCD-I	Type 1 refractory celiac disease
RCD-II	Type 2 refractory celiac disease
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse events
$t_{1/2}$	Terminal half-life
TB	Tuberculosis
TK	Toxicokinetics
$t_{max}$	Time to maximum concentration
tTG	Tissue transglutaminase
VH:CD	Villous height to crypt depth ratio
$V_z/F$	Volumes of distribution at elimination phase
WBC	White Blood Cell
WHO	World Health Organization

## PROTOCOL SYNOPSIS

<b>TITLE</b>	<b>A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of AMG 714 in Adult Patients with Celiac Disease</b>
<b>INTENDED INDICATION</b>	AMG 714 is a human anti-IL-15 monoclonal antibody indicated for the treatment of gluten-free diet (GFD) non-responsive celiac disease (NRCD) in adult patients.
<b>STUDY OBJECTIVES</b>	<p><u>Primary Objective:</u> To assess the efficacy of AMG 714 in attenuating the effects of gluten exposure in adults with celiac disease</p> <p><u>Secondary Objective:</u> To assess the safety and tolerability of AMG 714 when administered to adult patients with celiac disease exposed to a gluten challenge</p> <p><u>Exploratory Objective:</u> To assess the pharmacokinetics (PK), pharmacodynamics (PD), and PK/PD correlations of AMG 714</p>
<b>STUDY ENDPOINTS</b>	<p><u>Primary efficacy endpoint:</u></p> <ul style="list-style-type: none"> <li>• Attenuation of gluten-induced small intestinal mucosal morphological injury, measured morphometrically as villous height to crypt depth (VH:CD) ratio</li> </ul> <p><u>Secondary efficacy endpoints:</u></p> <ul style="list-style-type: none"> <li>• Attenuation of gluten-induced small intestinal mucosal inflammation measured as intraepithelial lymphocyte (IELs) density</li> <li>• Attenuation of gluten-induced small intestinal mucosal morphological injury using a grouped classification of Marsh score</li> <li>• Attenuation of gluten-induced serum antibodies:             <ul style="list-style-type: none"> <li>• Anti-tissue transglutaminase antibodies (anti-tTG IgA)</li> <li>• Anti-deamidated gliadin peptide (anti-DGP) IgA and IgG</li> </ul> </li> <li>• Attenuation of gluten-induced clinical symptoms as assessed by:             <ul style="list-style-type: none"> <li>• Bristol Stool Form Scale (BSFS)</li> <li>• Gastrointestinal Symptom Rating Scale (GSRS) and celiac disease GSRS (CeD-GSRS)</li> </ul> </li> </ul> <p><u>Exploratory endpoints:</u></p> <ul style="list-style-type: none"> <li>• Pharmacokinetics (PK), Pharmacodynamics (PD) and Exposure/Response (PK/PD)</li> <li>• Physician Global Assessment of Disease (PGA)</li> <li>• Biomarkers of disease activity</li> <li>• Celiac Disease Patient-Reported Outcome (CeD PRO)</li> </ul>



	<p><u>Safety endpoints:</u></p> <ul style="list-style-type: none"> <li>• Adverse events (AEs)</li> <li>• Clinical laboratory tests</li> <li>• Physical examination</li> <li>• Vital signs</li> <li>• Immunogenicity</li> </ul>
<p><b>STUDY DESIGN</b></p>	<p>Protocol CELIM-NRCD-001 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 attenuation of the effects of gluten exposure in adult patients with celiac disease during a gluten challenge.</p> <p>After signing consent, subjects will be screened for the study. All subjects who meet the study entry criteria will be randomized at a 1:1:1 ratio to receive 150 mg or 300 mg AMG 714 or placebo once every two weeks for 10 weeks. Randomization will be stratified by sex. The study drug (AMG 714 or placebo) will be administered at the clinical site in a double-blind fashion via subcutaneous (SC) injection.</p> <p>In addition to receiving study medication or placebo, all subjects will be required to consume either placebo gluten or active gluten administered in a single-blind fashion. Beginning on the day following Visit 1 (i.e. Week 0/Day 1, since Visit 1 is defined as Week 0/Day 0) through Visit 2 (Week 2/Day 14), all randomized subjects will consume placebo gluten, in the form of gluten-free foodstuffs (e.g., rusks) provided by the Sponsor, twice a day (BID) at the time of two regularly consumed gluten-free meals (chosen by the subject). Starting at Visit 2, subjects will switch to consuming a daily total of approximately 4g of active gluten, provided in the form of foodstuff identical in appearance to that provided during the two-week single-blind placebo-gluten period. These gluten-containing foodstuffs, supplied by the sponsor, will be consumed in approximately 2g doses BID at the time of two regularly consumed gluten-free meals (as chosen by the subject) from Visit 2 (Week 2/Day 14) through the end of the treatment period at Visit 7 (Week 12/Day 84). Consumption of additional products containing gluten will be prohibited and subjects will be expected to continue total adherence to their former GFD from the time of screening until the follow-up study visit (Visit 8, Week 16/Day 112).</p> <p>Subjects' adherence to GFD and consumption of provided gluten will be assessed via stool and urine sample testing using the iVYLISA gluten immunogenic peptide (GIP) stool and urine gluten tests. Subjects with known or suspected GFD transgressions or those suspected of non-compliance to protocol-specified gluten dosing will be counseled and allowed to continue in the study.</p>

	<p>A study staff member will contact each subject by telephone one day and one week after the first study drug dose in order to assess for any AEs. Subjects will return to the clinic every two weeks for study drug administration and/or efficacy and safety assessments as indicated in the study schedule of events (Table 1). The final study drug dose will be administered at Visit 6 (Week 10/Day 70). An end-of-study efficacy assessment will be collected at Visit 7 (Week 12/Day 84). A final study visit will be conducted 6 weeks after the last dose of study drug at Week 16 (Visit 8/Day 112).</p> <p>All study subjects will undergo upper gastrointestinal endoscopy and biopsy prior to baseline (Visit 1, Week 0/Day 0) and at the end of the 12-week study period while still on the gluten challenge and within 5 days before Visit 7 (Week 12/Day 84) in order to assess changes from baseline in VH:CD ratio, IELs, and Marsh score.</p> <p>All 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 8 (Week 16/Day 112). Subjects will complete the CeD PRO daily from baseline to the final study visit. Subjects will also complete the GSRS at screening and, thereafter, weekly from baseline through the study final study visit. The BSFS, GSRS, and the daily CeD PRO will be completed using a handheld electronic diary at the times specified in the Schedule of Events (Table 1).</p> <p>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. In addition to the investigators and the Sponsor, an independent Data Safety Monitoring Board (DSMB) will monitor safety.</p>
<b>STUDY SAMPLE SIZE</b>	A total of approximately 63 subjects will be randomized into the study in order to achieve approximately 51 evaluable subjects (17 subjects per treatment arm).
<b>ANTICIPATED NUMBER OF CLINICAL SITES</b>	The study will be conducted at approximately 3 clinical sites in Finland.
<b>INCLUSION CRITERIA</b>	<p>Subjects must fulfill all of the following inclusion criteria to be eligible for participation at screening and at Visit 1 (Week 0/Day 0):</p> <ol style="list-style-type: none"> <li>1. Adult males or females 18 to 80 years of age, inclusive.</li> <li>2. Demonstrate willingness to participate in the study as documented by signed informed consent.</li> </ol>

	<ol style="list-style-type: none"> <li>3. Subjects must have a diagnosis of celiac disease by intestinal biopsy at least 12 months prior to screening as confirmed by medical records, written physician statement or by the Kela statement, the national social security institution determining the governmental reimbursement for biopsy-proven celiac disease patients.</li> <li>4. Subjects must have been on a GFD for at least 12 consecutive months prior to screening and must be willing to remain on a GFD for the duration of study participation (apart from the Sponsor-supplied approximately 2g of gluten taken BID during the 10-week gluten challenge period of the study).</li> <li>5. Negative anti-tTG (IgA) at screening.</li> <li>6. Negative <i>H.-pylori</i> test prior to study drug administration.</li> <li>7. Human leukocyte antigen DQ (HLA-DQ) typing compatible with celiac disease provided or obtained before baseline biopsy.</li> <li>8. Body mass index (BMI) between 16.0 and 45.0 kg/m<sup>2</sup>, inclusive.</li> <li>9. Screening laboratory values within the following parameters (unless investigator considers an abnormality to be not clinically significant): <ol style="list-style-type: none"> <li>a) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) &lt; 2.5 x the upper limit of normal (ULN).</li> <li>b) Hemoglobin &gt; 10 g/dL (&gt;100 g/L in SI units)</li> <li>c) Platelet count &gt; 125,000 mm<sup>3</sup> (&gt;125 /L in SI units).</li> <li>d) White blood cell count &gt; 3,500 cells/mm<sup>3</sup> (&gt;3.5 x10<sup>9</sup>/L).</li> <li>e) Estimated glomerular filtration rate (eGFR) ≥ 60 ml/min.</li> <li>f) Glycosylated hemoglobin (HbA1C) &lt;7% (&lt;53 mmol/mol) in subjects with a diagnosis of Type 1 or Type 2 Diabetes Mellitus</li> </ol> </li> <li>10. Females of non-childbearing potential defined as postmenopausal (&gt;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 &gt;40 IU/L at Screening); or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, oophorectomy); or otherwise incapable of pregnancy</li> </ol> <p>OR</p> <p>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 8, Week 16/Day 112) and for 6 months after the end of the study.</p> <ol style="list-style-type: none"> <li>11. Willingness and ability to comply with study procedures and protocol stipulated concomitant medication guidelines.</li> <li>12. Willingness to return for all scheduled follow-up visits.</li> </ol>
<b>EXCLUSION CRITERIA</b>	Subjects will be excluded from the study if there is evidence of any of the following:

	<ol style="list-style-type: none"> <li>1. Current diagnosis of any severe complication of celiac disease, such as Refractory Celiac Disease Type I or Type II (RCD-I or RCD-II), enteropathy-associated T-cell lymphoma (EATL), ulcerative jejunitis or perforation.</li> <li>2. Diagnosis of any autoimmune disease, other than celiac disease or dermatitis herpetiformis (DH), that might interfere with the conduct of the study or require systemic immunomodulation therapy.</li> <li>3. Occurrence of celiac disease-related symptoms (CeD-GSRS &gt;2.3) as assessed by screening GSRS.</li> <li>4. Diagnosis of any chronic, <i>active</i> gastrointestinal (GI) disease other than celiac disease (e.g., active, untreated peptic ulcer, esophagitis, gastroesophageal reflux disease [GERD]; active ulcerative colitis; Crohn's disease, or irritable bowel syndrome] that might, in the Investigator's opinion, interfere with assessment of symptoms of abdominal pain, diarrhea, or other components of celiac disease.</li> <li>5. Any known, <i>symptomatic</i> food allergy, including an allergy to the ingredients of the gluten challenge vehicle that, in the opinion of the Investigator, might interfere with the conduct of the study or result in anaphylaxis.</li> <li>6. Presence of any of the following related to infection: <ol style="list-style-type: none"> <li>a) Active acute infection requiring systemic treatment (antibiotics, antifungal, or antiviral)</li> <li>b) Active GI infection</li> <li>c) Persistent or severe infection within the three months prior to randomization</li> <li>d) History of tuberculosis (TB)</li> <li>e) 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; subject can be enrolled if he or she has been successfully treated with appropriate chemoprophylaxis.</li> <li>f) History within 3 years prior to screening of an opportunistic infection typical of those seen in immunocompromised patients (e.g., herpes zoster, systemic candida infection, or systemic fungal infection).</li> </ol> </li> <li>7. Use of systemic immune suppressants (including steroids) within 3 months or 5 half-lives, whichever is longer, prior to randomization.</li> <li>8. Required use of a prohibited medication at the time of randomization (prohibited medications required for treatment of an AE occurring after randomization are permitted).</li> <li>9. Current diagnosis or history of cancer within the past 5 years, except successfully treated basal cell or squamous cell carcinoma, cervical carcinoma-in-situ, or early stage prostate cancer.</li> <li>10. Administration of a live vaccine within 14 days prior to the first administration of study drug.</li> </ol>
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	<p>11. 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:</p> <ul style="list-style-type: none"> <li>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 New York Heart Association [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)</li> <li>b) pulmonary disease (e.g., severe chronic pulmonary disease)</li> <li>c) renal, hematological, gastrointestinal, endocrine (e.g., poorly controlled diabetes), immunologic, dermatologic, neurological, or psychiatric disease</li> </ul> <p>12. History of significant drug or alcohol abuse during the year prior to study screening as obtained by medical record and/or subject report.</p> <p>13. History of clinically significant hypersensitivity to the study drug, any related drugs, or to any of the excipients.</p> <p>14. History of anaphylactic reactions (e.g. IgE-mediated reactions) to wheat or gluten.</p> <p>15. Positive Hepatitis B (Hep B), Hepatitis C (Hep C), or Human Immunodeficiency Virus (HIV) infection test results at the time of screening.</p> <p>16. Females who are pregnant or planning to become pregnant during the study participation period, or are currently breastfeeding.</p> <p>17. Participation in another investigational drug or device study or treatment with an investigational drug within 3 months or 5 half-lives, whichever is longer, prior to randomization.</p> <p>18. 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 including the endoscopies and biopsy collections.</p>
<p><b>STATISTICAL METHODS</b></p>	<p>The primary endpoint is the difference in the Baseline-to-Week-12 % reduction of VH:CD ratio between the two AMG 714 dose arms and the placebo arm.</p> <p>The primary endpoint will be tested for each of the two dose levels, 150 mg or 300 mg, separately as follows:</p> $H_{10}: \mu_{AMG\ 714\ (300mg)} = \mu_{Placebo}$

against the alternative

$$H_{11}: \mu_{\text{AMG 714 (300mg)}} \neq \mu_{\text{Placebo}}$$

$$H_{20}: \mu_{\text{AMG 714 (150mg)}} = \mu_{\text{Placebo}}$$

against the alternative

$$H_{21}: \mu_{\text{AMG 714 (150mg)}} \neq \mu_{\text{Placebo}}$$

where  $\mu_{\text{AMG 714 (300mg)}}$ ,  $\mu_{\text{AMG 714 (150mg)}}$  and  $\mu_{\text{Placebo}}$  denote the mean Baseline-to-Week-12 % reduction of VH:CD ratio in the high dose, low dose and placebo arm, respectively. Each of the two hypotheses will be tested using a two-sided type I error level of 5% without any adjustments for multiple comparisons.

The primary efficacy endpoint will be analyzed using analyses of covariance (ANCOVA), where baseline VH:CD ratio, site, and sex will be covariates and treatment group will be included to test the primary hypotheses. The primary analyses will be based on the intent-to-treat (ITT) population. Secondary analyses will be based on the per-protocol (PP) population.

The secondary efficacy endpoints will also be analyzed for both the ITT and the PP population. Change in IELs density will be analyzed using the same method as for the primary endpoint VH:CD ratio. Anti-tTG IgA and anti-DGP (IgA and IgG) will be analyzed using a linear mixed effects repeated measures model (MMRM), with baseline value, site, sex, time, treatment group, and a time-by-treatment group interaction term as fixed effects, subject as random effect, and an underlying correlation structure between the time points that provides the best fit for the model.

The Marsh scores will be analyzed using a multinomial logistic regression model, where treatment group, time point, and a time point by treatment group 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 (midscale)' will be explored. The GSRS and CeD PRO (daily and

	<p>weekly averages) will be analyzed using the same method as that for the secondary endpoint anti-tTG IgA.</p> <p>The exploratory variables such as PK parameters, PGA, and biomarkers of disease activity will be tabulated by treatment groups, and will be done using both the ITT and the PP populations. In addition, dose proportionality, achievement on steady-state, and accumulation ratio based on <math>C_{\text{trough}}</math> concentrations, comparison of <math>C_{\text{trough}}</math> levels with corresponding values in study 20060349, and correlation of <math>C_{\text{trough}}</math> concentrations with biomarkers of disease activity will be evaluated. Dose proportionality will be analyzed using a power model and PK/PD correlation will mainly be assessed graphically.</p> <p>The safety variables, including AEs (coded using the Medical Dictionary for Regulatory Activities [MedDRA]), clinical laboratory tests, physical examination, vital signs, and immunogenicity, will be summarized by treatment group. Some of the variables will be tabulated by treatment and by visit.</p>
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**Table 1. Schedule of Study Procedures**

Study Procedures	Screening Period (Up to 28 Days)	Double-Blind Randomization Period									Final Visit
		Visit 1	Phone Call 1	Phone Call 2	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
		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)
			+1 Day	±1 Day	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days
Informed consent	X										
Demographics	X										
Medical history	X										
Physical examination	X	X		X	X		X		X	X	
Body weight	X					X			X	X	
Height, BMI calculation	X										
Vital signs	X	X <sup>1</sup>		X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X	X	
12-lead ECG	X										
Collection of blood and urine for clinical laboratory tests	X <sup>2,3</sup>	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	
Urine for gluten detection <sup>4</sup>		X		X	X		X		X	X	
iVYLISA GIP Stool Test <sup>5</sup>	X	X		X	X	X	X	X	X	X	
Randomization		X									
Serum biomarkers <sup>6</sup>		X		X	X		X	X	X	X	
Serum PK <sup>7,8</sup>		X		X	X		X	X	X	X	
Serum ADA		X		X	X		X		X	X	



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		Visit 1	Phone Call 1	Phone Call 2	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
		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)
			+1 Day	±1 Day	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±7 Days
Anti-tTG <sup>9</sup>	X	X			X		X		X	X	
DGP <sup>10</sup>		X			X		X		X	X	
Blood cell pellet <sup>11</sup>		X									
Eligibility confirmation	X	X									
Study drug administration		X		X	X	X	X	X			
Single-blind gluten challenge <sup>12, 13, 14</sup>		X	—————→							X	
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	
Assessment of adverse events	X	X	X	X	X	X	X	X	X	X	
Endoscopy and biopsy <sup>15, 16</sup>	X								X <sup>17,18</sup>		
BSFS, CeD PRO <sup>19</sup>		X	—————→							X	
GSRS <sup>20</sup>	X	X	—————→							X	
PGA		X		X	X		X		X	X	

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, tTG=tissue transglutaminase.

- 1) Vital signs will be taken prior to and 30 minutes after study drug administration.
- 2) Including blood sample for HLA typing if report not previously supplied.
- 3) HbA1C should be tested in those subjects with known or suspected diagnosis of Type 1 or Type 2 DM only.

- 4) An aliquot of urine will be collected from the urine supplied for urinalysis test for future iVYDAL urine sampling.
- 5) The mandatory screening iVYLISA GIP sample will be collected after the signing of informed consent either at the time of the screening visit or within the first 7 days following the initial screening visit. The iVYLISA GIP stool samples collected during the randomization period are optional, except Week 12 which is mandatory. The samples will ideally be collected by the patient the day before each scheduled study visit or during the visit (with a window of three days before or after the visit).
- 6) Biomarker samples should be taken prior to study drug administration. The time and date of these samples must be accurately recorded.
- 7) The PK sample should be collected before study drug administration.
- 8) Exact time and date of sample collection must be recorded.
- 9) Anti-tTG IgA antibodies will be determined in blood at screening (by Biocard test) and in serum thereafter (by ELISA).
- 10) Anti-DGP antibodies IgA and IgG will be measured in serum.
- 11) Collected and stored for future testing. This sample can be collected at any time during the study.
- 12) Placebo gluten will be dispensed in a single-blind fashion. Subjects will be instructed to consume the provided placebo gluten BID beginning on the day following Visit 1 (Week 0/Day 0) until Visit 2 (Week 2/Day 14). Subjects will return any unused placebo gluten to the study site.
- 13) Active gluten will be dispensed in a single-blind fashion from Visit 2 to Visit 6. Subjects will return any unused gluten to the study site at each follow-up study visit.
- 14) Subjects will start the gluten challenge with the next main meal (e.g., breakfast) on the day after Visit 2 (Week 2/Day 14), i.e., Day 15. Subjects will be instructed to consume the provided gluten BID with two main gluten-free meals of their choosing (e.g., at breakfast and dinner) for 10 weeks through Visit 7 (Week 12/Day 84).
- 15) The screening biopsy can be collected any time prior to the day of randomization. The biopsy should only be collected from those subjects who meet all other entry criteria.
- 16) If the screening biopsy shows villous atrophy with a VH:CD of less than 1.5 (1.4 or lower), and after notification to the sponsor, the subject may be allowed to stay in the study but the gluten challenge will not be started, or will be interrupted if it had already started, and the subject will not be included in the main efficacy assessments. Subjects with a VH:CD of 1.5 or higher will receive the gluten challenge.
- 17) The end-of-study biopsy can be collected within 5 days before Visit 7, while the subject is still consuming the single-blind gluten challenge.
- 18) A Visit 7 or Early Termination endoscopy and biopsy are required for all subjects. Early Termination endoscopies and biopsies should be conducted unless a medical condition suggests otherwise, at the investigator's discretion.
- 19) The BSFS is collected episodically at the time of each bowel movement from baseline to the end of participation the subject's involvement in the study. The CeD PRO is captured daily.
- 20) The GSRS is collected at screening to establish inclusion/exclusion criteria based on CeD-GSRS. The GSRS will be collected weekly from randomized subjects from baseline to the end of participation.

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# 1 INTRODUCTION

## 1.1 BACKGROUND

The disease intended to be treated is gluten-free diet (GFD) non-responsive celiac disease (NRCD). Celimmune is also investigating AMG 714 for the treatment of a rare yet potentially fatal complication of NRCD, Type II refractory celiac disease (RCD-II), which appears to be independent of gluten consumption. IL-15 plays an overlapping, yet distinct, pathophysiological role in these two diseases, responsible for mucosal damage in NRCD and aberrant IEL proliferation in RCD-II.

### 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<sup>+</sup> 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- $\alpha$ ) 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-15R $\alpha$ ) genes in mice has been shown to result in the loss of NK, NK-T, TCR $\gamma\delta$ <sup>+</sup> intraepithelial lymphocytes, and memory CD8<sup>+</sup> 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-15R $\alpha$  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  $\beta$  chain that is shared with the IL-2 receptor (CD122 or IL-2/IL-15R $\beta$ ), the common  $\gamma$  chain ( $\gamma$ C), shared with the IL-2, -4, -7, -9, and -21 receptors, and a unique  $\alpha$  chain. IL-15 binds with high affinity to the IL-15R $\alpha$  chain, which then interacts with the IL-2/IL-15R $\beta$  and the  $\gamma$ C. The association of the IL-15/IL-15R $\alpha$  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/IL15R $\alpha$  pair is on one cell and the receptor  $\beta$  and  $\gamma$ C chains are on another (Schluns *et al.* 2005). IL-15 can also associate with IL-15R $\alpha$  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. The prevalence is twice that in countries with very high hygiene standards and/or very high gluten consumption. It is estimated that 15-20 million patients are affected by celiac disease, although only 1-1.5 million have been 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 50mg/day of gluten triggers the disease (Catassi *et al*, 2007). A normal diet contains >10 g/day, 200 times the amount that causes damage and intestinal histological abnormalities. As such, celiac patients face enormous challenge to follow a strict gluten-free diet (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).

Celiac disease causes debilitating symptoms and serious medical complications. In many patients, gastrointestinal symptoms derived from intestinal mucosal damage dominate the

patient reported symptoms at diagnosis. The normal villi (absorptive finger-like prolongations) present in the gut of healthy individuals are lost in active celiac disease as a result of mucosal atrophy and crypt enlargement. The ratio of the villous height (VH) to the intestinal crypt depth (CD), the VH:CD ratio, is one of the main descriptors of the severity of celiac disease (Taavela *et al*, 2013). Small bowel damage often leads to nutrient malabsorption that can result in a range of further clinical manifestations (anemia, osteopenia, failure to thrive in children). In addition, extra-intestinal symptoms and systemic manifestations are often present, such as dermatitis, infertility, or neurological and skeletal disorders (Green and Cellier, 2007). Mortality is increased in subjects with persistent intestinal mucosal damage (Ludvigsson *et al*, 2009).

The most serious complication of celiac disease is the development of an in situ small bowel T cell lymphoma after many years of exposure, voluntary or inadvertent, to gluten (Lebwohl *et al*, 2013). This malignant complication of NRCd, which appears to be independent of gluten or responsive to a strict GFD, is termed Type II refractory celiac disease (RCD-II) when the % of aberrant IELs is >20% and Type I refractory celiac disease (RCD-I) when the % is <20%. 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. RCD-II affects approximately 0.5% of celiacs and can lead to overt and systemic enteropathy-associated T cell lymphoma (EATL) (Nijeboer *et al*, 2015a), with very poor prognosis and >80% mortality in 5 years (Nijeboer *et al*, 2015b). The incidence of EATL is increasing, and this increase could be related to increasing rates of gluten contamination in the diet over prolonged periods of time (Sharaiha *et al*, 2012). Finally, it should be noted that as many as 50% of undiagnosed patients with celiac disease are asymptomatic despite the underlying intestinal damage and malabsorption (Walker *et al*, 2010), which makes disease diagnosis and monitoring even more challenging.

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

	<b>Nature of the Disease</b>	<b>Gluten Dependence</b>	<b>Aberrant IELs</b>	<b>Clonality</b>	<b>Progression to Overt Systemic Lymphoma</b>
<b>Celiac Disease</b>	Autoimmune	Yes	No	Polyclonal	No
<b>RCD-I</b>	Unknown	Probably	Yes, <20%	Oligo-clonal	No
<b>RCD-II</b>	Malignant, slow growing	Probably not	Yes, >20%	Monoclonal (in situ lymphoma)	>50%
<b>EATL</b>	Malignant, rapid progression	No	Yes, >20%	Monoclonal	N/A

### 1.2.1 Current Management of Celiac Disease: The Gluten-Free Diet

Celiac disease is the only common autoimmune disorder with no approved medication. The only current available strategy for the management of celiac disease is a lifelong total avoidance of gluten. While simple in theory, the ubiquity of gluten in foodstuffs, medications, household substances, cosmetics, and gluten-free items makes total avoidance of gluten difficult – if not impossible.

The main challenge to the successful maintenance of a gluten-free diet is that cereal flours are widely used in the food industry and are present in numerous food products either naturally or as additives. Although gluten-free products can be purchased, commercially manufactured gluten-free products may be difficult to find, tend to be less flavorful and are more expensive than regular gluten containing foods. In addition, labeling of food products is deficient in many countries. Even in countries with superior labeling guidelines foods labeled “gluten-free” may nevertheless contain gluten. For example, in northern European countries amounts of up to 100 parts per million (ppm) are permitted in gluten-free products designated apt for celiac sufferers (Gibert *et al*, 2006).

For these reasons, celiac sufferers are regularly exposed to gluten contamination in the food and beverages they consume. This exposure to gluten contamination and the associated physiological and psychological consequences results in a self-limitation of social activities and/or a reduction in the variety of foods consumed. Thus, the only currently available management option of a gluten-free diet (GFD) presents both a considerable challenge and substantial burden for patients. 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 condition that requires multiple, weekly dialysis treatments.

As a result of the difficulty in maintaining total avoidance of gluten while on a GFD, gluten contamination causes 50% or more of all diagnosed celiac patients on a GFD to continue to experience disease activity (Lee, 2003; Cranney, 2007; Hopper, 2007; Midhagen 2003). Patients who continue to have symptoms despite attempting to maintain a GFD are deemed to have diet “non-responsive celiac disease” or NRCD. Non-responsive celiac disease 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). As requested by patient support groups and experts, alternative treatment options that can be administered independently or in combination with a GFD, as well as treatments for refractory celiac disease, are required in order to improve the quality of life for celiac patients.

## 1.3 ROLE OF IL-15 IN CELIAC DISEASE

Substantial evidence suggests a pathophysiological role for IL-15 in celiac disease (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).

#### 1.4 AMG 714

AMG 714, a fully human immunoglobulin (IgG1 $\kappa$ ) 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-15R $\alpha$ ). AMG 714 inhibits IL-15-induced T cell proliferation and shows a dose-dependent inhibition of IL-15-induced TNF- $\alpha$  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).

AMG 714 is now produced by a Chinese hamster ovary (CHO) cell line (referred to in this document as AMG ).

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 *in 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- $\alpha$  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- $\alpha$  production, or on IL-2 induced cytotoxic T cell line (CTLL2) cell proliferation.

#### AMG 714-CHO

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  $\leq 300$  mg/kg Hu714MuXHu. In this study, the no-observed-effect level (NOEL) was  $\geq 300$  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]

[REDACTED]

[REDACTED]

[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 three 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
<b>AMG 714-CHO</b>				
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) <sup>a</sup> 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 <sup>b</sup>
<b>AMG 714-HYB</b>				
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 <sup>c</sup>	Completed
20030210 <sup>d</sup> (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
<p><sup>a</sup> Dose escalation occurred approximately every 4 weeks; dosing cohorts initiated sequentially.</p> <p><sup>b</sup> Terminated early due to lack of efficacy in psoriasis</p> <p><sup>c</sup> 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)</p> <p><sup>d</sup> Genmab initiated study as Hx-IL15-002</p> <p>IV = intravenous; RA = rheumatoid arthritis; SC = subcutaneous</p>				

**1.6.1 Pharmacokinetics of AMG 714 in Humans**

**1.6.1.1 *Pharmacokinetics of AMG 714-HYB***

[REDACTED]

[REDACTED]

**1.6.1.2 *Pharmacokinetics of AMG 714-CHO***


[REDACTED]

[REDACTED]

[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 (non-responder 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 280mg 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  $\leq 8$  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 280mg 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  $\geq 1$  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  $\geq 1$  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-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, as determined by the 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.



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.

## 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, especially in NRCD and Type II refractory celiac disease 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 refractory celiac disease. AMG 714 is a fully human monoclonal antibody which binds to bioactive IL-15 and has been well-tolerated and 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 NRCD and RCD-II.

The most efficient trial design for exploring proof-of-concept (POC) in celiac disease and, by extension, NRCD, is a gluten challenge study done in well-controlled celiac patients who are exposed to a known amount of gluten for a few months. A substantial peer-reviewed body of work exists demonstrating the value of gluten challenge as a diagnostic method (e.g., to diagnose celiac disease in subjects who initiated a GFD before receiving an accurate diagnosis) and well as in clinical trials (Lähdeaho *et al*, 2011; Lähdeaho *et al*, 2014). In clinical drug trials, the subjects continue their normal gluten-free diet and a controlled amount of gluten is added into an otherwise gluten-free foodstuff. A gluten challenge trial design allows POC testing with minimum sample size and short time of exposure to an experimental medication. Well-controlled gluten challenge studies with doses of gluten of up to 6 g/day for 12 weeks have been reported to be safe in celiac patients [Lähdeaho *et al*, 2011], as the gut mucosa recovers after the challenge is completed and subjects return to a strict GFD.

The main hypothesis of this study is that AMG 714 administered once every two weeks via SC administration will be significantly more efficacious than placebo in attenuating gluten-induced small intestinal mucosal morphological injury, and that it will be safe and well tolerated in subjects with celiac disease.

The study will enroll clinically well controlled patients on a GFD. After a two-week single-blind administration of placebo gluten, subjects will be exposed to 4 grams of gluten per day for 10 weeks in the presence or absence of 150 mg or 300 mg of AMG 714-CHO administered every other week, beginning at the time of the single-blind placebo gluten dosing, for a total of 10 weeks. Toxicology and human studies to date support the dosing regimens selected for this celiac study. The highest doses of AMG 714 tested in clinical trials are 700 mg single dose and 300 mg every two weeks for 12 weeks with no safety signals identified to date. Given the acceptable safety profile observed in previous trials, Celimmune intends to dose at or below the levels previously demonstrated as safe in this proposed trial in celiac disease.

The iVYLISA GIP assay will be used in the study to assess whether subjects are compliant with the GFD before enrollment and during the single-blind placebo gluten period (i.e., below a threshold of positivity) and thereafter, to confirm GFD compliance and correct consumption of the active gluten challenge material (i.e., neither above nor below a threshold appropriate for the consumption of approximately 4 grams of gluten daily for 10 weeks; this threshold will be specified in the SAP and will be used for subgroup and sensitivity analyses).

## **4 OBJECTIVES**

### **4.1 PRIMARY OBJECTIVE**

The primary objective of this study is to assess the efficacy of AMG 714 in attenuating the effects of gluten exposure in adults with celiac disease.

### **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 celiac disease exposed to a gluten challenge.

### **4.3 EXPLORATORY OBJECTIVE**

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

## **5 ENDPOINTS**

### **5.1 PRIMARY EFFICACY ENDPOINT**

- Attenuation of gluten-induced small intestinal mucosal morphological injury, measured morphometrically as VH:CD ratio.

### **5.2 SECONDARY EFFICACY ENDPOINTS**

- Attenuation of gluten-induced small intestinal mucosal inflammation as measured by the density of IELs.
- Attenuation of gluten-induced small intestinal mucosal morphological injury using a grouped classification of Marsh score.
- Attenuation of gluten-induced serum antibodies:
  - Anti-tTG IgA
  - Anti-DGP IgA and IgG
- Attenuation of gluten-induced clinical symptoms, as assessed by:
  - Bristol Stool Form Scale (BSFS)
  - Gastrointestinal Symptom Rating Scale (GSRS) and celiac disease GSRS (CeD-GSRS)

### **5.3 EXPLORATORY ENDPOINTS**

- Pharmacokinetics (PK), Pharmacodynamics (PD) and Exposure/Response (PK/PD)
  - Dose proportionality, time to steady-state, and accumulation ratio based on  $C_{\text{trough}}$  concentrations
  - Comparison of  $C_{\text{trough}}$  levels with corresponding values in study 20060349
  - Correlation of  $C_{\text{trough}}$  concentrations with biomarkers of disease activity



- Physician Global Assessment of Disease (PGA)
- Biomarkers of disease activity
- Celiac Disease Patient-Reported Outcome (CeD PRO)

In subjects with dermatitis herpetiformis (DH), photography will be conducted according the study manual. Skin biopsies will be allowed per investigator's discretion but will not be part of this protocol. Any skin information on DH will be summarized for descriptive purposes without formal statistical analysis.

#### 5.4 SAFETY ENDPOINTS

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

## 6 STUDY DESIGN

Protocol CELIM-NRCD-001 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 attenuation of the effects of gluten exposure in adult patients with celiac disease during a gluten challenge.

After signing consent subjects will be screened for the study. All subjects who meet the study entry criteria will be randomized at a 1:1:1 ratio to receive 150 mg or 300 mg AMG 714 or placebo once every two weeks for 10 weeks. Randomization will be stratified by sex. The study drug (AMG 714 or placebo) will be administered at the clinical site in a double-blind fashion via subcutaneous (SC) injection. Subjects will remain confined to the study site for a minimum of 1 hour after each administration of study medication. During this time the Investigator and study site staff will assess the subject for AEs and collect the required PK samples and post dose vital signs as outlined in the study schedule of events (Table 1).

In addition to receiving study medication (AMG 714 or placebo), all subjects will be required to consume either placebo gluten or active gluten administered in a single-blind fashion. Beginning on the day following Visit 1 (i.e. Week 0/Day 1, since Visit 1 is defined as Week 0/Day 0) through Visit 2 (week 2/Day 14), all randomized subjects will consume placebo gluten, in the form of gluten-free foodstuffs (e.g. rusks) provided by the Sponsor, twice a day (BID) at the time of two regularly consumed gluten-free meals (chosen by the subject). Starting at Visit 2, subjects will switch to consume a daily total of approximately 4g of active gluten, provided in the form of foodstuff identical in appearance to that provided during the two-week single-blind placebo-gluten period. These gluten-containing foodstuffs, supplied by the sponsor, will be consumed in approximately 2g doses BID at the time of two regularly consumed gluten-free meals (as chosen by the subject) from Visit 2 (Week 2/Day 14) through the end of the treatment period at Visit 7 (Week 12/Day 84). Consumption of additional products containing gluten will be prohibited and subjects will be expected to continue total

adherence to their former GFD from the time of screening until the follow-up study visit (Visit 8, Week 16/Day 112).

Subjects' adherence to GFD and consumption of provided gluten will be periodically assessed via stool and urine sample testing using the iVYLISA GIP stool and urine gluten tests. Subjects with known or suspected GFD transgressions or those suspected of non-compliance to protocol specified gluten dosing will be counseled and allowed to continue in the study.

A study site staff member will contact each subject by telephone both one day and one week after the first study drug administration in order to assess for AEs. Subjects will return to the clinic every two weeks for study drug administration and/or efficacy and safety assessments as indicated in the study schedule of events (Table 1). The final study drug administration will occur at Visit 6 (Week 10/Day 70). An end-of-study efficacy assessment will be collected at Visit 7 (Week 12/Day 84). A final study visit will be conducted six weeks after the last administration of study drug at Week 16 (Visit 8/Day 112).

Subjects who meet all other study entry criteria will undergo upper gastrointestinal endoscopy and biopsy prior to baseline (Visit 1, Week 0/Day 0) and at the end of the 12-week randomized period while still on the gluten challenge within five days before Visit 7 (Week 12/Day 84) in order to assess changes from baseline in VH:CD ratio, IELs, and Marsh score. If the screening biopsy shows villous atrophy with a VH:CD less than 1.5 (1.4 or lower), and after notification to the sponsor, the subject may be allowed to stay in the study but the gluten challenge will be not be started (or will be interrupted if the patient has been started in the challenge) and the subject will not be included in the main efficacy assessments. Subjects with VH:CD 1.5 or above will receive the gluten challenge.

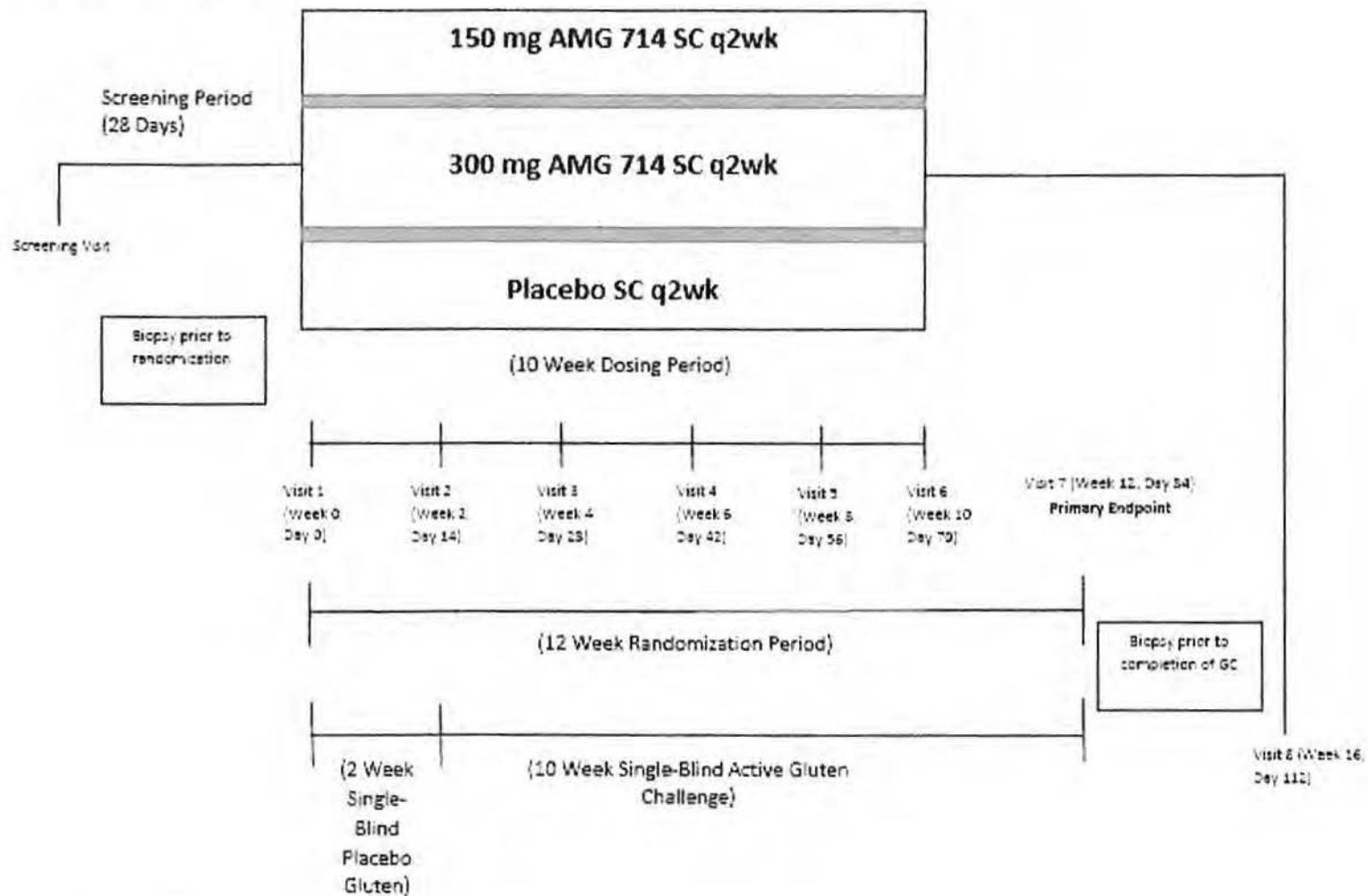
All subjects will complete the BSFS at the time of each bowel movement from baseline (Visit 1; Week 0/Day 0) up to the final study visit, Visit 8 (Week 16/Day 112). Subjects will complete the CeD PRO daily from baseline up to the final study visit. Subjects will also complete the GSRS at screening and, thereafter, weekly from baseline through the study final study visit. The BSFS, GSRS and CeD PRO will be completed using a handheld electronic diary at times specified in the Schedule of Events (Table 1).

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 signs, and AE monitoring.

**NOTE:** The Sponsor may arrange with the study sites the conduct of some of the intermediate visits at the subject's home, provided that appropriate healthcare personnel conducts the visit with similar standards to visits conducted at the study site. Visits amenable for home administration include Visits 3 through 5

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

Figure 1. Study Schematic





## **7 RANDOMIZATION AND TREATMENT ASSIGNMENT**

Subjects will be randomized at a 1:1:1 allocation to receive 150 mg AMG 714 or 300 mg AMG 714, or placebo once every two weeks for a total of six administrations over ten weeks. Randomization will be stratified by site and sex.

## **8 DURATION OF STUDY**

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

## **9 SUBJECT POPULATION**

A total of approximately 63 males and females between the age of 18 and 80 years, inclusive, will be randomized into the study in order to obtain 51 evaluable subjects. If the number of evaluable subjects is expected to be below 51 after exclusion of withdrawn and non-evaluable subjects (i.e. subjects dropping out of the study before Week 6, subjects with a diagnosis of DH and subjects with villous atrophy at baseline not provided the gluten challenge), enrollment in excess of 63 may be required in order to reach 51 evaluable subjects.

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 to 80 years of age, inclusive.
2. Demonstrate willingness to participate in the study as documented by signed informed consent.
3. Subjects must have a diagnosis of celiac disease by intestinal biopsy at least 12 months prior to screening as confirmed by medical records, written physician statement or by the Kela statement, the national social security institution determining the governmental reimbursement for biopsy-proven celiac disease patients.
4. Subjects must have been on a GFD for at least 12 consecutive months prior to screening and must be willing to remain on a GFD for the duration of study participation (apart from the Sponsor-supplied approximately 2g gluten taken BID during the 10-week gluten challenge period of the study).
5. Negative anti-tTG (IgA at screening).
6. Negative *H-pylori* test prior to study drug administration.
7. HLA-DQ typing compatible with celiac disease provided or obtained before baseline biopsy.

8. BMI between 16.0 and 45.0 kg/m<sup>2</sup>, inclusive.
9. Screening laboratory values within the following parameters: (unless investigator considers an abnormality to be not clinically significant)
  - a) ALT and AST < 2.5 x the ULN.
  - b) Hemoglobin > 10 g/dL (>100 g/L in SI units).
  - c) Platelet count > 125,000 mm<sup>3</sup> (>125 x10<sup>9</sup>/L).
  - d) White blood cell count > 3,500 cells/mm<sup>3</sup> (>3.5 x10<sup>9</sup>/L).
  - e) eGFR ≥ 60 ml/min.
  - f) HbA1C <7% (<53 mmol/mol) in subjects with a diagnosis of Type 1 or Type 2 Diabetes Mellitus.
10. 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 (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, oophorectomy); or otherwise incapable of pregnancy.

**OR**

Females of childbearing 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 8, Week 16/Day 112) and for 6 months after the end of the study.

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 the study if there is evidence of any of the following:

1. Current diagnosis of any severe complication of celiac disease, such as RCD-I or RCD-II, EATL, ulcerative jejunitis, or perforation.
2. Diagnosis of any autoimmune disease (other than celiac disease and DH) that might interfere with the conduct of the study or require systemic immunomodulation therapy.
3. Occurrence of celiac disease-related symptoms (CeD-GSRS >2.3) as assessed by screening GSRS.
4. Diagnosis of any chronic, *active* GI disease other than celiac disease (e.g. active, untreated peptic ulcer, esophagitis, GERD; active ulcerative colitis; Crohn's disease; or irritable bowel syndrome) that might, in the Investigator's opinion, interfere with assessment of symptoms of abdominal pain, diarrhea, or other components of celiac disease.
5. Any known, *symptomatic* food allergy, including an allergy to the ingredients of the gluten challenge vehicle that, in the opinion of the Investigator, might interfere with the conduct of the study or result in anaphylaxis.
6. Presence of any of the following related to infection:
  - a) Active acute infection requiring systemic treatment (antibiotics, antifungal, or antiviral)
  - b) Active GI infection

- c) Persistent or severe infection within the 3 months prior to randomization
  - d) History of TB
  - e) 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.
  - f) History within the 3 years prior to screening of an opportunistic infection typical of those seen in immunocompromised patients (e.g. herpes zoster, systemic candida infection, or systemic fungal infection).
7. Use of systemic immune suppressants (including steroids) within 3 months or 5 half-lives, whichever is longer, from randomization.
  8. Required use of a prohibited medication at the time of randomization (prohibited medications required for treatment of an AE occurring after randomization are permitted).
  9. Current diagnosis or history of cancer within the past 5 years, except successfully treated basal cell or squamous cell carcinoma, cervical carcinoma-in-situ, or early stage prostate cancer.
  10. Administration of a live vaccine within 14 days prior to the first dose of study drug.
  11. 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 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
  12. History of significant drug or alcohol abuse during the year prior to study screening as obtained by medical record and/or subject report.
  13. History of clinically significant hypersensitivity to the study drug, any related drugs, or to any of the excipients.
  14. History of anaphylactic reactions (e.g. IgE-mediated reactions) to wheat or gluten.
  15. Positive Hep B, Hep C, or HIV infection test results at the time of screening.
  16. Females who are pregnant or planning to become pregnant during the study participation period, or are currently breastfeeding.
  17. Participation in another investigational drug or device study or treatment with an investigational drug within 3 months or 5 half-lives, whichever is longer, prior to randomization.
  18. 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 including the endoscopies and biopsies collections

## 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, including steroids. Inhaled steroids for respiratory diseases such as asthma, and topical steroids (except intestinal) are permitted.
- Oral pharmaceutical presentations (e.g., capsules) of probiotic supplements. Probiotics in foods (e.g. yogurt) are accepted.
- Chronic or continuous oral and IV antibiotics (>2 weeks use). Topical antibiotic use is allowed.
- Systemic anti-virals.
- Systemic anti-fungals.
- 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 (see Section 21).

### 10.2 GUIDELINES FOR THE MANAGEMENT OF ANTI-COAGULANT AND ANTI-PLATELET CONCOMITANT MEDICATIONS

Patients on concomitant anticoagulant or antiplatelet therapy are allowed to participate in the study.

The investigators will follow the Guidelines of the Endoscopy Committee of the British Society for Hematology for management of these medications. These guidelines (Veitch *et al*, 2008) have been translated to Finnish and endorsed by the Finnish University Hospitals (Peräaho *et al*, 2010).

In short, anticoagulation or antiplatelet therapy should be continued. If warfarin is continued, then it should be ensured that the international normalized ratio (INR) does not exceed the therapeutic range 1 week before the endoscopy. If the INR is above the therapeutic range, but less than 5, then the daily warfarin dose should be reduced until the INR returns to within the therapeutic range.



**If the INR is greater than 5, then the endoscopy should be postponed and the investigator should discuss the situation with the medical monitor in order to ensure the subject's safety.**

## **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 calls after Visit 1, the Visit 7 endoscopy and biopsy, and Visit 8 (Week 16/Day 112), should be conducted within  $\pm 3$  days from the scheduled visit day relative to the randomization (unless otherwise indicated). The follow-up phone calls should be conducted within +1 day from the scheduled dates. The Visit 7 endoscopy and biopsy should be conducted while the subject is still on the gluten challenge within 5 days before Visit 7 (but no later than Visit 7), and Visit 8 (Week 16/Day 112) should be within +7 days of the scheduled date.

All study visits occurring after randomization (Visit 1, Week 0/Day 0) should be based on the Visit 1 study visit date. During the 12-week randomization period, defined as the period from Visit 1 to Visit 7, if a visit occurs no more than 4 days outside of the visit window, the study drug can be administered and the next visit scheduled in accordance with the original 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 should be recorded. Under no circumstances should any two doses of study drug be administered within fewer than 7 days of each other.

If a subject misses two consecutive doses of study drug, the subject should be terminated from the study after consultation with the Sponsor. The subject should complete the Early Termination visit. A final study visit should be conducted at least 6 weeks (+7 days) after the last administration of study drug. The final study visit is not required if the last administration of study drug occurs 6 or more weeks prior to the Early Termination visit.

**NOTE:** The Sponsor may arrange with the study sites the conduct of some of the intermediate visits at the subject's home, provided that appropriate healthcare personnel conducts the visit with similar standards to visits conducted at the study site. Visits amenable for home administration include Visits 3 through 5

### **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 of all other parameters 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.

## 11.2 SCREENING PERIOD

- Obtain informed consent.
- Register the visit in the Electronic Data Capture (EDC) system.
- Allow subject to complete GSRS. If subject does not meet the inclusion/exclusion criteria for celiac-related symptoms (i.e., if subject's CeD-GSRS in past week is  $>2.3$ ), no further testing should be conducted. The subject may be re-tested for CeD-GSRS once after at least a week and resume the rest of the screening procedures if  $\leq 2.3$ .
- Review inclusion/exclusion criteria. For interpretation of hepatitis testing, 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.

- Calculate BMI.
- 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 five 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 and *H-pylori* testing. The stool sample should be collected after the subject has signed the informed consent form.
- Collect blood and urine specimens for clinical laboratory testing (see Appendix B and/or Laboratory manual for the parameters).
- Collect blood for serum pregnancy test for all FOCBP subjects.
- Conduct INR if the subject is on warfarin (see section 10.2)
- Begin assessment of AEs
- Schedule subject for endoscopy and biopsy procedure.

When possible, screening clinical laboratory test results should be reviewed by the Investigator or appropriate, qualified designee for clinically significant abnormalities before proceeding with the endoscopy and biopsy. If this is not possible due to site scheduling or subject preference (i.e., subject lives too far away and does not want to make multiple visits site) review of the laboratory results before the biopsy procedure is not required. .

### 11.3 12-WEEK RANDOMIZATION PERIOD

#### 11.3.1 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. .

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

#### 11.3.2 Visit 1 (Week 0/Day 0)

- Review inclusion/exclusion criteria
- Document visit in EDC system.
- Assign e-diary and allow subject to complete the first weekly GSRS and first daily CeD PRO
- Collect vital signs prior to 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.
- Complete PGA *before* study drug administration.
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK, biomarkers and anti-drug antibodies (ADA) *before* start of study drug administration. Record exact date and time of sampling.
- Optional: Collect iVYLISA GIP stool sample. The stool sample may be collected in the clinic at the study visit or at the subject's home or preferred location no more than 3 days before or after the scheduled study visit (a +/-3 day window).
- Perform urine pregnancy test on all FOCBP subjects.

- Administer study medication. See Section 18 for administration procedures.

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

- Collect vital signs 30 minutes after study drug administration. Record time and date of collection.
- 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.
- Dispense single-blind placebo gluten product and instruct subject to begin consuming the product the next day at the first regularly scheduled gluten-free meal. The product should be consumed BID at two regularly scheduled gluten-free meals of the subject's choosing. The placebo gluten should be consumed at the same time each day at the same meal.

**NOTE:** At no time should subject be made aware that he or she is consuming placebo or active gluten.

- Provide subject with iVYLISA GIP test kit(s) and instructions for home collection.

### 11.3.3 Safety Phone Calls (Week 0/Day 1 & Week 1/Day 7)

- 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.

### 11.3.4 Visit 2 (Week 2/Day 14)

- Document visit in EDC system.
- Collect vital signs.
- Perform physical examination to include an examination of general appearance; HEENT; lymph nodes; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological, psychological and dermatological systems.
- Complete the PGA *before* study drug administration
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK, biomarkers and ADA *before* study drug administration. Record exact date and time of sampling.
- Optional: Collect stool for iVYLISA GIP test. The stool sample will be collected no more than three days prior to or after the scheduled study visit.
- Perform urine pregnancy test on all FOCBP subjects.

- Administer study medication. See Section 18 for administration procedures.

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

- Collect vital signs 30 minutes after study drug administration. Record time and dose of collection.
- Collect any unused placebo gluten. Dispense active gluten challenge product provided by the Sponsor in a single-blind fashion to the subject and instruct subject to continue consuming the product BID at two regularly scheduled gluten-free meals (morning, midday or evening). The active gluten challenge should be consumed the same time each day with each selected meal.

**NOTE:** At no time should the subject be made aware that he or she is consuming placebo or active gluten.

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

### 11.3.5 Visit 3 (Week 4/Day 28)

- Document visit in the EDC system.
- Collect unused gluten challenge product.
- Collect vital signs.
- 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.
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK, biomarkers and ADA *before* study drug administration. Record exact date and time of sampling.
- Optional: Collect stool for iVYLISA GIP test. The stool sample will be collected no more than three days prior to or after the scheduled study visit.
- Perform urine pregnancy test on all FOCBP subjects.
- Administer study medication. See section 18 for administration procedures.

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

- Collect vital signs 30 minutes after study drug administration. Record time of collection.

- Dispense active gluten challenge product provided by the Sponsor in a single-blind fashion to the subject and instruct subject to continue consuming the product BID at two regularly scheduled gluten-free meals (morning, midday or evening). The active gluten challenge should be consumed the same time each day with each selected meal.
- Assess AEs.
- Monitor for changes to concomitant medication.
- Remind subject 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 instruction for home collection.

#### 11.3.6 Visit 4 (Week 6/Day 42)

- Document visit in EDC system.
- Collect unused gluten challenge product
- Collect vital signs.
- Measure body weight.
- Perform urine pregnancy test on all FOCBP subjects.
- Optional: Collect stool for iVYLISA GIP test. The stool sample will be collected no more than three 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 study drug administration to monitor for new AEs.

- Collect vitals 30 minutes after study drug administration. Record time of collection.
- Dispense active gluten challenge product provided by the Sponsor in a single-blind fashion to the subject and instruct subject to continue consuming the product BID at two regularly scheduled gluten-free meals (morning, midday or evening). The active gluten challenge should be consumed the same time each day with each selected meal.
- Assess AEs.
- Monitor for changes to concomitant medication.
- 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.

#### 11.3.7 Visit 5 (Week 8/Day 56)

- Document visit in the EDC system.
- Collect unused gluten challenge product.
- Collect vital signs.

- 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.
- Collect blood and urine for clinical laboratory testing.
- Collect blood sample for PK, biomarkers and ADA *before* study drug administration. Record exact time and date of sampling.
- Perform urine pregnancy test on all FOCBP subjects.
- Optional: Collect stool for iVYLISA GIP test. The stool sample will be collected no more than three 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 study drug administration to monitor for new adverse events.

- Collect vitals 30 minutes after study drug administration. Record time of collection.
- Dispense active gluten challenge product provided by the Sponsor in a single-blind fashion to the subject and instruct subject to continue consuming the product BID at two regularly scheduled gluten-free meals (morning, midday or evening). The active gluten challenge should be consumed the same time each day with each selected meal.
- Assess AEs.
- Monitor for changes to concomitant medication.
- Remind subjects to complete the BSFS at each occurrence of a bowel movement and CeD PRO daily.
- Remind subject to complete the weekly GSRS.
- Provide subject with iVYLISA GIP test kit and instructions for home collection.

#### 11.3.8 Visit 6 (Week 10/Day 70)

- Document visit in the EDC system
- Collect unused gluten challenge product.
- Collect vital signs.
- Perform urine pregnancy test on all FOCBP subjects.
- Collect blood sample for PK and biomarker testing *before* study drug administration. Record exact time and date of sample.
- Optional: Collect stool for iVYLISA GIP test. The stool sample will be collected no more than three 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 study drug administration to monitor for new AEs.

- Collect vitals 30 minutes after study drug administration. Record time of collection.

- Dispense active gluten challenge product provided by the Sponsor in a single-blind fashion to the subject and instruct subject to continue consuming the product BID at two regularly scheduled gluten-free meals (morning, midday or evening). The active gluten challenge should be consumed the same time each day with each selected meal.
- 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 collection.

### 11.3.9 Visit 7 (Week 12/Day 84)

#### **NOTE: DO NOT ADMINISTER STUDY MEDICATION AT THIS VISIT**

- Document visit in the EDC system.
- Collect all remaining unused gluten challenge product.
- 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.
- Collect blood and urine for clinical laboratory testing.
- Collect blood for PK, biomarkers and ADA. Record exact date and time of sampling.
- Perform serum pregnancy test on all FOCBP subjects.
- Mandatory: Collect stool for iVYLISA GIP testing. The stool sample will be collected no more than three days prior to or after the scheduled visit.
- 
- 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.
- Perform endoscopy and collect biopsy specimens within 5 days prior to visit.

## 11.4 FINAL STUDY VISIT

### 11.4.1 Visit 8 (Week 16/Day 112) or 6 Weeks After Last Study Drug Administration

- 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.
- Collect blood and urine for clinical laboratory testing.
- Collect blood for PK, biomarkers and ADA. Record exact date and time of sampling.
- Perform urine pregnancy test on all FOCBP subjects.
- Optional: Collect stool for iVYLISA GIP testing. The stool sample will be collected no more than three days prior to or after the schedule visit.
- Monitor for ongoing AEs.
- Monitor for changes to concomitant medications.
- Collect eDiary and register subject as complete.

### 11.5 EARLY TERMINATION

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

- Document visit in the EDC system.
- Collect all remaining unused placebo gluten or gluten challenge product.
- 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.
- Collect blood and urine for laboratory testing, including urine for gluten testing.
- Collect blood sample for PK, biomarkers and ADA. Record exact date and time of sampling.
- Perform serum pregnancy test on all FOCBP subjects.
- All attempts should be made to collect a final iVYLISA GIP stool sample during the Early Termination visit, if a subject does not bring to the study site a sample that was collected no more than three days prior to the visit.
- Collect eDiary and register subject as withdrawn or Early Termination.
- Assess ongoing AEs.
- Monitor for changes to concomitant medications.
- Perform endoscopy and collect biopsy specimens, unless not indicated based on the subject's condition, at the PI's discretion.
- Schedule Follow-up Visit. A follow-up visit is not required if the Early Termination visit occurs six or more weeks after the last study drug administration.

## 12 DEFINITION OF END OF STUDY

The end of study is defined as the final study visit (Visit 8; Week 16/Day 112) for the last subject.

## 13 EFFICACY ASSESSMENTS

### 13.1 HISTOLOGICAL ASSESSMENT OF DUODENO-JEJUNAL BIOPSY: VH:CD RATIO, IEL DENSITY AND MARSH SCORE

At each time point specified in Table 1, small-bowel biopsies will be collected in order to perform the histological assessment of mucosal inflammation. The primary endpoint in the study is the attenuation of gluten-induced reduction in small intestinal villous height to crypt depth (VH:CD) ratio, assessed with a validated morphometric analysis (Taavela *et al.*, 2013). Small bowel morphological injury as measured by VH:CD ratio is the most robust endpoint with which to assess efficacy of a medication targeting the underlying pathophysiology of celiac disease (Lähdeaho *et al.*, 2014). A key secondary endpoint is the attenuation of gluten induced small intestinal mucosal inflammation as measured by intraepithelial CD3-positive lymphocyte (IEL) density. The Marsh-Oberhuber score will also be calculated as a secondary endpoint (Marsh, 1992; Oberhuber 2000).

At each time point specified in Table 1, approximately six to nine (6-9) 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 done in the duodenum D2 segment, avoiding ulcerative lesions. 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 also be captured. 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. The fragments or specimens will be prioritized as follows:

- 1) The first four (4) specimens collected will be fixed in 10% formalin or other fixative. One (1) of them will be used for standard pathology at the site and three (3) of them will be 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, which is the primary efficacy measure. 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 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.
- 2) The second two (2) specimens will be placed in mRNA preservative for future mRNA analysis of inflammatory pathways (e.g. expression analysis of IL-15-related pathways to potentially identify predictive biomarkers of response to AMG 714)
- 3) The last specimens, up to three (3), are optional and for research use. They will only be collected at sites with fresh tissue culture capabilities or able to ship immediately to such a site, and will be used for functional experiments and analysis of IL-15 related biomarkers or the impact of IL-15 on epithelial cell biology. In particular, one specimen

from approximately 15 subjects (baseline and Week 12) will be used in Finland for crypt cell mini-gut cultivation to study biomarkers of epithelial cell differentiation in the crypt-villus axis.

Every effort will be made to collect all 6-9 specimens, but if this number cannot be reached, the specimens will be allocated in the order indicated.

### 13.2 **SEROLOGY: ANTI-TISSUE TRANSGLUTAMINASE AND ANTI-DEAMIDATED GLIADIN PEPTIDES ANTIBODIES**

Anti-tTG auto-antibodies, while not very responsive to modest dietary transgressions, are very specific for celiac disease activity and constitute an important tool to assess disease modification (Lähdeaho *et al*, 2011; Kelly *et al*, 2013). Blood will be collected for determination of serum anti-tTG (IgA throughout the study and IgG also at screening) by immunoassay at times indicated on the Schedule of Events (Table 1).

Anti-deamidated gliadin peptide (DGP) antibodies (anti-DGP), IgA or IgG, may be positive in some patients with celiac disease who are negative for anti-tTG, due to their different kinetics and to the possibility of IgA deficiency, in which case, DGP IgG are the most reliable antibodies (Brusca, 2015). Blood will be collected for determination of serum DGP antibodies (IgA and IgG) at times indicated on the Schedule of Events (Table 1).

### 13.3 **BRISTOL STOOL FORM SCALE**

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 8; 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.

### 13.4 **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). The “Celiac Disease GSRS” (CeD-GSRS; Leffler *et al*, 2015) is a subset of the GSRS that focuses on the ten questions of the GSRS which are most relevant to celiac disease: 1(Pain), 4 (Hunger), 5 (Nausea), 6 (Rumbling), 7 (Bloating), 8 (Burping), 9 (Gas), 11 (Diarrhea), 12 (Loose stool), 14 (Urgency).

Subjects will be asked to complete this questionnaire at the Screening Visit, in order to determine the CeD-GSRS. After screening randomized subjects will complete the questionnaire weekly using an electronic diary, from the day of randomization through the final study visit.

### 13.5 CELIAC DISEASE PATIENT-REPORTED OUTCOME (CED PRO)

Subjects will be asked to maintain a daily e-diary for the CeD PRO instrument (Appendix I) 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.

## 14 EXPLORATORY ASSESSMENTS

### 14.1 PHARMACOKINETICS AND PHARMACODYNAMICS

Dose proportionality, time of achievement of steady-state, and accumulation ratio between the first and sixth dose will be explored based on  $C_{\text{trough}}$  serum concentrations.  $C_{\text{trough}}$  values for each dose group following the sixth dose will also be compared with the corresponding values in 20060349.

The correlation between  $C_{\text{trough}}$  values after the sixth dose and Pharmacodynamics (PD), based on biomarkers, will be explored.

PK samples must be collected 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 electronic case report forms (eCRFs).

### 14.2 IVYLISA GIP TESTS

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 the evaluation of a potential therapeutic effect of any experimental celiac-related medication, since histologic, serologic 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 stool and urine gluten tests, gluten assays developed to detect inadvertent gluten consumption by measuring gluten immunogenic peptides (GIP) in feces (Comino *et al.*, 2012) and urine (Moreno *et al.*, 2015).

The iVYLISA GIP-S test for stools is validated and will be used at screening and study end (mandatory) and intermediate visits (optional) per Table 1. This test has a CE mark and is

commercially available in Europe from Biomedal SL (as a research test) and several central laboratories, 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 signs and symptoms 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 Deliac study. The urine test, soon to become commercially available, has shown close correlation with intestinal mucosal atrophy in celiac patients on a purported GFD (Moreno *et al*, 2015).

These assays will be used in the study to assess whether the patient population is compliant with the GFD prior to enrollment (i.e., below a threshold of positivity in the stool test) and, thereafter, to confirm consumption of the gluten challenge and lack of consumption of additional non-protocol gluten during the trial. The stool test detects gluten for up to seven days after consumption, and the urine test for 1-2 days. Testing will be done every two weeks – subjects should provide a urine and optional stool sample collected up to three days before or after the visit to the sites, in order to have a good probability of identifying dietary transgressors.

Testing will be done at a central lab. Pre-specified sensitivity analyses for dietary gluten will be conducted based on serial iVYLISA GIP-S stool and urine testing. Stool samples may also be used for microbiome analysis, as microbiomes are known to affect gluten composition and the biology of IL-15.

In Finland, celiac patients consume oats as a part of their diet. The trace amounts of gluten present in oats will not interfere with the iVYLISA GIP test at screening or during the study (Real *et al*, 2012).

### 14.3 PHYSICIAN GLOBAL ASSESSMENT OF DISEASE

The PGA (Appendix E) is designed to be used by the Investigator or qualified designee to assess the subject's 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. Assessments should be made prior to study drug administration using all tools available to the assessor, including laboratory test values.

### 14.4 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.

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 mRNA (for expression profiling, such as IL-15 signature for potential predictive biomarkers), biopsy fragments (for mRNA, protein), 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 CSR. The sample retention timelines will be described in the informed consent and will not be longer than 15 years.

The DNA sample for HLA testing at screening (HLA DQ2/DQ8) to confirm celiac disease 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.

#### **14.5 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.

### **15 SAFETY ASSESSMENTS**

In addition to AE monitoring (Section 22), 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)

#### **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.

## 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 Events (Table 1). Blood and urine samples collected at the Screening visit will require a minimum of 8 hours of fasting.

A subject with a clinically significant laboratory finding identified at Screening 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 compromises subject 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 Specimen Collection and Processing Manual or equivalent document supplied by the Sponsor.

### 15.3.1 Pregnancy Testing

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

## 16 LOCAL AND CENTRAL LABORATORIES

Detailed information about local and central laboratory activities will be provided in a separate study specific Specimen Collection and Processing 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.
- Subject must consume the placebo gluten/active gluten product provided by the Sponsor 2 times daily as indicated in Section 19 of the study protocol
- Subjects must be willing to return for all scheduled study visits and complete required study diaries
- Subjects must refrain from blood donation, 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 subcutaneous injection and will be administered at the study site by a qualified staff member in a double-blind fashion via two SC injections once every two weeks a total of 6 times for a maximum of 10 weeks (+/- 3 days).

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 two SC infusions once every two weeks a total of six 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 levels for the study is based on a desire to strike the appropriate benefit/risk balance. On the one hand, striving for efficacy by testing an adequate dose of AMG 714 in an attempt to prevent the presumed effects of IL-15; and, on the other hand, using a dose that is similar to doses used in prior studies with tolerability comparable to placebo. The selection of dosing levels for the CELIM-NRCD-001 study (150 and 300 mg q2w SC) is thus based on the efficacy and safety information from completed studies. The goal of the proposed study is to assess POC in celiac disease, hence the choice of 300 mg q2w AMG 714-CHO as the top dose based on the efficacy and safety of 280 mg q2w AMG 714-HYB in RA and the safety of 300 mg q2w AMG 714-CHO in psoriasis, given SC for 12 weeks in both studies.

Toxicology and human studies to date support the dosing regimen selected for this study. The highest doses of AMG 714 studied in clinical trials are a single SC dose of 700 mg and SC doses of 300 mg every two weeks for 12 weeks, with no safety signals identified to date.

Initial dose selection for RA studies was based on in vitro potency and animal models. In vitro potency was assessed by the ability to inhibit human IL-15 mediated proliferation of the murine cytotoxic T cell line, CTLL-2.

A study conducted in cynomolgus monkeys showed that these proteins, when given at the maximum feasible dose of 150 mg/kg, had nearly identical PK profiles and generally comparable pharmacodynamic effects as assessed by NK cell counts.



The dosing regimen is expected to provide trough levels above the concentration of AMG 714 used *in vitro* (10 µg/mL) to induce apoptosis of activated IELs in biopsies of patients with active celiac disease (Malamut *et al.*, 2010).

While there is no prior experience with AMG 714 in celiac disease nor any understanding of the potential PK/PD relationship in this disease, the proposed approach of testing the maximum doses tested in psoriasis, doses which have been found efficacious in RA, will allow the exploration of POC without increasing the risk of side effects.

Serum exposure will be monitored with frequent PK sampling. Tissue effects will be monitored with experimental biomarkers to be measured in the biopsies to be obtained throughout the study.

In summary, toxicology and human studies to date support the dosing regimens chosen for the celiac study, given the acceptable safety profile observed and the necessity to test high doses for POC in celiac.

#### 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, the Sponsor will supply the assigned unblinded staff member at each site with syringe labels and translucent colored tape to wrap around each dosing syringe before allowing the syringes to be provided to blinded study staff members.

#### 18.5 **UNBLINDING**

If there is a need to unblind a subject's treatment assignment for emergency medical management, the Investigator will contact the Lead Medical Monitor. The Lead 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 1:1:1 allocation ratio to receive AMG 714 150 mg or 300 mg AMG 714, or placebo every two weeks for up to 10 weeks. The randomization will be stratified by site and sex.

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

## 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 distribution procedures of Celimmune's chosen centralized distribution warehouse.

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 (eg, 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. Unblinded study site staff must notify the Unblinded Sponsor Representative 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

The unblinded study staff member responsible for receiving and preparing the study medication must obtain the vial assignment via the EDC system a minimum of 24 hours prior to the scheduled subject visit. This will allow for proper thawing and preparation of the study drug.

A separate Investigational Product Manual will provide information with regard to specific materials/manufacture of ancillary supplies to be provided by the study site. At a minimum these materials will include:

- Latex free syringe and needle for study drug preparation
- Needle for study drug administration
- Gauze, alcohol wipes

On the day before investigational product administration, AMG 714 must thaw overnight at 2 to 8° C. Once thawed, vials should be transferred to room temperature and gently swirled to ensure mixing. Vigorous shaking or vortexing should be avoided. Mixing may result in the

formation of small bubbles, which is normal. Preparation of the clinical supplies should be performed using aseptic techniques and under sterile conditions. Vials containing visible foreign particles should not be dispensed. Prolonged exposure to light should be avoided. AMG 714 should be warmed to room temperature, for a minimum of 1 hour before administration. Light exposure should continue to be avoided. After thawing, the product may be stored for up to 72 hours at  $5 \pm 3^{\circ}\text{C}$ , and no longer than 12 hours at room temperature.

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

- Study number
- Subject identification number
- Date and time of preparation
- Initials of pharmacist

Any remaining medication in the vials should not be used. All used vials of study medication should be kept under quarantined conditions until accountability is conducted and destruction instructions have been received from the Sponsor. If site SOPs do not permit retaining unused vials of medication alternate procedures should be agreed upon with the Sponsor in order to assure adequate drug accountability.

#### **18.7.4 Administration of Study Drug**

On any given day, if more than one subject is scheduled to receive study drug at the same research facility, each dose administration must be given at least 15 minutes apart.

All doses will be split into two separate syringes, one for each assigned vial, and administered into different sites on the subject's anterior abdominal wall. The SC injections should be administered in a consecutive fashion approximately 2cm apart, with the injections separated no more than 30 seconds. The side of the abdominal wall should be alternated at every visit (i.e., left side at one visit, right side at the next visit).

The syringe should be inspected by the study staff member responsible for administering study drug for any visible foreign particles. If the study drug is not suitable for injection, it should be returned to the unblinded study staff member for processing.

The study drug should be administered following the guidelines provided in the Investigational Product Manual.

#### **18.7.5 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. At the end of the study, or as directed by the Sponsor, all investigational product will be destroyed or returned. Study drug must not be destroyed until destruction is approved by the Sponsor and written notification of destruction approval is obtained and filed.

### **18.7.6 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 GLUTEN CHALLENGE**

### **19.1 PLACEBO GLUTEN AND ACTIVE GLUTEN CHALLENGE PRODUCT**

The placebo gluten and active gluten challenge products must always be dispensed in a single-blind fashion so as not to alert the subject to the material being consumed.

The first consumption of placebo gluten should occur at the time of the first regular gluten-free meal on the day after the first study drug administration visit (Week 0/Day 1) and should be taken BID thereafter, at the time of the two main gluten-free meals (either breakfast, lunch, or dinner at the subject's choosing) up to Visit 2 (Week 2/Day 14). At Visit 2 active gluten challenge will be dispensed to the subject in a single-blind fashion. The subject will continue to consume the gluten challenge material BID at the time of two regularly scheduled gluten-free meals (as chosen by the subject) until Visit 7; Week 12/Day 84. If a subject misses a dose of the placebo gluten or active gluten challenge materials at the time of a meal, the missed dose of gluten should be consumed as soon as possible or at the next main meal. No more than two doses of placebo gluten or active gluten challenge material should be consumed on any one day.

Screening biopsies will be read before Visit 2 if at all possible. If a subject's screening biopsy result shows villous atrophy with a VH:CD ratio less than 1.5 (1.4 or lower), the subject may be allowed to stay in the study but the gluten challenge will not be started, and the subject will not be included in the PP population analyses.

Any remaining unused placebo gluten or active gluten challenge product should be returned to the study site and accounted for on the appropriate Sponsor provided documentation.

## 19.2 GLUTEN CHALLENGE COMPLIANCE ASSESSMENT

Compliance to the gluten challenge will be assessed retrospectively using the iVYLISA GIP gluten and urine stool tests. Any subject with known non-compliance to the gluten challenge during the study will be counseled by a study staff member. Subjects with known or suspected GFD transgressions or those suspected of non-compliance to protocol specified gluten dosing will be counseled and allowed to continue in the study.

## 20 STOPPING CRITERIA

### 20.1 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 AE merits discontinuation of dosing in a given subject.

If a subject is found to have villous atrophy with crypt hyperplasia (for the purpose of this study, defined as VH:CD ratio less than 1.5 (1.4 or lower)) in the screening biopsy, the subject may be allowed to stay in the study and receive study drug but without active gluten challenge. These subjects will be excluded from the PP analysis.

Dose escalation or reduction is not allowed.

### 20.2 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 AE in any subject

The Sponsor will assemble an Independent Safety Committee (the Data Safety Monitoring Board, DSMB) to review the case. The committee and Sponsor will determine if a study-wide interruption in dosing is required.

## 21 SUBJECT COMPLETION AND WITHDRAWAL

### 21.1 SUBJECT COMPLETION

Subjects will be considered study completers at Visit 7 (Week 12/Day 84), regardless of whether or not the Visit 8 (Week 16/Day 112) final study visit is attended.

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

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

## 21.2 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 who 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, jejunitis, 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 will be considered screen failures.

### 21.2.1 Withdrawal Procedures

If for any reason a subject is withdrawn or discontinues before completing the final study 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.

## 22 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 22.1 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 AEs 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 study 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).

## 22.2 DEFINITION OF AN ADVERSE EVENTS

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 Adverse Events (TEAEs). Untoward experiences occurring prior to initiation of first administration of study drug are considered non-TEAEs.

## 22.3 SEVERITY

Severity is used to describe the intensity of a specific event. The event itself, however, may be of minor medical significance. Severity, thus, is not the same as seriousness, 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

## 22.4 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 as

- 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.

## 22.5 **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).

### **Unexpected adverse drug reaction**



An adverse reaction whose nature, severity, specificity and outcome are not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product).

**SUSARs, Suspected Unexpected Serious Adverse Reactions** will be reported to FIMEA (Finnish Medicines Agency) within 15 days (or within 7 days for death or life threatening) as expedited reports.

## 22.6 SPECIAL REPORTING SITUATIONS

### 22.6.1 Death

Death is an outcome of an event. The AE that resulted in the death should be recorded and reported as the SAE. All SAEs that are fatal or life-threatening shall be reported expeditiously (within seven days) to Fimea. If an autopsy is performed, efforts should be made to obtain the results.

### 22.6.2 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.

### 22.6.3 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.

### 22.6.4 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 on the appropriate eCRF forms.

### 22.6.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs shall be reported by the Sponsor to the regulatory authority in Finland (Fimea) and to the relevant ethics committee to fulfill national (Medical Research Act; Regulation on Clinical trials on Medicinal Products in Human Subjects 2/2012) and 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 Fimea. The Annual Safety Report will be accompanied by a report of the safety of participating study subjects prepared and signed by the Coordinating Investigator.

The Sponsor will also inform the investigators and Fimea of any significant new observations relating to the safety of the AMG 714 during the study.

## 22.7 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.

PIs 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. The MeDRA dictionary will be used for coding the event terms.

## 22.8 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 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:

**+1 301 789 4988**

The completed SAE Report should be emailed immediately upon completion 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.

## **22.9 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.

## **22.10 SAFETY REVIEW COMMITTEE**

Safety will be monitored throughout the study by the Sponsor and by a panel of independent experts, the DSMB. The DSMB 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 a statistician. 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.

Safety findings insufficient to trigger the stopping rules may, if judged appropriate by the DSMB, lead to suspension of enrollment during the review.

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 outlines the specific guidelines for all DSMB activities. DSMB decisions will be communicated to the Investigators by the clinical study team.

## 23 DATA ANALYSIS AND STATISTICS

In addition to this section of the study protocol, a Statistical Analysis Plan (SAP) 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:

- Dietary transgressions (insufficient or excessive gluten consumption) based on serial iVYLISA GIP testing.
- Sex
- Site

**Non-evaluable subjects** are subjects participating in the study whose endpoint data will not be part of the primary analysis because they are expected to behave differently with respect to the key study endpoints. Non-evaluable subjects are pre-specified before database lock and will include subjects dropping out of the study before Week 6 (insufficient duration of the gluten challenge), subjects with a diagnosis of DH (expected to have less histological impact and less intestinal symptoms), and subjects with atrophy at baseline (VH:CD ratio 1.4 or lower) not provided the gluten challenge. The non-evaluable subjects will be excluded from the PP population but will be included in the analyses of the ITT population. Non-evaluable subjects are allowed to participate, as they are expected to derive benefit and the information obtained could result in future studies focusing on their populations.

### 23.1 SAMPLE SIZE DETERMINATION

The sample size of approximately 63 subjects (21 subjects/arm) has been calculated to achieve at least ~ 80% power in the primary endpoint, the difference in the Baseline-to-Week-12 %-reduction of VH:CD ratio between the two AMG 714 arms and placebo. This sample size provides close to 90% (88.8%) power to detect a 40-point difference between the placebo arm and the 300 mg high-dose arm, and close to 80% (79.3%) power to detect a 35-point difference between the placebo arm and the 150 mg low-dose arm.

This sample size calculation is based on the following assumptions:

- $\alpha=0.05$ ,  $\beta=80\%$
- Analysis method: one-way ANOVA by SAS® (proc power)
- SD=36 and 45%-change (decrease) in the placebo group
- %-change (decrease) of 10% in the 150 mg and 5% in the 300 mg arms

- Drop-out rate ~19% (assuming non-evaluable drop-outs plus DH  $\leq$ 15% and non-evaluable due to technical issues or villous atrophy at baseline  $<$ 5%).

These assumptions are based on the observations made in a similar 12-week gluten challenge study done with 3-5 grams of gluten per day (Lähdeaho *et al*, 2011). According to this sample size calculation including a 19% drop-out rate, 17 completed evaluable subjects/arm (51 subjects) will be needed for the primary analyses.

## 23.2 POPULATIONS FOR ANALYSIS

The populations for analysis will be PP and ITT.

**PP Population:** The Per Protocol 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 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 to which they are randomized. Subjects with only one measurement available will be excluded from the ITT population for all endpoints that are defined as change from baseline. Safety population is by definition the same as the ITT population.

The primary analyses of the primary and secondary endpoints will be based on the ITT population. The efficacy parameters will also be analyzed using the PP population. Demographics and Safety parameters will be analyzed using the ITT population. Exploratory endpoints will use both the ITT and the PP populations.

## 23.3 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 imputations will be done.

## 23.4 STATISTICAL ANALYSES

### 23.4.1 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 also be tabulated.

#### 23.4.2 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.

#### 23.4.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group.

### 23.5 EFFICACY ANALYSES

#### 23.5.1 Primary Endpoint

The primary endpoint is the difference in the Baseline-to-Week-12 % reduction of VH:CD ratio between the two AMG 714 arms and the placebo arm. The villous height and crypt depth are measured and their ratio (VH:CD ratio) is calculated.

The primary endpoint will be tested for each of the two dose levels, 150 mg or 300 mg, separately as follows:

$$H_{10}: \mu_{\text{AMG 714 (300mg)}} = \mu_{\text{Placebo}}$$

against the alternative

$$H_{11}: \mu_{\text{AMG 714 (300mg)}} \neq \mu_{\text{Placebo}}$$

and

$$H_{20}: \mu_{\text{AMG 714 (150mg)}} = \mu_{\text{Placebo}}$$

against the alternative

$$H_{21}: \mu_{\text{AMG 714 (150mg)}} \neq \mu_{\text{Placebo}}$$

where  $\mu_{\text{AMG 714 (300mg)}}$ ,  $\mu_{\text{AMG 714 (150mg)}}$  and  $\mu_{\text{Placebo}}$  denote the mean Baseline-to-Week-12 % reduction of VH:CD ratio in the high-dose, low-dose and placebo arm, respectively. Each of the two hypotheses will be tested using a two-sided type I error level of 5% without any adjustments for multiple comparisons.

The primary analyses of the primary endpoint will be analyzed using analyses of covariance (ANCOVA), where baseline VH:CD ratio, site, and sex will be covariates, and treatment group is added as an additional covariate in order to test the primary hypothesis. The primary analyses will be based on the ITT population. Secondary analyses will be based on the PP population.

As an additional exploratory analysis, active (both doses combined) will be tested against placebo.

### **23.5.2 Secondary Efficacy Endpoints**

The secondary endpoints will be described in the SAP and will include:

- IEL: For mucosal inflammation the density of CD3-positive intraepithelial lymphocytes/100 epithelial cells will be calculated.
- Marsh-Oberhuber classes, Marsh 0, 1, 2, 3a-c. Grouping by converting the morphometric results into Marsh classes (Mäki-Jilab converter).
- GSRS and CeD-GSRS by week
- BSFS and number bowel movements by day and week
- Serology: Anti-tTG IgA and anti-DGP IgA and IgG

The secondary efficacy endpoints will also be analyzed using both the ITT and the PP populations. Change in IELs density will be analyzed using the same method as for the primary endpoint VH:CD ratio. Anti-tTG IgA and anti-DGP (IgA and IgG) will be analyzed using an MMRM approach, with baseline value, site, sex, and treatment group, time and a time-by-treatment group interaction as fixed effects, subject as random effect, and an underlying correlation structure between the time points providing the best fit for the model.

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

The GSRS and CeD-GSRS will be analyzed using the same method as that for the secondary endpoint anti-tTG IgA.

The secondary variables of change in IELs density and anti-tTG/DGP will be analyzed using the same method as for the primary endpoint.

### **23.5.3 Exploratory Endpoints**

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

- PK
- PD and Biomarkers of disease activity
- PK/PD relations
- PGA
- CeD PRO

For PK, PD, and PK/PD correlations the following will be evaluated:

- Dose proportionality, achievement on steady-state, and accumulation ratio based on  $C_{\text{trough}}$  concentrations.
- Comparison of  $C_{\text{trough}}$  levels with corresponding values in study 20060349.
- Correlation of  $C_{\text{trough}}$  concentrations with biomarkers of disease activity

Dose proportionality will be analyzed using a power model, which will be described in more detail in the SAP. The PK/PD correlation will be mainly assessed graphically.

The exploratory variables will be summarized by treatment groups for both the ITT and the PP populations.

## 23.6 SAFETY ANALYSES

### 23.6.1 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.

### 23.6.2 Other Safety Assessments

The following safety variables will be assessed:

- Clinical laboratory tests
- Physical examination
- Vital signs

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

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

### 23.6.3 Prior and Concomitant Medications

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

## 24 INTERIM ANALYSIS

No interim analysis is planned for this protocol.

## 25 DATA MANAGEMENT

### 25.1 CASE REPORT FORMS

Data will be collected on electronic case report forms (eCRFs) that are specifically designed for this study. The Investigator or designated study personnel will enter subject data into the



eCRFs. Only persons authorized by the Investigator to make original eCRF entries are allowed to make corrections.

All eCRF entries must be verifiable from hospital or subject records.

## 25.2 DATA MANAGEMENT PLAN AND DATABASE DESIGN

Detailed information on data management will be available in the Data Management Plan (DMP) specifically written for this study. The study database and data entry screen design as well as edit checks will be defined according to the corresponding eCRFs and the study protocol.

## 25.3 DATA VALIDATION

Data validation or data cleaning procedures are designed to assure validity and accuracy of clinical data. A Data Validation Plan will specify the checks that are to be performed on subject data to raise data discrepancies, and will define the electronic edit checks, and data validation queries to be created for the study. All study specific and standard data validation programming will be tested in a separate testing environment prior to use on production data.

## 25.4 MEDICAL CODING

AEs and medical history verbatim terms will be coded using the MedDRA, latest version available when approving the DMP.

Concomitant Medications verbatim terms will be coded using the WHO DD, most recent version held by data management vendor.

## 25.5 DATABASE LOCK

All data entry, validation, SAE-reconciliation and medical coding activities will be finalized before the database will be locked. All unnecessary user privileges to the study will be removed, except for the data manager who will perform the database lock.

In exceptional circumstances, when critical reasons justify, there may be a need to perform updates to the database after it has been locked. A database that is locked and released for analysis will only be unlocked if an error is identified that will significantly affect the statistical outcome of the primary analysis or change the safety profile of the study.

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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**

Before starting the study, the Sponsor will obtain written positive opinion for the start of the study from the Independent Ethics Committee (IEC), and written approval from the Regulatory Authority, Fimea, to conduct the study in Finland.

### **Informed Consent Form**

An Informed Consent Form (ICF) will be prepared by the Sponsor or its designees and will be approved by the Ethics Committee and Regulatory Authorities before study start.

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 eCRFs 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 appropriate, 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 advertising materials and relevant supporting information must be submitted by the Sponsor to, and approved by, the Fimea/IEC prior to study initiation.

The Sponsor is responsible for keeping Fimea and the IEC informed of amendments or changes to the protocol, and the progress of the study, as appropriate. The Sponsor is also responsible for fulfilling any conditions of approval imposed by Fimea/IEC. The Sponsor is responsible for keeping Fimea/IEC informed of safety events. The Sponsor is required to promptly notify Fimea/IEC of all AEs which are both serious and unexpected. This generally means SAEs that are not already identified in the IB or protocol, and that are suspected to be related to the study drug by the Investigator (i.e., SUSARs, Suspected Unexpected Serious Adverse Reactions). Other AEs and SAEs will be reported annually to Fimea/IEC (in the DSUR, Development Safety Update Report).

### **Case Report Forms**

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

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

The completed eCRF should be reviewed and the case book electronically signed, and dated by the Investigator. Instructions regarding eCRF 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 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; 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).

### **Study Medication Accountability**

All study drug will be manufactured by Amgen, Inc. and provided by Sponsor and its designated representative. 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 as appropriate.

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 during 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. The regulatory authority responsible for pharmaceuticals and their safety (in Finland, the Finnish Medicines Agency Fimea), has the right to conduct source data verification and ensure the appropriate conduct of the trial. This is done by comparing the trial information to the patient's original medical records and information regarding the patient's state of health. On patient's consent and upon request by representatives of the Therapeutic Goods Administration (TGA), European Agency for the Evaluation of Medicinal Products (EMA), FDA, other national or local health authorities, and the HREC/IEC, if appropriate, it will be permissible to conduct source data verification also for those regulatory authorities responsible for pharmaceuticals and their safety in other countries where the medicine will be used.

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 Investigator is responsible for compliance with the Finnish laws, 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**

The original trial documents must be stored for at least 15 years from the end of the trial according to the Fimea Administrative Regulation 2/2012.

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 eCRFs 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 the Investigator or qualified designee for corrections and/or clarifications of discrepant data. All data will be entered into a study database for analysis and reporting. A Clinical Monitoring Plan and DPM 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 during 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, Platelet Count, White Blood Cell count (WBC) with Differential, Red Blood Cell count (RBC))
- Complement C3 & C4
- HbA1C (Subjects with a diagnosis of Type 1 or Type 2 Diabetes only)
- BioCard Celiac Test (anti-tTG IgA)
- HLA-DQ (as needed)
- HCV Antibodies
- HBsAg
- HIV Antibodies
- Interferon Gamma Release Assay (IGRA)
- Urinalysis (Protein/Albumin, Glucose, Ketones, Blood Cells)
- IELs
- VH:CD
- mRNA/DNA
- iVYLISA GIP Stool Test
- H-pylori 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, Platelet Count, WBC with Differential, RBC)
- Complement C3 & C4
- Anti-tissue transglutaminase antibodies (IgA)
- Deamidated Gliadin Peptide (IgA and IgG)
- PK/PD/Biomarkers (including CRP)
- Anti-drug antibodies
- Urinalysis (Protein/Albumin, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test (optional)
- iVYDAL Urine Sample
- Urine Pregnancy (All FOCBP)

### 3) Visit 2 (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, Platelet Count, WBC with Differential, RBC)
- Complement C3 & C4
- PK/PD/Biomarkers (including CRP)
- Anti-drug antibodies
- Urinalysis (Protein/Albumin, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test (optional)
- iVYDAL Urine Sample
- Urine Pregnancy (All FOCBP)

#### **4) Visit 3 (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, Platelet Count, WBC with Differential, RBC)
- Complement C3 & C4
- Anti-tissue transglutaminase antibodies (IgA) and anti-DGP (IgA and IgG)
- PK/PD/Biomarkers (including CRP)
- Anti-drug antibodies
- Urinalysis (Protein/Albumin, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test (optional)
- iVYDAL Urine Sample
- Urine Pregnancy (All FOCBP)

#### **5) Visit 4 (Week 6/Day 42)**

- iVYLISA GIP Stool Test (optional)
- Urine Pregnancy (All FOCBP)

#### **6) Visit 5 (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, Platelet Count, WBC with Differential, RBC)
- Complement C3 & C4
- Anti-tissue transglutaminase antibodies (IgA) and anti-DGP (IgA and IgG)
- PK/PD/Biomarkers (including CRP)

- Anti-drug antibodies
- Urinalysis (Protein/Albumin, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test (optional)
- iVYDAL Urine Sample
- Urine Pregnancy (All FOCBP)

**7) Visit 6 (Week 10/Day 70)**

- PK/PD/Biomarkers (including CRP)
- iVYLISA GIP Stool Test (optional)
- Urine Pregnancy (All FOCBP)

**8) Visit 7 (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, Platelet Count, WBC with Differential, RBC)
- Complement C3 & C4
- Anti-tissue transglutaminase antibodies (IgA) and anti-DGP (IgA and IgG)
- PK/PD/Biomarkers (including CRP)
- Anti-drug antibodies
- Urinalysis (Protein/Albumin, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test
- iVYDAL Urine Sample
- IELs
- VH:CD
- mRNA/DNA
- Serum Pregnancy (All FOCBP)

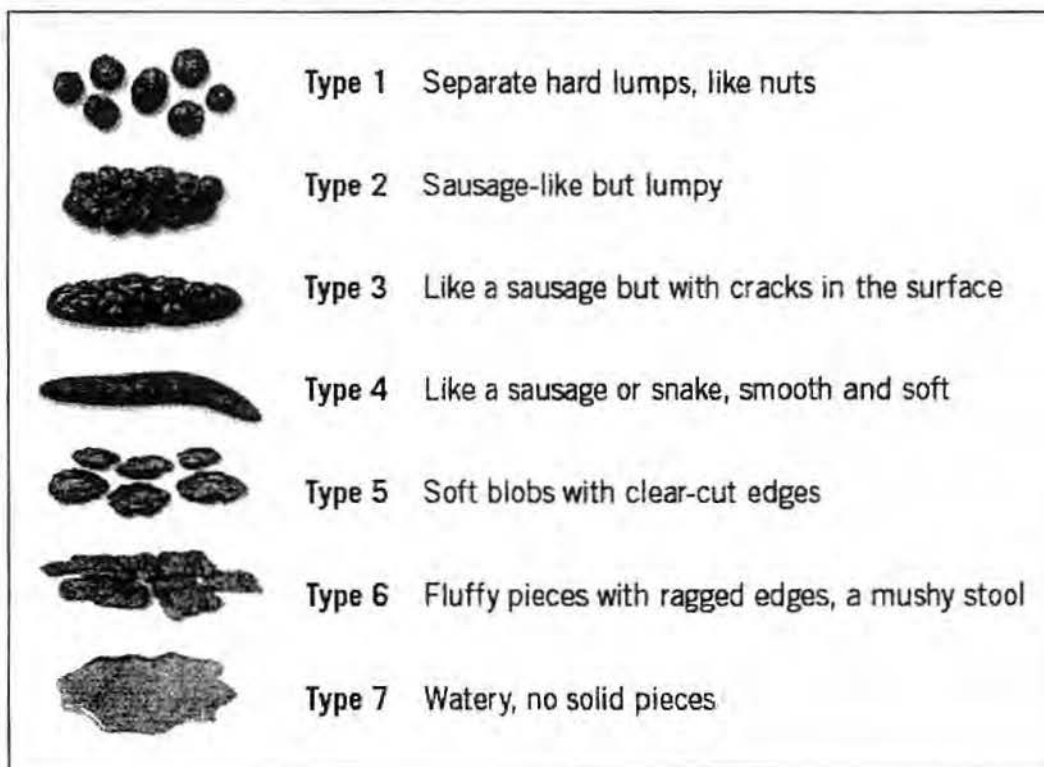
NOTE: The Early Termination biopsy will only be required for subjects who terminate on or after Week 6

**9) Visit 8 (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, Platelet Count, WBC with Differential, RBC)
- Complement C3 & C4
- Anti-tissue transglutaminase antibodies (IgA) and anti-DGP (IgA and IgG)
- PK/PD/Biomarkers (including CRP)
- Anti-drug antibodies

- Urinalysis (Protein/Albumin, Glucose, Ketones, Blood Cells)
- iVYLISA GIP Stool Test (optional)
- iVYDAL Urine Sample
- Urine Pregnancy (All FOCBP)

### APPENDIX C. BRISTOL STOOL FORM SCALE (BSFS)



**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 PHYSICIAN GLOBAL ASSESSMENT OF DISEASE

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

Inactive Disease     
      
  Mild Disease     
      
  Moderate Disease     
      
  Severe Disease

### Symptoms & Signs

Category	Abdominal Pain	Diarrhea	Fatigue	Activity	Lab Tests
Inactive Disease – Minimal or no symptoms thought to be related to celiac disease	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 celiac disease	Mild pain secondary to celiac disease occurring several times a week	Mild diarrhea thought to be secondary to celiac disease	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 celiac disease 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 celiac disease	Moderate abdominal pain thought to be secondary to celiac disease	Moderate diarrhea thought to be secondary to celiac disease	Significant fatigue thought to be due to celiac disease	In ability to maintain normal activities due to fatigue or other symptoms	Significant laboratory abnormalities felt to be secondary to celiac disease 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 celiac disease	Severe abdominal pain thought to be secondary to celiac disease	Significant diarrhea thought to be secondary to celiac disease	Significant fatigue thought to be secondary to celiac disease	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

## 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):

10. Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs) are eligible for this study.
11. Subjects who test **positive** for surface antigen (HBsAg+) are not eligible for this study, regardless of the results of other hepatitis B tests.
12. 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.
13. Subjects who test **positive only** for **surface antibody** (anti-HBs+) are eligible for this study unless local guidelines require additional testing.
14. 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			
Action	Hepatitis B test result		
	Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (anti-HBs)	Hepatitis B core antibody (anti-HBc total)
<b>Exclude</b>	+	— or +	— or +
<b>Include</b>	—	—	—
	—	+**	—
	—	+**	+
<b>Require Hepatitis B viral DNA (HBV DNA) testing*</b>	—	—	+
* 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. SAMPLE INVESTIGATION PRODUCT LABEL

AMG 714:

<p><b>AMG 714 100 mg/ml / 100 mg/mL</b>                  2 ml / mL Vial number _____                  s.c. / Sous-cutanée (SC)                  i.v. / Intraveineuse (IV)   # _____ 14003692</p>	<p><b>FI</b> # = Potilasnumero / Käynnin numero                  Valmistaja                  Amgen Inc., Thousand Oaks, CA 91320-1799, USA                  Valmistustapa                  Celimmune, 110 Old Driftway Lane,                  Lebanon, NJ 08833</p>	<p><b>SE</b> # = Patentinr. / Besök nr.                  Tillverkad för Celimmune av Amgen, Inc.                  Thousand Oaks, CA 91320-1799, USA                  Celimmune, 110 Old Driftway Lane,                  Lebanon, NJ 08833</p>	<p><b>FR</b> Numéro de visite                  Fabriqué pour Celimmune par Amgen, Inc.                  Thousand Oaks, CA 91320-1799, USA                  Celimmune, 110 Old Driftway Lane, Leban, NJ 08833</p>
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<p><b>NL</b> # = Patentinummer / Bezoeknummer                  Geproduceerd voor Celimmune door Amgen, Inc.                  Thousand Oaks, CA 91320-1799, USA                  Celimmune, 110 Old Driftway Lane,                  Lebanon, NJ 08833</p>	<p><b>ES</b> Número de visita                  Fabricado para Celimmune por Amgen, Inc.                  Thousand Oaks, CA 91320-1799, EE.UU.                  Celimmune, 110 Old Driftway Lane,                  Lebanon, NJ 08833</p>	<p><b>EN</b>                  Solution for injection / Solution for infusion                  Store at -30°C ± 10°C (-20°C to -40°C)                  Protect from light                  For direction for use, see protocol</p>	<p><b>CAUTION</b> New drug - Limited by United States Law                  to Investigational Use                  Manufactured for Celimmune by Amgen, Inc.                  Thousand Oaks, CA 91320-1799, USA, Celimmune,                  110 Old Driftway Lane, Lebanon, NJ 08833</p>
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PLACEBO:

<p><b>Placebo</b>  # _____                  1 ml / mL s.c. / Sous-cutanée (SC)                  i.v. / Intraveineuse (IV)                  Vial number _____ 14003690</p>	<p><b>FI</b> # = Potilasnumero / Käynnin numero                  Valmistaja                  Amgen Inc., Thousand Oaks, CA 91320-1799, USA                  Valmistustapa                  Celimmune, 110 Old Driftway Lane, Lebanon, NJ 08833</p>	<p><b>SE</b> # = Patentinr. / Besök nr.                  Tillverkad för Celimmune av Amgen, Inc.                  Thousand Oaks, CA 91320-1799, USA                  Celimmune, 110 Old Driftway Lane, Lebanon, NJ 08833</p>	<p><b>FR</b> Numéro de visite                  Fabriqué pour Celimmune par Amgen, Inc.                  Thousand Oaks, CA 91320-1799, USA                  Celimmune, 110 Old Driftway Lane, Leban, NJ 08833</p>
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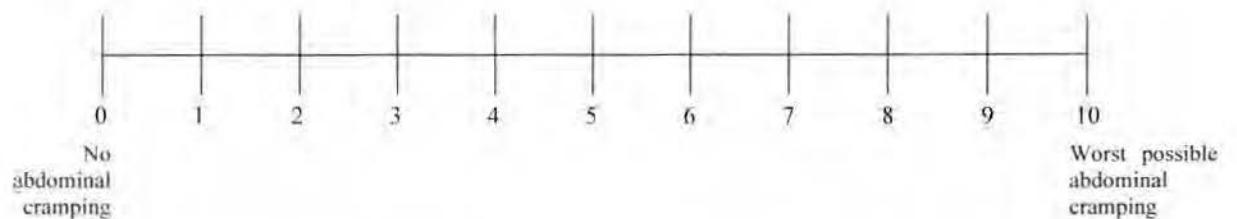
<p><b>NL</b> # = Patentinummer / Bezoeknummer                  Geproduceerd voor Celimmune door Amgen, Inc.                  Thousand Oaks, CA 91320-1799, USA                  Celimmune, 110 Old Driftway Lane, Lebanon, NJ 08833</p>	<p><b>ES</b> Número de visita                  Fabricado para Celimmune por Amgen, Inc.                  Thousand Oaks, CA 91320-1799, EE.UU.                  Celimmune, 110 Old Driftway Lane, Lebanon, NJ 08833</p>	<p><b>EN</b> Solution for injection / Solution for infusion / Store -30°C ± 10°C                  (-20°C to -40°C) / Protect from light / For direction for use, see protocol  <b>CAUTION</b> New drug - Limited by United States Law to Investigational Use                  Manufactured for Celimmune by Amgen, Inc., Thousand Oaks, CA 91320-1799,                  USA, Celimmune, 110 Old Driftway Lane, Lebanon, NJ 08833</p>	
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## APPENDIX I. SAMPLE CELIAC DISEASE PRO (CeD PRO)

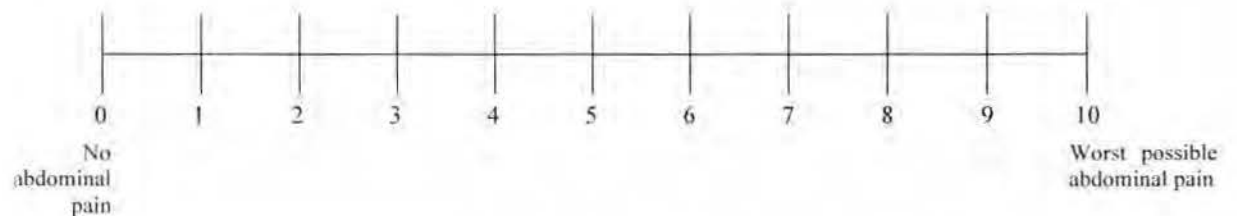
*Instructions: These questions ask about how you feel each day. Please complete the daily diary every evening, at approximately the same time.*

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.**

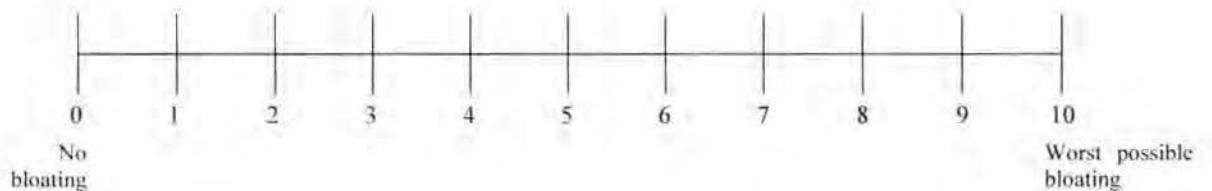
- a. How severe was your abdominal cramping?



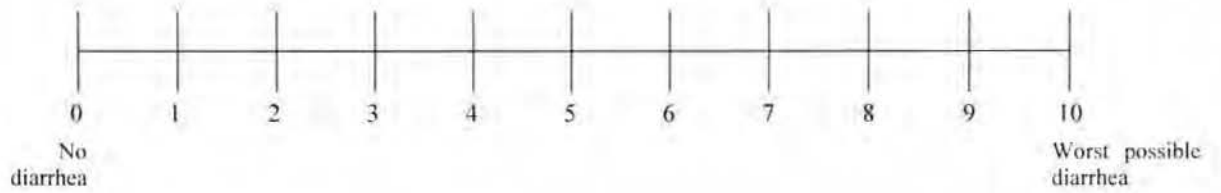
- b. How severe was your abdominal pain?



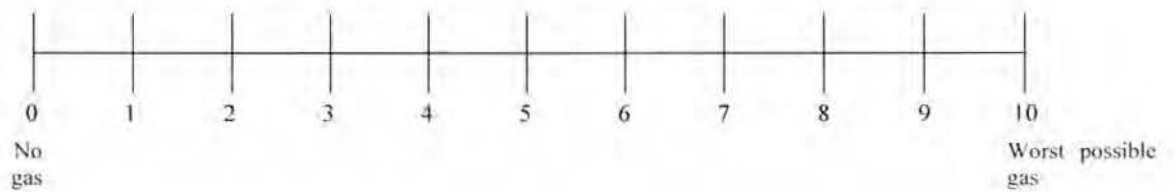
- c. How severe was your bloating?



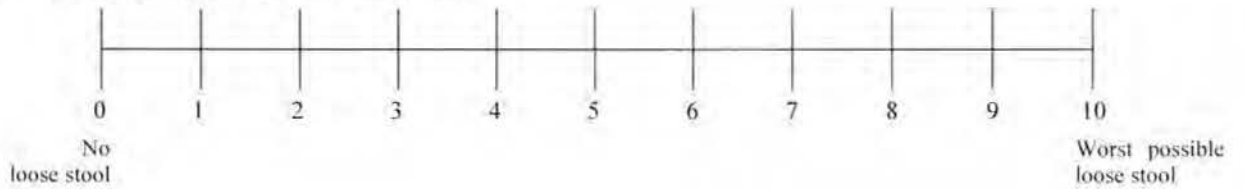
d. How severe was your diarrhea?



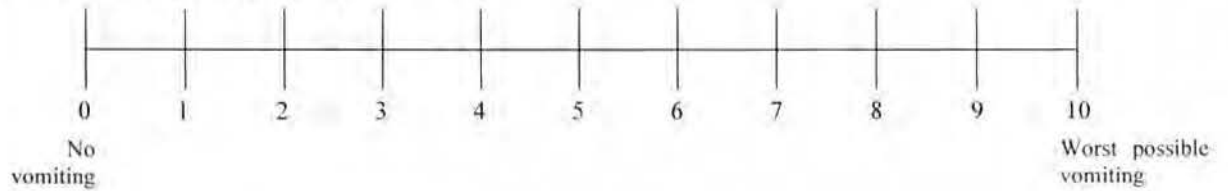
e. How severe was your gas (flatulence)?



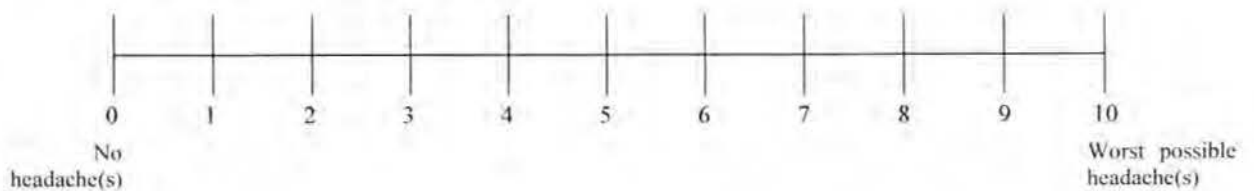
f. How severe was your loose stool?



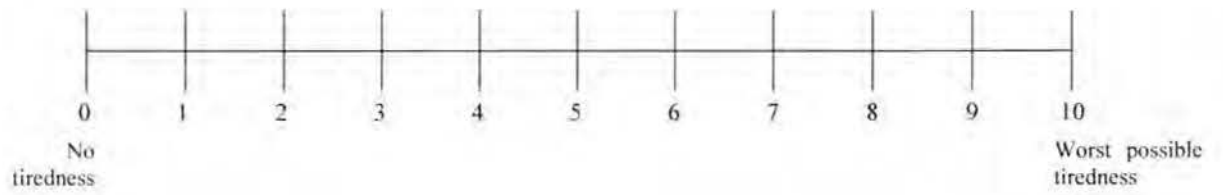
g. How severe was your nausea?



h. How severe was your headache(s)?



i. How severe was your tiredness?



## APPENDIX J. PROTOCOL AMENDMENTS

**The protocol was modified to create version 3 on 29 August 2016. The following changes and clarifications were made in the sections specified:**

- 1) Elimination of the stool test as an eligibility criterion, since endoscopy and biopsy already identify patients with gluten contamination, as revealed by mucosal atrophy (Inclusion Criterion #6; Table 1 footnote 5; Sections 11.1, 11.2)
- 2) Removal of blood donation 3-month pre-study exclusion, initially meant to prevent anemia by avoiding administering gluten challenge to patients who may have had a recent blood donation; a precaution now considered to be unnecessary and preventing otherwise eligible patients from enrolling in the study (Exclusion Criterion #17). Blood donation remains prohibited during the study (Section 17).
- 3) Modest villous atrophy threshold change for patients not receiving the gluten challenge to avoid excluding a few candidates, which would otherwise be considered eligible for the study (Table 1, footnote 16; Section 6).

Additional editorial changes and minor clarifications were made throughout the protocol.

**The protocol was modified to create version 2 on 20 May 2016. The following changes and clarifications were made in the sections specified:**

1. To reduce burden on patients, gluten stool sample collection was made optional except for the two samples collected at the time of the endoscopy and biopsy collection (Screening and Week 12 -or Early Termination, which remain mandatory). The urine gluten samples remain mandatory (Table 1, Footnote 5; Section 11; Section 14.2; Appendix B; and minor changes throughout the protocol as needed).
2. The rules for collection of stool samples have also 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 5; Section 11; Section 14.2).
3. The time of collection of the blood cell pellet has been changed to allow collection at any time during study (Table 1, Footnote 11).
4. The cut-off of mucosal damage, under which subjects do not receive the gluten challenge, was modestly lowered from 2 to 1.8. Subjects with VH:CD 1.8 or below will not receive gluten challenge, subjects with VH:CD 1.9 or above will receive challenge (Table 1, Footnote 16; Section 6; Section 19.1; Section 20.1; Section 23).
5. The age limit was increased to 80 years old (Inclusion Criteria 1).
6. The cut-off of symptoms at baseline was modestly increased from a CeD-GSRS of 2 to 2.3 (Exclusion Criterion 3).
7. The following discretion was added to Inclusion Criterion 10: "...unless investigator considers the abnormalities to be not clinically significant".

8. A Note was added to indicate that the Sponsor may arrange with the study sites the conduct of some of the intermediate visits at the subject's home, provided that appropriate healthcare personnel conducts the visit with similar standards to visits conducted at the study site (Sections 6 and 11).
9. A duplicated sentence on mini-gut experiments in biopsy fragments has been removed (Section 13.1.3) and minor inconsistencies have been corrected throughout Section 13.1 through 13.5.
10. Clarified procedure for retaining unused vials in Section 18.7.3.
11. It was clarified that the alternation of side of the abdomen for the SC injections is between visits, and not between the two injections in the same visit (Section 18.7.4).
12. It has been clarified that the DSMB may, and is expected to, review unblinded data. And that safety findings insufficient to trigger the stopping rules may, if judged appropriate by the DSMB, lead to suspension of enrollment during the review (Section 22.10).

Additional editorial changes and minor clarifications were made throughout the protocol.

**The original protocol was modified to create version 1.1 on 12 November 2015. The following major changes and clarifications were made in the sections specified:**

1. Addition of contact information for study vendors and responsible staff.
2. Addition of SAE telephone contact numbers (Section 22.7).
3. Revision of SAE email contact number (Section 22.7).
4. Addition of sample Investigational Product labels (Appendix H).

Additional editorial changes and minor clarifications were made throughout the protocol.

Protocol version 1.0 was not reviewed by Ethics Committees or used in this trial. As such, a formal documentation of changes was not prepared to accompany this protocol amendment.