Safety and efficacy of AMG 714 in patients with type 2 refractory coeliac disease: a phase 2a, randomised, double-blind, placebo-controlled, parallel-group study

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SUMMARY

Background

Refractory Coeliac Disease Type II (RCD-II) is a rare subtype of coeliac disease with high mortality. Interleukin-15 is strongly implicated in the pathophysiology of RCD-II, an in situ intestinal lymphoma and a precursor to enteropathy-associated T cell lymphoma (EATL). This trial aimed to investigate the effects of AMG 714, an anti-IL-15 monoclonal antibody, on the activity and symptoms of RCD-II.

Methods

This was a randomized, double-blind, placebo-controlled, phase 2a study of adult patients with confirmed diagnosis of RCD-II. Patients were randomly assigned at a 2:1 ratio to receive AMG 714 intravenous infusion at a dose of 8 mg/kg or matching placebo for seven doses over 10 weeks. Biopsies were obtained at baseline and Week 12 for cellular analysis and histology. The change in the proportion of aberrant intraepithelial lymphocytes (IELs) from baseline to Week 12 was the primary endpoint and was quantified using flow cytometry. In addition, the T cell receptor clonality of aberrant IELs was analysed by polymerase chain reaction. Clinical assessments of gastrointestinal symptoms, including diarrhoea, were conducted using validated tools. Safety and immunogenicity were also evaluated. Main analyses were conducted on the per protocol population.

Findings

Twenty-eight patients were randomized; 19 received AMG 714 and 9 received placebo. The mean (90% confidence interval) difference between AMG 714 and placebo in the relative change from baseline in aberrant IEL percentage was -4.85% (-30.26%, 20.56%), which was not

statistically significant (p=0.75). Eight (88.9%) subjects in the placebo group and 17 (89.5%) in the AMG 714 group had treatment-emergent adverse events, including 1 (11.1%) subject on placebo and 5 (26.3%) on AMG 714 who had serious adverse events. The most common adverse event in the AMG 714 group was nasopharyngitis (8 [42.1%] patients).

Interpretation

In RCD-II patients who were treated with AMG 714 or placebo for 12 weeks, the primary endpoint of aberrant IEL reduction from baseline was not met. However, favourable findings in T cell receptor clonality and in symptom relief support further study of AMG 714 in this rare and serious disease.

Trial registration
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Introduction

Refractory coeliac disease (RCD) is a rare complication of coeliac disease characterized by the lack or loss of the clinical and histological response to a gluten-free diet (GFD).[1,2] RCD is characterized by severe malabsorption and gastrointestinal symptoms without gluten consumption and persistent villous atrophy in the absence of others causes despite a strict GFD for at least 6 months.[1,2] Up to 1% of all coeliac patients are believed to be affected by RCD, and an estimated annual incidence of 0.83 per 10,000 coeliac disease patients has been reported.[3,4] It is often observed that patients diagnosed with celiac disease above age 50 or 60 years tend to respond slowly to GFD.[5] Patients with coeliac disease who have persistent symptoms for at least 6 to 12 months despite adherence to a GFD should be evaluated for possible RCD.[1,2,6]

RCD can be further classified as type I (RCD-I) and type II (RCD-II) based on the number of aberrant IELs present. Aberrant IELs have an abnormal phenotype (surface CD3-, intracellular CD3+) that can be identified by flow cytometry; these cells display clonal rearrangement of the T cell receptor (TCR), which is detected by molecular analysis.[1,2,7,8] Patients with few aberrant IELs, with a threshold of <20% of total IELs, are classified as having RCD-I. RCD-I is not associated with a substantially increased risk of developing lymphoma[9] and can be treated with aggressive nutritional support, adherence to GFD, and pharmacologic therapies (topical steroids or thiopurines).[6] Histopathologically, RCD-I resembles active coeliac disease. In RCD-II, aberrant IELs make up ≥20% of total IELs. RCD-II is a clinically well-defined rare disease that may develop from long-standing, pre-existing coeliac disease and is precursor to a rare type of lymphoma known as enteropathy-associated T cell lymphoma (EATL).[3]

RCD-II is considered a low-grade *in-situ* non-Hodgkin lymphoma, which arises first in the epithelial compartment of the small bowel.[1,2] It can, however, secondarily involve the colonic

and gastric epithelia, extend to *lamina propria,* and finally to blood and extraintestinal sites. Patients with RCD-II have a >50% risk of developing EATL, a high-grade lymphoma with a 5-year survival rate of less than 20%.[10-12] Hence, RCD-II is also known as pre-EATL. RCD-II is associated with a poor prognosis[13] and does not have an approved treatment by US or European regulatory agencies; its management is limited to (topical) corticosteroids for reducing symptoms and aggressive off-label therapies such as chemotherapy (cladribine) and haematopoietic stem cell transplant.[14]

Interleukin-15 (IL-15), produced in the small intestine by antigen-presenting cells and epithelial cells, plays a key role in the progression to EATL, as illustrated by the following evidence.[15] Aberrant IELs in RCD-II are derived from a T cell-like subset of innate lymphocytes present in the normal gut epithelium, where they differentiate in response to Notch and IL-15 signals.[16] In RCD-II patients, IELs display somatic gain-of-function mutations in JAK1 or STAT3, which are elements of the IL-15 signalling cascade. These mutations potentiate IEL responses to proliferative and anti-apoptotic signals provided by IL-15 and allow them to outcompete normal intestinal T cells in the IL-15-rich environment of the coeliac intestine.[16,17] In *ex vivo* cultures of intestinal biopsies from RCD-II patients, the neutralization of IL-15 using AMG 714 blocks anti-apoptotic signalling via JAK3 and STAT5 and leads to apoptosis of the clonal aberrant IELs.[18] This evidence indicates that IL-15 plays a non-redundant role in the survival and growth of aberrant IELs, driving the proliferation of aberrant IELs and promoting their accumulation.

Taken together, it is reasonable to expect that the inhibition of IL-15 could block the disease process in RCD-II.

AMG 714 is a fully human immunoglobulin (IgG1κ) monoclonal antibody that binds to IL-15 and inhibits IL-15-induced T cell activation and proliferation. AMG 714 may halt the

progression of RCD-II and alleviate clinical symptoms. We conducted the first study of AMG 714 aiming to investigate its safety and efficacy in the treatment of RCD-II.

Methods

This was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of AMG 714 for the treatment of adult patients with RCD-II. This study was conducted at six clinical sites in France, the Netherlands, Finland, Spain, and the United States after approvals by local ethics committees and institutional review boards.

Patient Population

Patients who were enrolled into this study were adults aged 18 years or older with a previously confirmed diagnosis of RCD-II, defined as coeliac disease confirmed by histology and/or serology; persistent and recurrent symptoms (eg, diarrhoea, weight loss, abdominal pain); abnormal small bowel histology; and aberrant intraepithelial lymphocytosis with >20% aberrant IELs per 100 CD45+ cells with respect to total IELs, as determined by flow cytometry, or >50% aberrant IELs, as determined by an immunohistochemistry (IHC) method described elsewhere.[8] Patients were required to have persistent IEL abnormalities despite adherence to a strict GFD for at least 6 months before screening, after excluding other potential causes of such abnormality (eg, microscopic colitis, bacterial overgrowth, lactose intolerance, exocrine pancreatic insufficiency, hyperthyroidism) and intestinal histological abnormality (eg, autoimmune enteropathy, giardiasis, immunodeficiency, collagenous sprue, Whipple's disease). Subjects who had been treated for RCD-II before the study had to continue to show elevated aberrant IELs and abnormal small bowel histology and must have had prior history of symptoms. However, given the rarity of the disease and because the primary endpoint was the enumeration of aberrant IELs, the presence of symptoms was not required for study entry regardless of previous treatment.

Patients were also required to have weakly positive or negative levels of anti-tissue transglutaminase (anti-tTG) antibodies (IgA and IgG) at screening, human leukocyte antigen DQ (HLA-DQ) genotyping compatible with coeliac disease, and a life expectancy of more than 4 months.

Patients were excluded if they had a diagnosis of RCD-I or EATL, current active or recent severe infection, a history of or suspected tuberculosis, a history of opportunistic infections, a history of most cancers, or other clinically significant diseases. Patients with significant immune suppression due to bone marrow transplant or cladribine treatment within 6 months of baseline or potent systemic immunosuppressant use (e.g., azathioprine) within 3 months of baseline were excluded.

Randomisation and masking

After screening, eligible patients were randomized at a 2:1 ratio to receive either AMG 714 or matching placebo for a total of seven doses of intravenous (IV) infusion over 10 weeks. The biostatistician generated the randomization code using permuted blocks. No stratification was applied due to the small sample size and lack of clearly established confounding factors.

Each dose of study drug (AMG 714 or placebo) was prepared by an unblinded study pharmacist at each site. The prepared solutions were identical in appearance between the active drug and placebo. The study patients and study personnel involved in patient enrolment, study drug administration, patient assessments, data collection, and analysis remained blinded to treatment assignment until the study ended.

Study treatment

Study drug (AMG 714 or placebo) was administered to each patient at the clinical site in a double-blind fashion starting on Day 0. The second and third doses were administered weekly on Day 7 and Day 14. The subsequent four doses were given every 2 weeks thereafter through Day 70. The dose of AMG 714 administered at each visit was 8 mg/kg. The dosing regimen was chosen to deliver approximately twice the amount of AMG 714 previously studied in rheumatoid arthritis, while remaining within toxicology safety margins. This level of dosing was intended to saturate IL-15 with a loading dose in the first three weeks and then maintain a high level of target binding. Each infusion was administered over a duration of approximately 2 hours. Patients were confined to the study site after the end of infusion for at least one hour for safety monitoring.

In addition to the study drug, concomitant background treatment with a corticosteroid up to 20 mg per day of prednisone, prednisolone, or equivalent and/or oral budesonide up to 9 mg per day was allowed. These doses remained stable from 4 weeks before randomization through the end of the study. To note, budesonide has been shown to improve the symptoms of RCD-II and is considered adequate background therapy.[19] Inhaled steroids for respiratory diseases such as asthma, and topical steroids were permitted. Other systemic or intestinal immune suppressants were not allowed. Also prohibited during the study were chronic or continuous systemic antibiotics (>2 weeks use), systemic antivirals, parenteral antifungals, anticoagulants, live vaccines, and any other investigational drugs or devices.

Patients were required to maintain total adherence to a GFD from 6 months before randomization through the final study visit (Day 112). Adherence to the GFD was assessed by an expert dietitian and the iVYLISA test, a quantitative Sandwich enzyme-linked immunosorbent assay that quantifies gluten immunogenic peptide (GIP) in stool samples. The cut-off value for a positive result was 250 ng of gluten per gram of stool.[20]

Patients could be withdrawn from the study at the investigator's discretion for safety reasons; protocol violation or noncompliance, including the use of prohibited medications; or patients' own decision to withdraw at any time.

Endpoints

Small bowel biopsies from the second portion of the duodenum were obtained at baseline and at Week 12 (Day 84) to evaluate the key efficacy endpoints. The primary endpoint of the study was the percentage of aberrant IELs with respect to all IELs, as quantified by flow cytometry (defined as Immunological Response 1); this analysis was conducted in a blinded manner at each site following a common protocol. Prior to the initiation of the study, the flow cytometrists from all sites attended a practical session, during which they were trained on patient samples using the same gating hierarchy, under the supervision of a central coordinator. A key secondary endpoint was the percentage of aberrant intestinal IELs with respect to intestinal epithelial cells, as assessed in a blinded manner by IHC (defined as Immunological Response 2). Secondary histological endpoints included small intestinal villous height-versus-crypt depth (VH:CD) ratio and total IEL count by IHC. The IHC and histology analyses were conducted in a blinded manner at a central expert laboratory (JiLab, Tampere, Finland).

Clinical symptoms were measured by patient-reported instruments, Bristol Stool Form Scale (BSFS, including a post-hoc analysis of weeks with at least one episode of diarrhoea, defined as BSFS or 6 or 7) and Gastrointestinal Symptom Rating Scale (GSRS, an endpoint developed for gastroesophageal reflux and often used, albeit not validated, in celiac disease). Patients were given an electronic diary and instructions to record their daily symptoms. The results were collected and reviewed at each study visit.

The TCR gamma-chain clonality in IELs obtained from the biopsy samples was analysed qualitatively, in a blinded manner, at a central expert laboratory (Necker Hospital, Paris, under the direction of E. Macintyre) using polymerase chain reaction (PCR), as described by Derrieux et al.[21], at baseline and Week 12 (2 weeks after the final dose). While the PCR analysis was not quantitative, changes in the size of the PCR peaks (increase, decrease, stable) were determined visually by the central lab without knowledge of the treatment assigned to each subject.

Safety endpoints included adverse events, clinical laboratory tests, physical examination, and immunogenicity of AMG 714.

Statistics

Because RCD-II is a rare disease, the sample size was not based on any statistical power calculation. All patients who received at least one dose of the study drug were included in the intent-to-treat (ITT) population. The per-protocol (PP) population included patients who received study treatment and provided evaluable data (ie, biopsies before and after treatment) for efficacy analysis. The PP population was used for analyses of IEL-related and histological endpoints, while the ITT population was used for clinical and safety endpoints.

The primary endpoint, the change from baseline to Week 12 in the percentage of aberrant IELs with respect to total IELs by flow cytometry, was compared between the AMG 714 and placebo groups using analysis of covariance where the baseline value was included as a covariate and treatment group as a fixed effect. The same analysis was used for the secondary immunological and histological endpoints.

The proportion of patients with diarrhoea, defined as BSFS score of 6 or 7, over time was plotted, and the difference in the area under the curve was compared between the treatment

groups using one-way analysis of variance. The change from baseline in GSRS weekly total score was analysed using a linear mixed effects model repeat measurement.

Safety endpoints were summarized using descriptive statistics.

All statistical analyses were performed using SAS® for Windows (SAS Institute Inc., Cary, NC, USA), version 9.4.

Subsets of RCD-II patients

Most patients (n=24) had the classic phenotype of aberrant IELs (surface CD3-, intracellular CD3+) as identified by flow cytometry; these patients are considered to have "typical" RCD-II. Four patients had aberrant IELs >20% of total IELs without the classic phenotype of aberrant IELs. These patients had been diagnosed with RCD-II by their physicians, met all of the protocol's eligibility criteria, and were considered as "atypical" RCD-II for the purpose of the study. The phenotypes of the aberrant cells in the atypical patients were surface CD3+ CD4+ (one patient), CD3+ T cell receptor gamma-delta+ T cells (2 patients), or natural killer (NK)-like (surface CD3-, intracellular CD3-, CD45+, CD19-, CD122+) (one patient). The aberrant cells in these patients expressed IL-15-driven biomarkers, such as NKG2D and Granzyme B, and they may potentially benefit from anti-IL-15 therapy. The patients with atypical RCD-II were allowed to participate in the study but not included in the analysis involving aberrant IELs, since these endpoints were based on the enumeration of surface CD3- cells. Therefore, these patients were not included in primary endpoint analysis. However, these patients' data were included in other endpoint analyses.

In addition, ad hoc analyses were conducted on a subset of patients referred to as "pure" RCD-II patients, which was comprised of the majority of the patients (N=19) after excluding patients

with major protocol deviations (N=1, insufficient washout period post cladribine), early terminations (N=1, adverse event), atypical RCD-II (N=4), and patients with only polyclonal/irregular polyclonal T cell Receptor gamma chain clonality (N=4; one patient had both atypical RCD-II and polyclonal IELs). Thus, the Pure RCD-II population refers here to patients who completed the study and had the classic phenotype and clonal aberrant IELs, which is a stricter definition of RCD-II. TCR clonality was not an eligibility criterion in the study, and the enrolled patients with polyclonality met all eligibility criteria, including RCD-II diagnosis. Nevertheless, the Pure RCD-II population (monoclonal) is considered more representative of the disease pathology and was therefore analysed separately in this post-hoc subgroup analysis.

Safety oversight and informed consent

The study protocol was approved by local ethics committees before initiation. All patients gave written informed consent before undergoing any study-related procedures. Randomization and initial dosing of the first 10 patients were staggered to ensure that the study drug was given to no more than one patient per day and no more than two patients per week. An independent Data Safety Monitoring Board reviewed the safety data from these patients and determined whether subsequent patients could proceed with study treatment.

This study is registered with ClinicalTrials.gov (number: NCT02633020) and EudraCT (number: 2015-004063-36).

Role of the funding source

The funding sources had a role in the study design, conduct, analysis, data interpretation, and report writing, as some authors are employees of the companies that funded the study. The lead

and corresponding author (CC) and senior author (CJM) have full access to all study data and take final responsibility for the content of this manuscript.

Results

This study was conducted from 13 April 2016 (first patient enrolment) to 02 May 2017 (last patient completing the final visit).

Demographics and disposition

Of the 45 patients screened, 16 patients did not meet the eligibility criteria and one patient withdrew before randomization. Overall, 28 patients were randomized, including 19 patients randomized to the AMG 714 8 mg/kg group and 9 patients to the placebo group (Figure 1). All of these patients had previously received treatment for RCD-II, including haematopoietic stem cell transplant, chemotherapy (cladribine), and/or immunosuppressants (azathioprine, high-dose systemic steroids). Extra-intestinal manifestations were not common, except for musculoskeletal and connective tissue disorders, reported in approximately half of the patients. Concurrent autoimmune diseases, such as autoimmune thyroiditis, diabetes or dermatitis herpetiformis, were reported but heterogeneous, and no two patients had the same autoimmune comorbidity. Baseline haemoglobin levels were borderline low and similar between the groups, with an average value of 13.6 g/dL (SI units: 8.44 mmol/L), which did not change during the study. Similarly, baseline albumin levels were low and similar between groups: The mean values were 42.1 g/dL (6.33 mmol/L) in the AMG 714 group and 39.4 g/dL (5.93 mmol/L) in the placebo group and did not change during the study.

All 28 randomized patients received at least one dose of the study drug (AMG 714 or placebo) and were included in the ITT population. One patient in the AMG 714 group discontinued the

study treatment after 3 doses because of an adverse event (mild cerebellar disorder). The other 27 patients completed the study. All 28 patients were followed through the final visit at approximately 16 weeks after the first dose of study drug, including the patient who discontinued treatment early.

Two randomized patients, both in the AMG 714 group, were excluded from the PP population because of significant protocol deviation (n=1) and insufficient biopsy samples for evaluation (n=1). Of the 26 patients in the PP population, 4 (3 in the AMG 714 group and 1 in the placebo group) had atypical IELs and were excluded from the IEL-related efficacy analyses as pre-specified in the statistical analysis plan. All 26 patients in the PP population were included for the analyses of other endpoints. Thus, the typical RCD-II PP population comprised 22 patients (14 in the AMG 714 group and 8 in the placebo group). Three patients had polyclonal IELs, so that the Pure RCD-II PP population included 19 patients with monoclonal IELs (13 in the AMG 714 group and 6 in the placebo group).

Despite the randomization, the majority of patients in the placebo group were female (6 [66.7%] of 9 patients), while the majority of patients in the AMG 714 group were male (11 [57.9%] of 19 patients), which was not unexpected given the small sample size (Table 1). The mean age and body mass index were generally similar between the groups. The baseline median (minimum, maximum) body mass index (BMI) was 21.9 (16.2, 29.8) kg/m^2 in the AMG 714 group, slightly lower than that in the placebo group, 23.0 (20.7, 35.9) kg/m^2. One patient in each group was positive for anti-tTG antibody at baseline. In addition, approximately two-thirds of the patients in each group received background budesonide treatment during the study.

Compliance with the GFD was generally high (>70% of all given doses) in both groups throughout the study. Most patients (more than 70% of patients at each visit) were found to have

no transgression by the iVYLISA GIP stool test and dietitian counselling. Patients in the AMG 714 group had a slightly higher rate of dietary transgressions than those in the placebo group.

Aberrant intraepithelial lymphocyte results

The primary endpoint of the study was the relative (%) change from baseline to Week 12 in aberrant IELs with respect to total IELs, assessed by flow cytometry, in the PP population (Immunological Response 1). The least square (LS) mean change was an increase of 7.30% in the placebo group and 2.45% in the AMG 714 group. The LS mean treatment difference (90% CI) between the groups was -4.85% (-30.26%, 20.56%), which was not statistically significant (p=0.75). In the Pure RCD-II population, the increase from baseline in aberrant IELs was 14.1% in the placebo group and 0.36% in the AMG 714 group. The LS mean treatment difference between AMG 714 and placebo was -13.74%, also not statistically significant (p=0.43) (Table 2).

The key secondary endpoint was the relative change from baseline to Week 12 in aberrant IELs assessed by flow with respect to IEL/intestinal epithelial cell ratio assessed by IHC, in the PP population (Immunological Response 2). The LS mean change was an increase of 49.88% in the placebo group and 11.66% in the AMG 714 group (nominal p=0.18). In the Pure RCD-II population, the increase from baseline was 61.35% on placebo and 11.28% on AMG 714 (nominal p=0.12) (Table 3).

Effects on T cell receptor clonality

In the Pure RCD-II population, 3 (50%) of the 6 patients in the placebo group had an increase in TCR clonality from baseline to Week 12, while the other 3 (50%) patients had stable or decreased TCR clonality. In the AMG 714 group, all 13 (100%) patients had stable or decreased

TCR clonality at Week 12 compared with baseline. The difference between the two groups had a nominal p value <0.05 (nominal p=0.02).

In the PP population, 6 (66%) of 9 patients in the placebo group and all 17 (100%) patients in the AMG 714 group had stable or decreased TCR clonality from baseline to Week 12 (difference between groups: nominal p=0.032).

Histological findings

In the PP population, both groups had mean increases in the VH:CD ratio from baseline to Week 12, which indicated an improvement in the histology of intestinal mucosa. In the PP population, the LS mean increase was 15.77% in the placebo group and 26.44% in the AMG 714 group (Table 4) (nominal p=0.66). Similar to the aberrant IEL-related endpoints, the difference between AMG 714 and placebo was numerically larger in the Pure RCD-II population than in the PP population. The placebo group showed a lack of improvement (LS mean change: 0.15%); the AMG 714 group had a substantial mean improvement of 26.86%, although the difference was not statistically significant (nominal p=0.39).

Clinical findings

At Week 0, the mean number of bowel movements per week was 7.4 in the placebo group and 10.3 in the AMG 714 group. At Week 12, the mean number of bowel movements per week was 8.3 in the placebo group and 11.3 in the AMG 714 group. The difference between groups was not significant. In the AMG 714 group, the percentage of patients with at least one episode of diarrhoea (BSFS ≥6) per week decreased from 52.6% (10 of 19 patients) at baseline to 36.8% (7 of 19) at Week 12. In the placebo group, patients with diarrhoea per week increased from 22.2%

(2 of 9) at baseline to 44.4% (4 of 9) at Week 12. The comparison between the groups in change from baseline (Figure 2) had a nominal p value <0.001.

For the change from baseline in total weekly GSRS score, the LS mean (SE) difference between AMG 714 and placebo over the 12-week treatment period was -0.14 (0.19) (nominal p=0.48).

Safety

In the AMG 714 group, three patients had one dose held because of adverse events and one patient discontinued treatment because of adverse events. In the placebo group, one patient had one dose held because of an adverse event.

Of the 28 patients who received at least one dose of the study drug, 25 (89.3%) had at least one treatment-emergent adverse event (TEAE). The proportion of patients with TEAEs was similar between the placebo (88.9% [8 of 9 patients]) and AMG 714 (89.5% [17 of 19]), as shown in Table 5. Slightly more patients in the AMG 714 had TEAEs that were considered related to the study drug (84.2% [16 patients] versus 77.8% [7]). The most common TEAEs in the AMG 714 group were nasopharyngitis, which occurred in 8 (42.1%) patients (versus 1 [11.1%] patient in the placebo group); diarrhoea in 3 (15.8%) patients (1 [11.1%] in the placebo group); eosinophil count increased in 3 (15.8%) patients (0 in the placebo group); and headache 3 (15.8%) patients (0 in the placebo group). Cases of infection were reported in 12 (63.2%) patients in the AMG 714 group, including 2 patients with urinary tract infection and single cases of pneumococcal infection, viral bronchitis, sinusitis, and tuberculosis. One patient each in the placebo group had bacteraemia, urinary tract infection, and nasopharyngitis. Nervous system disorder occurred in 6 (31.6%) patients in the AMG 714 group and 4 (44.4%) patients in the placebo group.

There were no deaths in either group during the study. Five (26.3%) patients in the AMG 714 group each experienced a serious adverse event, compared with one (11.1%) patient in the placebo group. The five serious adverse events in the AMG 714 group were pneumococcal infection (resolved while on AMG 714 treatment), transaminitis (a worsening of pre-existing condition, resolved while on AMG 714), balance disorder (pre-existing, resolved while on AMG 714), tuberculosis, and cerebellar syndrome. The patient with cerebellar syndrome discontinued the study because of this adverse event. The patient who developed tuberculosis had a history of asthma, severe chronic obstructive pulmonary disease, and empyema (current smoker) and negative TB test result at screening with concomitant medications of budesonide 3 mg twice daily, salbutamol inhalation, and beclomethasone dipropionate/formoterol fumarate inhalation. The patient was diagnosed with Mycobacterium tuberculosis based on a chest x-ray with miliary pattern and presence of Mycobacterium tuberculosis DNA in sputum after completing all doses of the study treatment. The patient was treated with rifampicin, isoniazid, pyrazinamide, ethambutol, and pyridoxine, and the tuberculosis was considered resolved four months later. The one serious adverse event in the placebo group was peroneal nerve palsy.

The mean count of eosinophils increased over time in both groups, particularly after Week 4, but returned to baseline at Week 16. The reason for this observation is unknown, but seasonal allergies could be a possible explanation. The mean count of lymphocytes decreased slightly over time in both groups with no clear difference between the two groups. The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels showed minor decrease in the placebo group and no apparent trend in the AMG 714 group, except the one patient with the serious adverse event of cytolytic hepatitis (transaminitis). No other clinically significant trends were observed in haematology and chemistry laboratory tests.

Immunogenicity

One patient in the AMG 714 group was positive for anti-drug antibody (ADA) at baseline, before receiving any dose of the study drug. The ADA was not neutralizing. This patient had negative ADA results for all subsequent visits. No other patients had positive antibody results during the study.

Discussion

This was the first ever industry-sponsored clinical trial of an experimental medication for the treatment of RCD-II. The experimental treatment is an anti-IL-15 monoclonal antibody, AMG 714 (also known as PRV-015). The drug was administered IV at the dose of 8 mg/kg for 10 weeks. While AMG 714 did not achieve statistical significance compared with placebo for the primary endpoint, i.e., the change in aberrant IELs assessed by flow cytometry, the results showed improvement in an important biological endpoint (TCR clonality) and, most relevant, a clinical endpoint (diarrhoea), with nominal p values <0.05. In addition, consistent trends of numerical differences in favour of AMG 714 treatment were observed in other endpoints, notably histology. It should be noted that the numerical differences between the active and placebo treatments were larger in patients with "pure" RCD-II, ie, patients with clonal IELs, in which IL-15 has been demonstrated to play a role in vitro. In these patients, background medication with topical corticosteroids (eg, budesonide) did not improve RCD-II endpoints, while several patients with polyclonal IELs responded to topical corticosteroids in endpoints such as aberrant IELs and histology (data not shown). This differential response to background topical corticosteroids may have led to improvement and decreased effect size of AMG 714.

The totality of the data, and specially the meaningful differences between AMG 714 and placebo in TCR clonality, confirm in vivo the purported role of IL-15 as a driving factor in the

pathophysiology of RCD-II. This finding was also supported by a clinical endpoint, the reduction of patients with diarrhoea as measured by BSFS. There are no validated symptom measures in RCD-II, and the BSFS results should be interpreted with caution. While these endpoints and results are sufficient for a proof-of-concept study, future studies will need to provide evidence of clinical benefit in other symptoms, progression-free survival, and/overall survival.

Currently available, although off-label, treatment options for RCD-II are limited and include chemotherapy (cladribine, alkylating agents), haematopoietic stem cell transplant, immunosuppressants (azathioprine), and long-term systemic and topical corticosteroids, including the use of "open capsule" budesonide.[19,22,23] These available options present substantial safety concerns and limited efficacy in eliminating all malignant clones in many patients. It should be noted that the patients in this study had failed previous treatment approaches (stem cell transplant, cladribine, azathioprine, steroids). Pending further evidence, AMG 714 may address the medical needs of patients with this difficult-to-treat disease. Although current data on long-term efficacy endpoints, such as progression and survival, are not yet available, this study has provided evidence to support further clinical investigations into the efficacy and safety of AMG 714.

AMG 714 was well tolerated in a parallel study of patients with coeliac disease subjected to gluten challenge.[24] In the present RCD-II study, patients were more severely ill and immune suppressed by prior treatment with haematopoietic stem cell transplantation and chemotherapy, as well as by concomitant treatment with corticosteroids. Thus, the higher number of adverse events reported in the RCD-II study was anticipated. Overall, the incidence of adverse events was similar between the AMG 714 and placebo group. Although adverse events involving infections and infestations occurred in more patients in the AMG 714 group than in the placebo

group, this difference was primarily attributed to mild nasopharyngitis, which accounted for 8 of 12 subjects with presumed infections in the AMG 714 group, compared with 1 of 3 subjects in the placebo group. Decrease in splenic size and function (hyposplenism) associated with RCD-II, although not assessed in this study, may also have led to higher susceptibility to infection and bacteremia.[25] Increased susceptibility to infections is not specifically expected with AMG 714, as it does not affect NK cells or other white cell counts in humans.[26] As with any immune-modulator, however, close monitoring of infection risk should be a part of any future research on AMG 714.

Adverse events classified as nervous system disorders occurred in a greater proportion of patients in the placebo group than the AMG 714 group. Two patients in the AMG 714 group experienced serious adverse events of mild functional balance disorder and cerebellar syndrome, which were likely to be due to the underlying coeliac disease, as AMG 714 was re-introduced in one of the patients and the balance symptoms improved while the patient was on drug. It should be noted that neurological complications, including cerebellar ataxia, have been associated with coeliac disease and gluten sensitivity[27-29]. Overall, the safety profile of AMG 714 appears acceptable for this serious condition.

Limitations

This study was necessarily limited by the small sample size given the low prevalence of RCD-II, contributing to modest imbalance in certain baseline characteristics. Patients in the AMG 714 group had, on average, more severe disease than those in the placebo group at baseline, as measured by aberrant IEL percentage (63.5% vs 57.9%) , VH:CD ratio (0.65 vs 0.75), symptoms (2.2 vs 1.63 on CeD PRO) , and TCR clonality (88% vs 66.7%), on the AMG 714 group vs placebo group, respectively. This might have reduced the effect size of AMG 714. In addition,

the use of budesonide as background therapy during study treatment likely affected the efficacy results. Concomitant use of budesonide was allowed in both groups for ethical reasons, but may have reduced the effect size of AMG 714 compared with placebo, particularly in the PP population. These findings suggest that future studies should stratify randomization based on baseline disease severity and corticosteroid use.

Another important limitation of this study was its relatively short duration. The chronically inflamed environment of the gut with pre-existing effector memory cells may provide signals other than IL-15 that allow aberrant IELs to survive. However, treatment with AMG 714 was associated with symptomatic improvement and prevented the expansion and increased clonality of IELs in the relatively short treatment duration of 10 weeks. Longer durations of AMG 714 treatment for 6 to 12 months may clarify its effects on these immunological, histological, and clinical outcomes and evaluate progression-free survival, possible RCD-II disease regression, and the prevention of EATL, a disease with poor prognosis.

In addition, patients who had been treated for RCD-II before or had concomitant treatment with topical budesonide at the time of the study could participate in this study, regardless of whether they were symptomatic. This may have contributed to the modest clinical benefit observed.

Lastly, despite the centralized training for study personnel, some variation among study sites in the IEL enumeration could not be ruled out in locally conducted flow cytometry.

Conclusion

Data from this study provide further evidence to support the role of IL-15 in the pathophysiology of RCD-II (pre-EATL). The primary endpoint of aberrant IEL reduction was not met. However, AMG 714 (PRV-015) was associated with symptom improvement and reduction in clonal progression. Further study of AMG 714 in RCD-II is warranted.

References

1. Cellier C, Patey N, Mauvieux L, et al. Abnormal intestinal intraepithelial lymphocytes in refractory sprue. *Gastroenterology* 1998; **114**(3): 471-81.

2. Cellier C, Delabesse E, Helmer C, et al. Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. French Coeliac Disease Study Group. *Lancet* 2000; **356**(9225): 203-8.

3. Lebwohl B, Granath F, Ekbom A, et al. Mucosal healing and risk for lymphoproliferative malignancy in celiac disease: a population-based cohort study. *Ann Intern Med* 2013; **159**(3): 169-75.

4. van Wanrooij RL, Bouma G, Bontkes HJ, et al. Outcome of Referrals for Non-Responsive Celiac Disease in a Tertiary Center: Low Incidence of Refractory Celiac Disease in the Netherlands. *Clin Transl Gastroenterol* 2017; **8**(1): e218.

5. Wahab PJ, Meijer JW, Mulder CJ. Histologic follow-up of people with celiac disease on a gluten-free diet: slow and incomplete recovery. *Am J Clin Pathol* 2002; **118**(3): 459-63.

6. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA, American College of G. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 2013; **108**(5): 656-76; quiz 77.

7. Verbeek WH, Schreurs MW, Visser OJ, von Blomberg BM, Al-Toma A, Mulder CJ. Novel approaches in the management of refractory celiac disease. *Expert Rev Clin Immunol* 2008; **4**(2): 205-19.

8. van Wanrooij RL, Muller DM, Neefjes-Borst EA, et al. Optimal strategies to identify aberrant intra-epithelial lymphocytes in refractory coeliac disease. *J Clin Immunol* 2014; **34**(7): 828-35.

9. Malamut G, Afchain P, Verkarre V, et al. Presentation and long-term follow-up of refractory celiac disease: comparison of type I with type II. *Gastroenterology* 2009; **136**(1): 81-90.

10. Nijeboer P, de Baaij LR, Visser O, et al. Treatment response in enteropathy associated T-cell lymphoma; survival in a large multicenter cohort. *Am J Hematol* 2015; **90**(6): 493-8.

11. Nijeboer P, van Wanrooij R, van Gils T, et al. Lymphoma development and survival in refractory coeliac disease type II: Histological response as prognostic factor. *United European Gastroenterol J* 2017; **5**(2): 208-17.

12. Rubio-Tapia A, Malamut G, Verbeek WH, et al. Creation of a model to predict survival in patients with refractory coeliac disease using a multinational registry. *Aliment Pharmacol Ther* 2016; **44**(7): 704-14.

13. Catassi C, Fabiani E, Corrao G, et al. Risk of non-Hodgkin lymphoma in celiac disease. *JAMA* 2002; **287**(11): 1413-9.

14. Malamut G, Cellier C. Refractory celiac disease: epidemiology and clinical manifestations. *Dig Dis* 2015; **33**(2): 221-6.

15. Abadie V, Jabri B. IL-15: a central regulator of celiac disease immunopathology. *Immunol Rev* 2014; **260**(1): 221-34.

16. Ettersperger J, Montcuquet N, Malamut G, et al. Interleukin-15-Dependent T-Cell-like Innate Intraepithelial Lymphocytes Develop in the Intestine and Transform into Lymphomas in Celiac Disease. *Immunity* 2016; **45**(3): 610-25.

17. Meresse B, Malamut G, Cerf-Bensussan N. Celiac disease: an immunological jigsaw. *Immunity* 2012; **36**(6): 907-19.

18. Malamut G, El Machhour R, Montcuquet N, et al. IL-15 triggers an antiapoptotic pathway in human intraepithelial lymphocytes that is a potential new target in celiac disease-associated inflammation and lymphomagenesis. *J Clin Invest* 2010; **120**(6): 2131-43.

19. Brar P, Lee S, Lewis S, Egbuna I, Bhagat G, Green PH. Budesonide in the treatment of refractory celiac disease. *Am J Gastroenterol* 2007; **102**(10): 2265-9.

20. Comino I, Fernandez-Banares F, Esteve M, et al. Fecal Gluten Peptides Reveal Limitations of Serological Tests and Food Questionnaires for Monitoring Gluten-Free Diet in Celiac Disease Patients. *Am J Gastroenterol* 2016; **111**(10): 1456-65.

21. Derrieux C, Trinquand A, Bruneau J, et al. A Single-Tube, EuroClonality-Inspired, TRG Clonality Multiplex PCR Aids Management of Patients with Enteropathic Diseases, including from Formaldehyde-Fixed, Paraffin-Embedded Tissues. *J Mol Diagn* 2019; **21**(1): 111-22.

22. Malamut G, Cellier C. Refractory celiac disease. *Expert Rev Gastroenterol Hepatol* 2014; **8**(3): 323-8.

23. Ciccocioppo R, Gallia A, Avanzini MA, et al. A Refractory Celiac Patient Successfully Treated With Mesenchymal Stem Cell Infusions. *Mayo Clin Proc* 2016; **91**(6): 812-9.

24. Lähdeaho M, Scheinin M, Vuotikka P, et al. Safety and effectiveness of the anti-IL-15 monoclonal antibody, AMG 714, in adult celiac disease patients exposed to high-dose Fchallenge: a phase 2a, randomized, double-blind, placebo-controlled study *Lancet Gastroenterology and Hepatology* In press.

25. van Gils T, Nijeboer P, van Waesberghe JHT, et al. Splenic volume differentiates complicated and non-complicated celiac disease. *United European Gastroenterol J* 2017; **5**(3): 374-9.

26. Lebrec H, Horner MJ, Gorski KS, et al. Homeostasis of human NK cells is not IL-15 dependent. *J Immunol* 2013; **191**(11): 5551-8.

27. McKeon A, Lennon VA, Pittock SJ, Kryzer TJ, Murray J. The neurologic significance of celiac disease biomarkers. *Neurology* 2014; **83**(20): 1789-96.

28. Green PH, Cellier C. Celiac disease. *N Engl J Med* 2007; **357**(17): 1731-43.

29. Hadjivassiliou M, Grunewald R, Sharrack B, et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain* 2003; **126**(Pt 3): 685-91.

Research in context

Evidence before this study

Currently there is no approved drug therapy to treat type 2 refractory coeliac disease (RCD-II, pre-EATL), which has a poor prognosis. Corticosteroids, chemotherapy, and hematopoietic stem cell transplant treatments for RCD-II have shown limited efficacy and carry substantial safety risk. We searched PubMed using the terms “refractory coeliac”, “RCD”, “interleukin 15”, “IL-15” for articles published in English through September 21, 2018. No clinical trials have been published in which anti-IL-15 therapy is tested as a treatment for RCD-II.

Added value of this study

This study confirms the role of IL-15 in aberrant IELs and other abnormalities in RCD-II. Although the anti-IL-15 treatment for 10 weeks did not achieve statistically significance in the primary endpoint (aberrant IELs enumerated by flow cytometry) in a small patient population in the study, significant benefits were seen in IEL T-cell receptor clonality and in the reduction of diarrhoea, with consistent trends in other endpoints such as histology. The safety profile was acceptable for this serious condition.

Implications of all the available evidence

These findings suggest that blocking the IL-15 pathway may be a promising treatment for RCD-II (pre-EATL), a rare disease with suboptimal treatment options. Further study with AMG 714 is warranted.

Data sharing statement

There is a plan to share data. This may include de-identified individual patient data for variables necessary to address the specific research question in an approved data-sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and 1) this product and indication (or other new use) have been granted marketing authorization in both the US and Europe, or 2) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labelling. A committee of internal advisors reviews requests. If not approved, a Data Sharing Independent Review Panel will arbitrate and make the final decision. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Further details are available at the following: http://www.amgen.com/datasharing

Contributors

CC, FL, EB, OH and CM designed the study. GB, TVG, SK, GM, LC, PC, PG, SEC, and CM conducted the study procedures and collected and analysed data. CC, FL, JRP, and WT analysed and interpreted data. EM contributed to the immunogenetic analyses and interpretation. NCB contributed to the study design and flow cytometry.

Medical writing support, provided by Jun Yan, Pharm.D. and funded by Amgen, was used in manuscript preparation.

Declaration of interests

Dr. Butz was a paid consultant to Celimmune during the conduct of the study.

Dr. Cellier reports nonfinancial support from Amgen outside the submitted work.

Dr. Cerf-Bensussan reports fees from Celimmune during the conduct of the study.

Dr. Hermine reports grants and personal fees from AB science and grants from Celgene, Novartis, and INatherys, outside the submitted work.

Dr. Khater reports fees from Celimmune during the conduct of the study.

Dr. Leon was the chief executive and medical officer of Celimmune during the conduct of the study and is currently a consultant for Amgen. Dr. Leon is also chief scientific officer of and owns stocks in Provention Bio, Inc., which is in a partnership with Amgen to develop AMG

714/PRV-015. Dr. Leon reports other relationship with Biomedal SA during the conduct of the study and has a pending patent Methods and Compositions for the Treatment of Celiac Disease, Non-Celiac Gluten Sensitivity, and Refractory Celiac Disease.

Dr. Macintyre reports fees from Celimmune during the conduct of the study. Dr. Macintyre has a patent 10185204.4-2402 with royalties paid to Euro-Clonality group of ESLHO (European Scientific foundation of Laboratory Hematology).

Dr. Parnes is an employee of Amgen.

Dr. Tsuji reports grants, personal fees and other from Amgen Inc and personal fees and other from Celimmune, during the conduct of the study and outside the submitted work. In addition, Dr. Tsuji has a patent Methods and compositions for the treatment of celiac disease, non-celiac gluten sensitivity, and refractory celiac disease.

Ethics Committee Approval

The study protocol was approved by local ethics committees and institutional review boards at all study sites before initiation.

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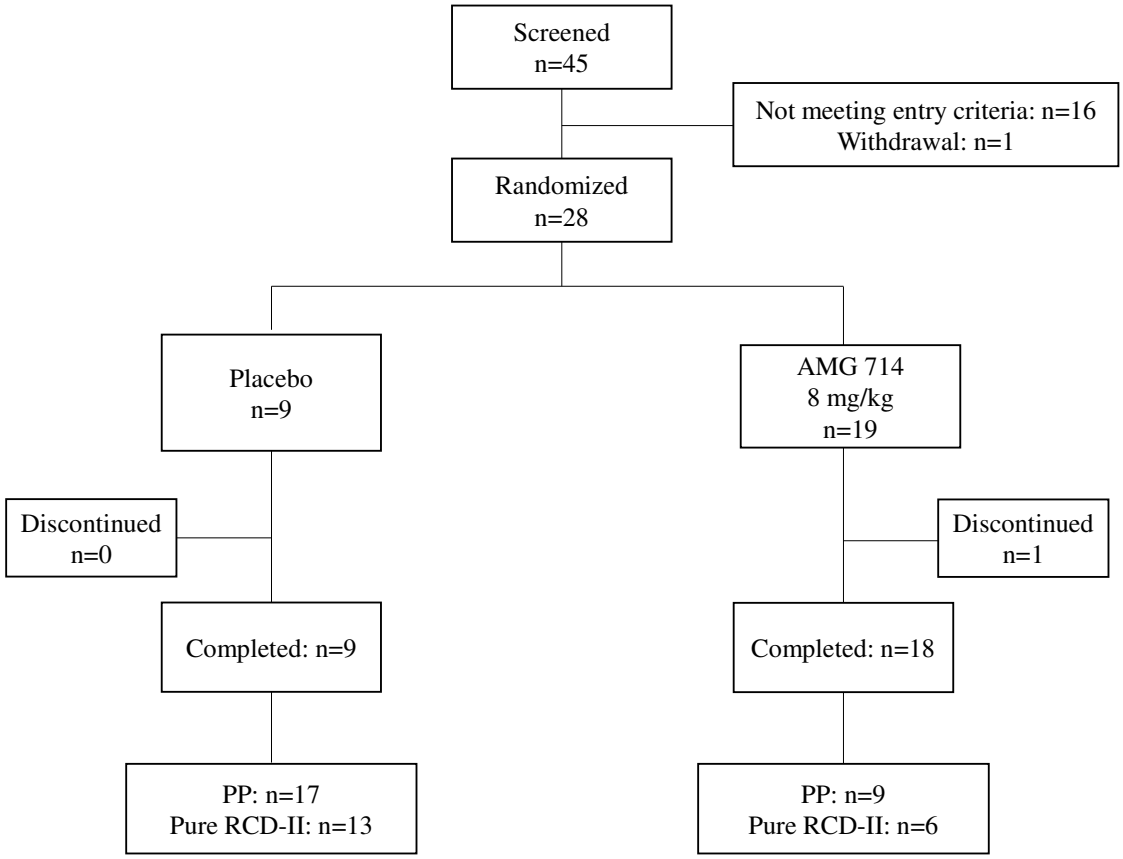
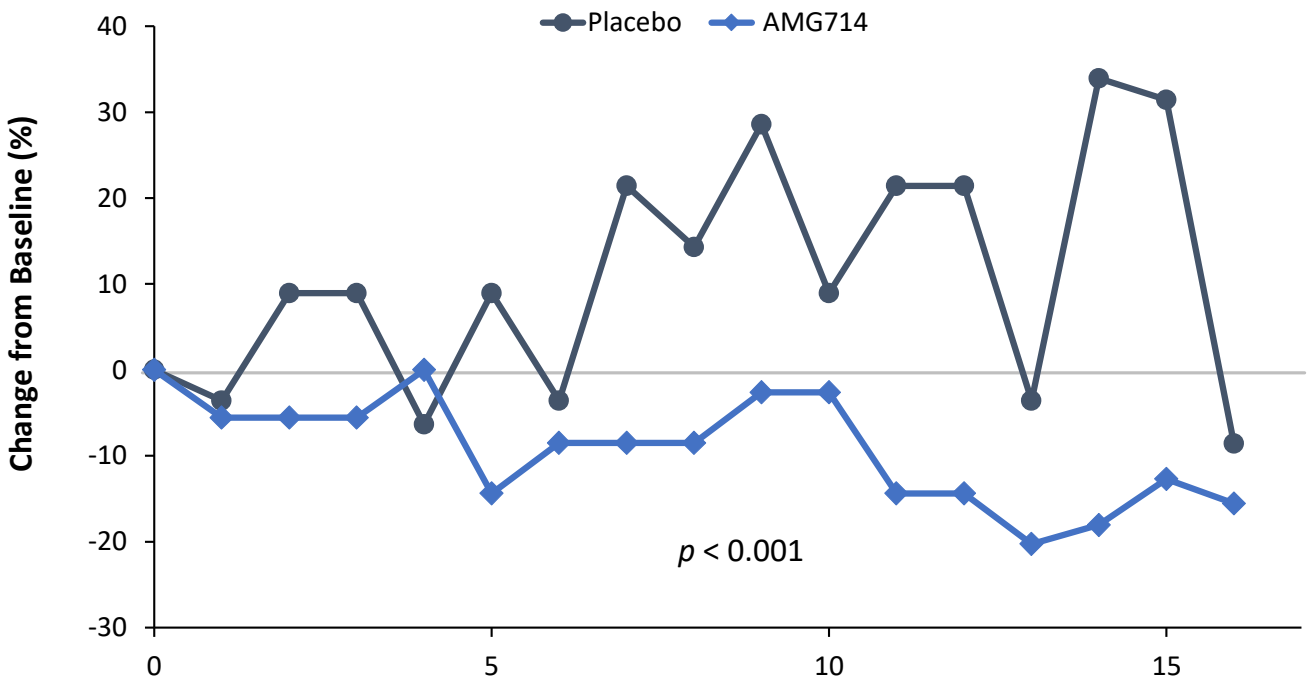
Figure 1. Flow diagram of patient disposition



Abbreviations: IEL: intraepithelial lymphocyte; ITT: intent to treat; PP: per protocol; RCD-II: type II refractory celiac disease.

Figure 2. Change from baseline in the proportion (%) of patients with at least one weekly episode of diarrhea (BSFS score ≥6), ITT population



Abbreviation: BSFS: Bristol Stool Form Scale. ITT: intent to treat.

Table 1. Demographic and baseline characteristics of ITT Population

	Placebo N=9	**AMG 714 N=19**	**Total N=28**
Age, mean (SD), years	68.4 (10.94)	63.0 (10.17)	64.8 (10.54)
Female, n (%)	6 (66.7)	8 (42.1)	14 (50.0)
Weight, mean (SD), kg	66.0 (16.97)	64.0 (11.46)	64.6 (13.18)
BMI, mean (SD), kg/m^2	24.8 (4.52)	22.4 (3.61)	23.2 (4.00)
HLA-DQ2 and/or DQ8, n (%)	6 (100)	13 (100)	19 (100)
Anti-tTG antibody positive, n (%)	1 (16.7)	1 (7.7)	2 (10.5)
Budesonide treatment, n (%)	4 (66.7)	8 (61.5)	12 (63.1)

Abbreviations: BMI: body mass index; HLA: human leukocyte antigen; tTG: tissue transglutaminase.

Table 2. Statistical analysis of relative (%) change from baseline to Week 12 in the proportion of aberrant IELs versus total IELs by flow cytometry

	Placebo	AMG 714
Typical RCD-II PP Population		
n	8	14
Change from Baseline to Week 12		
LS mean (SE)	7.30%	2.45%
90% CI	-12.93%, 27.53%	-12.82%, 17.72%
p value	0.54	0.78
Treatment difference		
LS mean (SE)		-4.85% (14.70)
90% CI		-30.26%, 20.56%
p value		0.75
Pure RCD-II PP Population		
n		
Change from Baseline to Week 12	6	13
LS mean (SE)	14.10% (14.00)	0.36% (9.51)
90% CI	-10.34%, 38.55%	-16.25%, 16.96%
p value	0.33	0.97
Treatment difference		
LS mean (SE)		-13.74% (16.93)
90% CI		-43.30%, 15.81%
p value		0.43

Abbreviations: CI: confidence interval, IEL: intraepithelial lymphocyte, LS: least square, SE: standard error

Table 3. Statistical analysis of relative (%) change from baseline to Week 12 in the proportion of aberrant IELs versus intestinal epithelial cells by immunohistochemistry

	Placebo	AMG 714
Typical RCD-II PP Population		
n	8	14
Change from Baseline to Week 12		
LS mean (SE)	49.88% (21.33)	11.66% (15.79)
90% CI	5.23%, 94.54%	-21.38, 44.71
p value	0.03	0.47
Treatment difference		
LS mean (SE)		-38.22%
90% CI		-95.73%, 19.29%
p value		0.18
Pure RCD-II PP population		
n	6	13
Change from Baseline to Week 12		
LS mean (SE)	61.35%	11.28%
90% CI	8.61%, 114.08%	-24.02%, 46.59%
p value	0.25	0.51
Treatment difference		
LS mean (SE)		-50.06% (30.44)
90% CI		-114.60%, 14.47%
p value		0.12

Abbreviations: CI: confidence interval, IEL: intraepithelial lymphocyte, LS: least square, SE: standard error

Table 4. Statistical analysis of relative (%) change from baseline to Week 12 in VH:CD ratio

	Placebo	AMG 714
PP Population		
n		
Change from Baseline to Week 12	9	17
LS mean (SE)	15.77% (19.36)	26.44% (14.06)
95% CI	-24.28%, 55.82%	-2.64%, 55.52%
p value	0.073	0.42
Treatment difference		
LS mean (SE)		10.67% (24.00)
95% CI		-38.97, 60.31
p value		0.66
Pure RCD-II PP population		
n	6	13
Change from Baseline to Week 12		
LS mean (SE)	0.15% (24.89)	26.86% (16.84)
95% CI	-52.62%, 52.92%	-8.85%, 62.57%
p value	1.00	0.13
Treatment difference		
LS mean (SE)		26.71% (30.19)
95% CI		-37.29%, 90.72%
p value		0.39

Abbreviations: CI: confidence interval, LS: least square, SE: standard error

Table 5. Summary of the most common treatment-emergent adverse events during treatment period in ITT Population

System Organ Class **Preferred Term**	**Placebo** **N=9**	**AMG 714** **N=19**	**Total** **N=28**
Patients with at least 1 TEAE	8 (88.9)	17 (89.5)	25 (89.3)
Patients with at least 1 TEAE related to study drug	7 (77.8)	16 (84.2)	23 (82.1)
Patients with at least 1 SAE	1 (11.1)	5 (26.3)	6 (21.4)
Patients who discontinued due to AE	0	1 (5.3)	1 (3.6)
Gastrointestinal disorders	4 (44.4)	7 (36.8)	11 (38.3)
Diarrhea	1 (11.1)	3 (15.8)	4 (14.3)
Infections and infestations	3 (33.3)	12 (63.2)	15 (53.6)
Nasopharyngitis	1 (11.1)	8 (42.1)	9 (32.1)
Investigations	2 (22.2)	5 (26.3)	7 (25.0)
Eosinophil count increased	0	3 (15.8)	3 (10.7)
Nervous system disorders	4 (44.4)	6 (31.6)	10 (35.7)
Headache	0	3 (15.8)	3 (10.7)
Dizziness	3 (33.3)	0	3 (10.7)

Abbreviations: SAE: serious adverse event; TEAE: treatment-emergent adverse event