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 2 is a rare subtype of coeliac disease with high mortality rates; interleukin 15 (IL-15) is strongly implicated in its pathophysiology. This trial aimed to investigate the effects of AMG 714, an anti-IL-15 monoclonal antibody, on the activity and symptoms of refractory coeliac disease type 2.

Methods This was a randomised, double-blind, placebo-controlled, phase 2a study of adults with a confirmed diagnosis of refractory coeliac disease type 2. Patients were randomly assigned at a 2:1 ratio to receive seven intravenous doses over 10 weeks of AMG 714 (8 mg/kg) or matching placebo. Biopsy samples were obtained at baseline and week 12 for cellular analysis and histology. The change in the proportion of aberrant intraepithelial lymphocytes from baseline to week 12 with respect to all intraepithelial lymphocytes was the primary endpoint and was quantified using flow cytometry. Secondary endpoints were the change in aberrant intraepithelial lymphocytes with respect to intestinal epithelial cells; intestinal histological scores (villous height-to-crypt depth ratio; VHCD); intraepithelial lymphocyte counts; Marsh score; and patient-reported symptom measures, including the Bristol stool form scale (BSFS) and gastrointestinal symptom rating scale (GSRS). Main analyses were done in the per-protocol population of patients who received their assigned treatment, provided evaluable biopsy samples, and did not have major protocol deviations; only patients with non-atypical disease were included in the analyses of aberrant intraepithelial lymphocytes, including the primary analysis. Safety was assessed in all patients who received at least one dose of study drug. This study is registered at ClinicalTrials.gov (NCT02633020) and EudraCT (2015-004063-36).

Findings From April 13, 2016, to Jan 19, 2017, 28 patients were enrolled and randomly assigned to AMG 714 (n=19) and placebo (n=9). Six patients were not included in the primary analysis because of protocol deviation (one in the AMG 714 group), insufficient biopsy samples (one in the AMG 714 group), and atypical intraepithelial lymphocytes (three in the AMG 714 group and one in the placebo group). At 12 weeks, the least square mean difference between AMG 714 and placebo in the relative change from baseline in aberrant intraepithelial lymphocyte percentage was –4·85% (90% CI –30·26 to 20·56; p=0·75). The difference between the AMG 714 and placebo groups in aberrant intraepithelial lymphocytes with respect to epithelial cells at 12 weeks was –38·22% (90% CI –95·73 to 19·29; nominal p=0·18); the difference in change in Marsh score from baseline was 0·09% (95% CI –1·60–1·90; nominal p=0·92); the difference in VHCD ratio was 10·67% (95% CI –38·97 to 60·31; nominal p=0·66); and the difference in change in total intraepithelial lymphocyte count was –12·73% (95% CI –77·57–52·12); nominal p=0·69). Regarding symptoms, the proportion of patients with diarrhoea per the BSFS score decreased from ten (53%) of 19 at baseline to seven (37%) of 19 at week 12 in the AMG 714 group and increased from two (22%) of nine at baseline to four (44%) of nine at week 12 in the placebo group (nominal p=0·0008); and the difference between the groups in change in GSRS score was –0·14 (SE 0·19; nominal p=0·48). Eight (89%) patients in the placebo group and 17 (89%) in the AMG 714 group had treatment-emergent adverse events, including one (11%) patient in the placebo group and five (26%) in the AMG 714 group who had serious adverse events. The most common adverse event in the AMG 714 group was nasopharyngitis (eight [42%] patients *vs* one [11%] in the placebo group).

Interpretation In patients with refractory coeliac disease type 2 who were treated with AMG 714 or placebo for 10 weeks, there was no difference between the groups in terms of the primary endpoint of aberrant intraepithelial lymphocyte reduction from baseline. Effects on symptoms and other endpoints suggest that further research of AMG 714 may be warranted in patients with refractory coeliac disease type 2.

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Research in context

Evidence before this study

No drug therapy is approved to treat type 2 refractory coeliac disease (also known as pre-enteropathy-associated T-cell lymphoma). Corticosteroids, chemotherapy, and hemopoietic stem-cell transplantation treatments for refractory coeliac disease type 2 have shown poor efficacy and carry substantial safety risks. We searched PubMed using the terms "refractory coeliac", "RCD", "interleukin 15", and "IL-15" for articles published in English up to Sept 21, 2018. No clinical trials have been published in which anti-IL-15 therapy is tested as a treatment for refractory coeliac disease type 2.

Added value of this study

This study confirms the role of IL-15 in driving aberrant intraepithelial lymphocytes and other abnormalities in refractory coeliac disease type 2. Although the anti-IL-15 treatment for 10 weeks did not achieve a statistically significant difference in the primary endpoint (aberrant intraepithelial lymphocytes enumerated by flow cytometry), benefits were seen in intraepithelial lymphocyte T-cell receptor clonality and in the reduction of diarrhoea in a small patient population in the study, with similar reductions 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 might be a promising treatment for refractory coeliac disease type 2, which is a rare disease with suboptimal treatment options. Further study of AMG 714 is warranted.

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See **Online** for appendix

Introduction

Refractory coeliac disease is a rare complication of coeliac disease characterised by the absence of clinical and histological response to a gluten-free diet.[1,2] Refractory coeliac disease is characterised by severe malabsorption and gastrointestinal symptoms without gluten consumption and persistent villous atrophy in the absence of others causes despite a strict gluten-free diet for at least 6 months.[1,2] Up to 1% of all patients with coeliac disease are believed to be affected by refractory coeliac disease and an estimated annual incidence of 0·83 per 10 000 patients with coeliac disease has been reported.[3,4] Patients diagnosed with coeliac disease when they are older than 50 or 60 years tend to respond slowly to a gluten-free diet.[5] Patients with coeliac disease who have persistent symptoms for at least 6–12 months despite adherence to a gluten-free diet should be assessed for possible refractory coeliac disease.[1,2,6]

Refractory coeliac disease can be further classified as type 1 and type 2 on the basis of the number of aberrant intraepithelial lymphocytes present. Aberrant intraepithelial lymphocytes have an abnormal phenotype (surface CD3– and intracellular CD3+) that can be identified by flow cytometry; these cells display clonal rearrangement of the T-cell receptor, which is detected by molecular analysis.[1,2,7,8] Patients with few aberrant intraepithelial lymphocytes, with a threshold of less than 20% of total intraepithelial lymphocytes, are classified as having refractory coeliac disease type 1. Type 1 is not associated with a substantially increased risk of developing lymphoma[9] and can be treated with nutritional support, adherence to a gluten-free diet, and pharmacological therapies (topical steroids or thiopurines).[6] Histopathologically, type 1 resembles active coeliac disease. In refractory coeliac disease type 2, aberrant intraepithelial lymphocytes make up 20% or more of total intraepithelial lymphocytes. Refractory coeliac disease type 2 is a clinically well defined rare disease that can develop from long-standing, pre-existing coeliac disease and is a precursor of a rare type of lymphoma known as enteropathy-associated T-cell lymphoma.[3]

Refractory coeliac disease type 2 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 refractory coeliac disease type 2 have a greater than 50% risk of developing enteropathy-associated T-cell lymphoma, a high-grade lymphoma with a 5-year survival rate of less than 20%.[10–12] Hence, refractory coeliac disease type 2 is also known as preenteropathy-associated T-cell lymphoma. Refractory coeliac disease type 2 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 haemopoietic stem-cell transplantation.[14]

Interleukin-15 (IL-15), produced in the small intestine by antigen-presenting cells and epithelial cells, is important in the progression to enteropathy-associated T-cell lymphoma.[15] Aberrant intraepithelial lymphocytes in refractory coeliac disease type 2 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 patients with refractory coeliac disease type 2, intraepithelial lymphocytes display somatic gain-of-function mutations in JAK1 or STAT3, which are elements of the IL-15 signalling cascade. These mutations potentiate intraepithelial lymphocyte 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 patients with refractory coeliac disease type 2, the neutralisation of IL-15 using AMG 714 blocks anti-apoptotic signalling via JAK3 and STAT5 and leads to apoptosis of the clonal

aberrant intraepithelial lymphocytes.[18] This evidence indicates that IL-15 has a non-redundant role in the survival and growth of aberrant intraepithelial lymphocytes, driving the proliferation of aberrant intraepithelial lymphocytes and promoting their accumulation. Thus, the inhibition of IL-15 could block the disease process in refractory coeliac disease type 2.

AMG 714 is a fully human immunoglobulin monoclonal antibody (IgG1κ) that binds to IL-15 and inhibits IL-15-induced T-cell activation and proliferation. AMG 714 might halt the progression of refractory coeliac disease type 2 and alleviate clinical symptoms. We did a study to investigate the safety and efficacy of AMG 714 in the treatment of patients with refractory coeliac disease type 2.

Methods

Study design

This was a randomised, double-blind, placebo-controlled, parallel-group phase 2a study to assess the safety and efficacy of AMG 714 for the treatment of adults with refractory coeliac disease type 2. This study was done at six clinical sites in France, Netherlands, Finland, Spain, and USA.

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

Participants

Inclusion criteria were age 18 years or older; a previously confirmed diagnosis of refractory coeliac disease type 2 (defined as coeliac disease confirmed by histology, capsule endoscopy, or serology; persistent and recurrent symptoms such as diarrhoea, weight loss, or abdominal pain; abnormal small bowel histology; and aberrant intraepithelial lymphocytosis with more than 20% aberrant intraepithelial lymphocytes per 100 CD45+ cells with respect to total intraepithelial lymphocytes, as measured by flow cytometry, or more than 50% aberrant intraepithelial lymphocytes, as measured by an immunohistochemistry method described elsewhere);[8] persistent intraepithelial lymphocyte abnormalities despite adherence to a strict gluten-free diet 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, or hyperthyroidism) and intestinal histological abnormality (eg, autoimmune enteropathy, giardiasis, immunodeficiency, collagenous sprue, or Whipple's disease); weakly positive or negative levels of anti-tissue transglutaminase (anti-tTG) antibodies (IgA and IgG) at screening; HLA-DQ genotyping compatible with coeliac disease; a life expectancy of more than 4 months; adequate haematological, renal, and hepatic laboratory parameters; and, for patients receiving systemic steroids, they must have been on a stable dose for at least 4 weeks before randomisation. Patients who had been treated for refractory coeliac disease type 2 before the study had to continue to show increases in aberrant intraepithelial lymphocytes and abnormal small bowel histology and must have had a history of symptoms. However, given the rarity of the disease and because the primary endpoint was the enumeration of aberrant intraepithelial lymphocytes, the presence of symptoms was not required for study entry regardless of previous treatment.

Patients were excluded if they had a diagnosis of refractory coeliac disease type 1 or enteropathy-associated T-cell lymphoma; current active or severe infection in 3 months before screening; a history of tuberculosis; positive interferon gamma release assay test at screening or exposure to a patient with tuberculosis in the 6 months before screening, unless treated with appropriate chemoprophylaxis; a history of opportunistic infections in the 3 years before screening; a history of most cancers in the 5 years before screening; other clinically significant diseases; significant immune suppression from bone marrow transplantation or cladribine treatment within 6 months of baseline or potent systemic immunosuppressant use (eg, azathioprine) within 3 months of baseline; history of alcohol or drug abuse; history of clinically significant hypersensitivity to study drug, related drugs, or the excipients; positive hepatitis B, hepatitis C, or HIV infection at the time of screening; pregnancy; or if participating in another study. All patients gave written informed consent before undergoing any study-related procedures.

Randomisation and masking

Eligible patients were randomly assigned at a 2:1 ratio to receive either AMG 714 or matching placebo. The biostatistician generated the randomisation code using permuted blocks. No stratification was applied because of the small sample size and absence of clearly established confounding factors.

Each dose of study drug (AMG 714 or placebo) was prepared by an unmasked 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 masked to treatment assignment until the study ended. Randomisation and initial dosing of the first ten 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.

Procedures

Study drug (AMG 714 or placebo) was administered intravenously to each patient at the clinical site in a

double-blind manner in seven doses over 10 weeks, with the first dose on day 0. The second and third doses were administered on day 7 and day 14. The subsequent four doses were given every 2 weeks thereafter through day 70. Patients visited study sites for the study drug injections at weeks 0, 1, 2, 4, 6, 8, and 10, and returned for tests and assessments at weeks 12 and 16. The dose of AMG 714 administered at each visit was 8 mg/kg. The dosing regimen was chosen to deliver about twice the dose of AMG 714 previously studied in rheumatoid arthritis, while remaining within toxicology safety margins. This dosing was intended to saturate IL-15 with a loading dose in the first 3 weeks and then maintain a high level of target binding. Each infusion was administered over a duration of about 2 h. Patients were confined to the study site after the end of infusion for at least 1 h 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 or oral budesonide up to 9 mg per day was allowed. These doses remained stable from 4 weeks before randomisation through the end of the study. Budesonide has been shown to improve the symptoms of refractory coeliac disease type 2 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 gluten-free diet from 6 months before randomisation through the final study visit (day 112). Adherence to the gluten-free diet was assessed by an expert dietitian once monthly during study visits and by the iVYLISA test at study visits at weeks 0, 2, 4, 6, 8, 10, 12, and 16, a quantitative sandwich enzyme-linked immunosorbent assay that quantifies gluten immunogenic peptide (GIP) in stool samples. The cutoff for a positive result was 250 mg of gluten per gram of stool.[20]

Small bowel biopsy samples from the second portion of the duodenum were obtained at baseline and at week 12 (day 84) to assess the key efficacy endpoints. Before the initiation of the study, 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. Immunohistochemistry and histology analyses were done in a masked manner at a central expert laboratory (JiLab, Tampere, Finland).

Patients returned to the study sites at weeks 0, 1, 2, 4, 6, 8, 10, 12, and 16 for safety and clinical assessments. Serum samples were collected at weeks 0, 1, 2, 4, 8, 10, 12, and 16 to analyse AMG 714 concentration and anti-drug antibodies. For patient-reported analyses (Bristol stool form scale [BSFS], coeliac disease patient-reported outcomes [CeD PRO], and gastrointestinal symptom rating scale [GSRS]), patients were given an electronic diary and instructions to record their daily symptoms through the final visit at week 16. The results were collected and reviewed at each study visit.

T-cell receptor γ-chain clonality in intraepithelial lymphocytes obtained from the biopsy samples was analysed qualitatively, in a masked manner, at a central expert laboratory (Necker Hospital, Paris, under the direction of E Macintyre) using polymerase chain reaction (PCR), as described by Derrieux and colleagues,[21] at baseline and week 12 (2 weeks after the final dose). Although the PCR analysis was not quantitative, changes in the size of the PCR peaks (increase, decrease, or stable) were established visually by the central laboratory without knowledge of the treatment assigned to each patient.

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

Outcomes

The primary endpoint of the study was the change from baseline to week 12 in the percentage of aberrant intraepithelial lymphocytes with respect to all intraepithelial lymphocytes (immunological response 1), as quantified by flow cytometry (appendix p 1).

The key secondary endpoint was the change from baseline to week 12 in the percentage of aberrant intestinal intraepithelial lymphocytes with respect to all intestinal epithelial cells, as assessed by immunohistochemistry (immunological response 2). Other secondary endpoints were small intestinal villous height-to-crypt depth (VHCD) ratio, Marsh score, and total intraepithelial lymphocyte count by immunohistochemistry; and clinical response measured by BSFS (including a post-hoc analysis of weeks with at least one episode of diarrhoea, defined as BSFS or 6 or 7) and GSRS (an endpoint developed for gastroesophageal reflux and often used, albeit not validated, in coeliac disease).

Exploratory endpoints were changes in enumeration of aberrant and abnormal intraepithelial lymphocytes (intracellular CD3, CD122, and NKG2D) by flow cytometry, immunohistochemistry, and T-cell receptor clonality analyses. Other exploratory endpoints not reported here were physician and patient global assessment of disease; quality-of-life questionnaires (short-form 12 version 2 and the EQ-5D); biomarkers of disease activity; CeD PRO; and pharmacokinetic, pharmacodynamic, and exposure and response analyses.

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

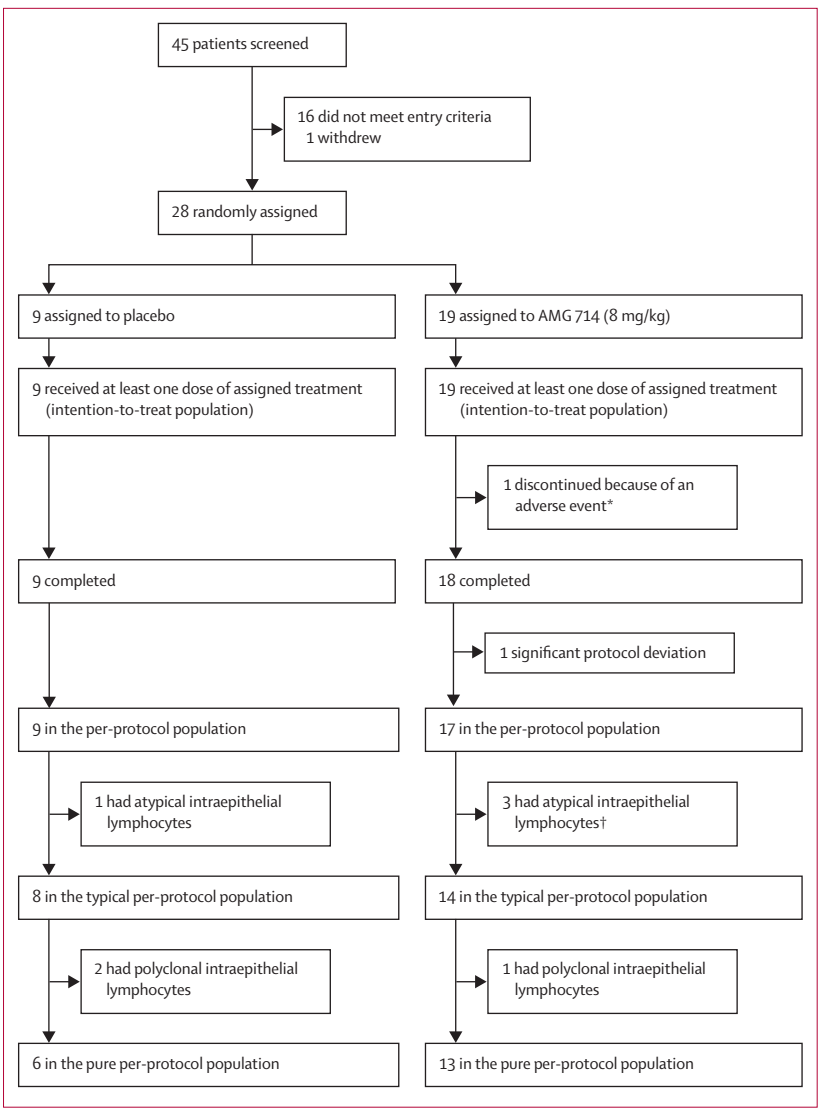

Figure 1: **Trial profile**
*This patient was excluded from the per-protocol population because of discontinuation before week 6, but also did not provide a second biopsy sample so was exluded from both the typical and pure per-protocol populations. †One of these patients also had polyclonal intraepithelial lymphocytes.

Statistical analysis

Because refractory coeliac disease type 2 is a rare disease, the sample size was not based on any statistical power calculation.

The primary endpoint was compared between the AMG 714 and placebo groups using analysis of covariance, in which 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 summarised using descriptive statistics.

All patients who received at least one dose of the study drug were included in the intention-to-treat (ITT) population. The per-protocol population included patients who received study treatment and provided evaluable data (ie, biopsy samples before and after treatment) for efficacy analysis. The per-protocol population was used for analyses of intraepithelial lymphocyte-related and histological endpoints, whereas the ITT population was used for clinical and safety endpoints.

Patients with atypical refractory coeliac disease type 2 would be allowed to participate in the study but would not be included in the analysis involving aberrant intraepithelial lymphocytes, since these endpoints were based on the enumeration of surface CD3– cells. Therefore, these patients were not included in the primary endpoint analysis. However, these patients' data were included in other endpoint analyses. Atypical refractory coeliac disease type 2 was defined as aberrant intraepithelial lymphocytes of more than 20% of total intraepithelial lymphocytes without the classic phenotype of aberrant intraepithelial lymphocytes. Patients with irregular polyclonal T-cell receptor γ chain clonality were additionally excluded to form the pure refractory coeliac disease type 2 subgroup—ie, patients who completed the study and had the classic phenotype and monoclonal aberrant intraepithelial lymphocytes. The pure refractory coeliac disease type 2 population is considered more representative of the disease pathology and were therefore analysed separately in a post-hoc subgroup analysis.

All statistical analyses were done using SAS for Windows, version 9.4. This study is registered with ClinicalTrials.gov (NCT02633020) and EudraCT (2015-004063-36).

Role of the funding source

Employees of the funders of the study had a role in the study design, data analysis, data interpretation, and writing of the report. CC and CJM had full access to all study data and final responsibility for the decision to submit for publication.

Results

We enrolled patients from April 13, 2016, to Jan 19, 2017, and the last patient visit was May 2, 2017. 45 patients were screened, of whom 16 did not meet the eligibility criteria and one withdrew before randomisation (figure 1). 28 patients were enrolled and randomly assigned to either the AMG 714 group (n=19) or the placebo group (n=9).

All 28 patients had previously received treatment for refractory coeliac disease type 2, including haemopoietic stem-cell transplantation, chemotherapy (cladribine), or

immunosuppressants (azathioprine or high-dose systemic steroids). Extraintestinal manifestations were not common, except for musculoskeletal and connective tissue disorders, reported in about 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 concentrations were borderline low and similar between the groups, with an average of 13·6 g/dL (8·44 mmol/L), which did not change during the study. Similarly, baseline albumin concentrations were low and similar between groups with mean values of 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 these did not change during the study.

All 28 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 three doses because of an adverse event (mild cerebellar disorder). This patient was excluded from the per-protocol population and did not provide a second biopsy sample. The other 27 patients completed the study. All 28 patients were followed up to the final visit at about 16 weeks after the first dose of study drug, including the patient who discontinued treatment early.

One other patient in the AMG 714 group was excluded from the per-protocol population, because of significant protocol deviation. Of the 26 patients in the per-protocol population, four (three in the AMG 714 group and one in the placebo group) had atypical intraepithelial lymphocytes and were excluded from the intraepithelial lymphocyte-related efficacy analyses. These patients would usually be excluded from this type of study because they do not strictly meet the criteria for refractory coeliac disease type 2, but were included here because the aberrant cells in these patients expressed IL-15-driven biomarkers, such as NKG2D and Granzyme B, and they might potentially benefit from anti-IL-15 therapy. Thus, the typical refractory coeliac disease type 2 per-protocol population comprised 22 patients (14 in the AMG 714 group and eight in the placebo group). Three patients had polyclonal intraepithelial lymphocytes, so the pure refractory coeliac disease type 2 per-protocol population included 19 patients with monoclonal intraepithelial lymphocytes (13 in the AMG 714 group and six in the placebo group).

Despite the randomisation, most patients in the placebo group were female (six [67%] of nine patients), while most patients in the AMG 714 group were male (11 [58%] of 19 patients), which was not unexpected given the small sample size (table 1).

Compliance with the gluten-free diet was generally high 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.

	AMG 714 group (n=19)	Placebo group (n=9)
Age, years	63·0 (10·2)	68·4 (10·9)
Sex		
Female	8 (42%)	6 (67%)
Male	11 (58%)	3 (33%)
Bodyweight, kg	64·0 (11·5)	66·0 (17·0)
Body-mass index, kg/m²	22·4 (3·6)	24·8 (4·5)
HLA-DQ2 or HLA-DQ8	19 (100%)	9 (100%)
Anti-tissue transglutaminase antibody positive	1 (5%)	1 (11%)
Budesonide treatment	8 (42%)	4 (44%)
Aberrant intraepithelial lymphocyte phenotype		
Classic	16 (84%)	8 (89%)
Atypical	3 (16%)	1 (11%)

Data are mean (SD) or n (%). The classic phenotype of the aberrant cells is surface CD3– and intracellular CD3+; the phenotypes of the aberrant cells in the atypical patients were surface CD3+ CD4+ (one patient), CD3+ T-cell receptor γ-δ+ T cells (two patients), or natural killer-like (surface CD3–, intracellular CD3–, CD45+, CD19–, and CD122+; one patient).

Table 1: **Demographic and baseline characteristics (intention-to-treat population)**

	AMG 714 group	Placebo group
Typical refractory coeliac disease type 2 per-protocol population		
Number of patients	14	8
Least square mean change (90% CI) from baseline to week 12	2·45% (–12·82 to 17·72); p=0·78	7·30% (–12·93 to 27·53); p=0·54
Least square mean difference (90% CI) versus placebo	–4·85% (–30·26 to 20·56); p=0·75	..
Pure refractory coeliac disease type 2 per-protocol population		
Number of patients	13	6
Least square mean change (90% CI) from baseline to week 12	0·36% (–16·25 to 16·96); p=0·97	14·10% (–10·34 to 38·55); p=0·33
Least square mean difference (90% CI) versus placebo	–13·74% (–43·30 to 15·81); p=0·43	..

Table 2: **Relative change from baseline to week 12 in the proportion of aberrant intraepithelial lymphocytes versus total intraepithelial lymphocytes (immunological response 1)**

The least square mean change in aberrant intraepithelial lymphocytes from baseline to week 12 (immunological response 1) in the typical refractory coeliac disease type 2 population was 7·30% (90% CI –12·93 to 27·53) in the placebo group and 2·45% (–12·82 to 17·72) in the AMG 714 group (table 2). The least square mean treatment difference between the groups was –4·85% (–30·26 to 20·56; p=0·75). In the pure population, the increase in aberrant intraepithelial lymphocytes was 14·10% (–10·34 to 38·55) in the placebo group and

	AMG 714 group	Placebo group
Typical refractory coeliac disease type 2 per-protocol population		
Number of patients	14	8
Least square mean change (90% CI) from baseline to week 12	11·66% (–21·38 to 44·71); p=0·47	49·88% (5·23 to 94·54); p=0·03
Least square mean difference (90% CI) versus placebo	–38·22% (–95·73 to 19·29); p=0·18	..
Pure refractory coeliac disease type 2 per-protocol population		
Number of patients	13	6
Least square mean change (90% CI) from baseline to week 12	11·28% (–24·02 to 46·59); p=0·51	61·35% (8·61 to 114·08); p=0·25
Least square mean difference (90% CI) versus placebo	–50·06% (–114·60 to 14·47); p=0·12	..

Table 3: **Relative change from baseline to week 12 in the proportion of aberrant intraepithelial lymphocytes versus all intestinal epithelial cells (immunological response 2)**

	AMG 714 group	Placebo group
Per-protocol population		
Number of patients	17	9
Least square mean change (95% CI) from baseline to week 12	26·44% (–2·64 to 55·52); p=0·42	15·77% (–24·28 to 55·82); p=0·073
Least square mean difference (95% CI) versus placebo	10·67% (–38·97 to 60·31); p=0·66	..
Pure refractory coeliac disease type 2 per-protocol population		
Number of patients	13	6
Least square mean change (95% CI) from baseline to week 12	26·86% (–8·85 to 62·57); p=0·13	0·15% (–52·62 to 52·92); p=1·00
Least square mean difference (95% CI) versus placebo	26·71% (–37·29 to 90·72); p=0·39	..

Table 4: **Relative change from baseline to week 12 in villous height-to-crypt depth ratio**

0·36% (–16·25 to 16·96) in the AMG 714 group and the least square mean treatment difference between AMG 714 and placebo was –13·74% (–43·30 to 15·81; p=0·43).

Regarding the key secondary endpoint of the relative change from baseline to week 12 in aberrant intraepithelial lymphocytes with respect to all intestinal epithelial cells (immunological response 2), the least square mean change was an increase of 49·88% (90% CI 5·23 to 94·54) in the placebo group and 11·66% (–21·38 to 44·71) in the AMG 714 group, with a difference of –38·22% (–95·73 to 19·29; nominal p=0·18; table 3). In the pure refractory coeliac disease type 2 population, the increase from baseline was 61·35% (8·61 to 114·08) in the placebo group and 11·28% (–24·02 to 46·59) in the AMG 714 group, with a difference of –50·06% (–114·60 to 14·47; nominal p=0·12). The AMG 714 group and the placebo group did not differ significantly in change in Marsh score from baseline to week 12 (0·09% difference [95% CI –1·60 to 1·90]; nominal p=0·92) or change in total intraepithelial lymphocyte count from baseline to week 12 (–12·73% difference [95% CI –77·57 to 52·12]; nominal p=0·69).

In the pure refractory coeliac disease type 2 population, three (50%) of the six patients in the placebo group had an increase in T-cell receptor clonality from baseline to week 12, whereas the other three (50%) patients had stable or decreased T-cell receptor clonality. In the AMG 714 group, all 13 (100%) patients had stable or decreased T-cell receptor clonality at week 12 compared with baseline (nominal p=0·021 for difference between groups).

In the per-protocol population, six (66%) of nine patients in the placebo group and all 17 (100%) patients in the AMG 714 group had stable or decreased T-cell receptor clonality from baseline to week 12 (nominal p=0·032 for difference between groups).

In the per-protocol population, both groups had mean increases in the VHCD ratio from baseline to week 12, which indicated an improvement in the histology of intestinal mucosa (table 4). In the per-protocol population, the least square mean increase was 15·77% (95% CI –24·28 to 55·82) in the placebo group and 26·44% (–2·64 to 55·52) in the AMG 714 group, with a difference of 10·67% (–38·97 to 60·31; nominal p=0·66; table 4). Similar to the aberrant intraepithelial lymphocyte-related endpoints, the difference between AMG 714 and placebo was numerically larger in the pure refractory coeliac disease type 2 population than in the per-protocol population. The placebo group showed no improvement (least square mean change 0·15% [–52·62 to 52·92]); the AMG 714 group had a mean improvement of 26·86% (–8·85 to 62·57), although the difference was not statistically significant (nominal p=0·39).

At week 0, the mean number of bowel movements per week was 7·4 (SD 4·0) in the placebo group and 10·3 (5·2) in the AMG 714 group. At week 12, the mean number of bowel movements per week was 8·3 (3·4) in the placebo group and 11·3 (5·7) in the AMG 714 group. The difference between groups was not significant. In the AMG 714 group, the proportion of patients with at least one episode of diarrhoea (BSFS ≥6) per week decreased from ten (53%) of 19 patients at baseline to seven (37%) of 19 at week 12. In the placebo group, patients with at least one episode of diarrhoea per week increased from two (22%) of nine at baseline to four (44%) of nine at week 12 (figure 2; nominal p=0·0008 for difference between groups in change from baseline).

For the change from baseline in total weekly GSRS score, the least square mean difference between AMG 714 and placebo over the 12-week treatment period was –0·14 (SE 0·19; nominal p=0·48).

In the AMG 714 group, three patients skipped one dose because of adverse events and one patient

discontinued treatment because of adverse events. In the placebo group, one patient skipped one dose because of an adverse event. Of the 28 patients who received at least one dose of the study drug, 25 (89%) had at least one treatment-emergent adverse event (TEAE; table 5). The proportion of patients with TEAEs was similar between the groups. Slightly more patients in the AMG 714 group had TEAEs that were considered related to the study drug. The most common TEAEs in the AMG 714 group were nasopharyngitis, diarrhoea, eosinophil count increased, and headache. 17 cases of infection were reported in 12 (63%) patients in the AMG 714 group (two cases of urinary tract infection, eight cases of nasopharyngitis, and one case each of pneumococcal infection, viral bronchitis, sinusitis, tuberculosis, conjunctivitis, pharyngitis, and respiratory tract infection). One patient each in the placebo group had bacteraemia, urinary tract infection, and nasopharyngitis. Nervous system disorder occurred in six (32%) patients in the AMG 714 group and four (44%) patients in the placebo group.

No deaths occurred in either group during the study. Five (26%) patients in the AMG 714 group each had a serious adverse event, compared with one (11%) 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 emphysema (current smoker) and negative tuberculosis test result at screening with concomitant medications of budesonide 3 mg twice daily, salbutamol inhalation, and beclomethasone dipropionate and formoterol fumarate inhalation. The patient was diagnosed with *Mycobacterium tuberculosis* based on a chest x-ray with miliary pattern and presence of *M 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 4 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 and aspartate aminotransferase concentrations showed minor decreases 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.

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

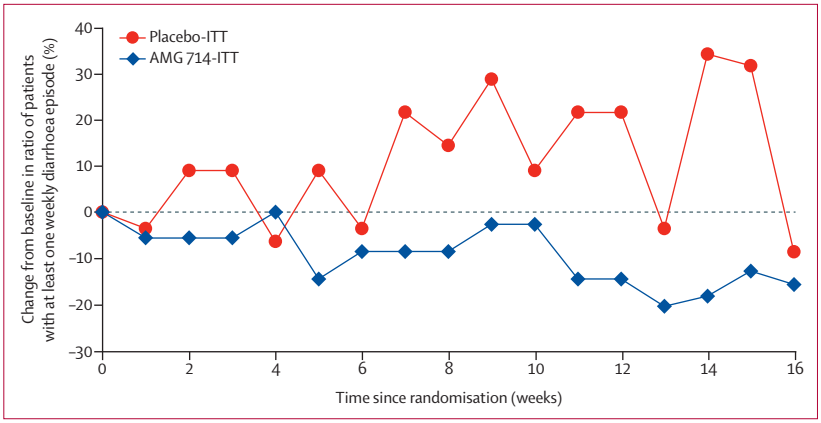

Figure 2: **Change from baseline in the proportion of patients with at least one weekly episode of diarrhoea (intention-to-treat population)**
Diarrhoea was defined as Bristol stool form scale score of at least 6.

	AMG 714 group (n=19)	Placebo group (n=9)
Patients with at least one TEAE	17 (89%)	8 (89%)
Patients with at least one treatment-related TEAE	16 (84%)	7 (78%)
Patients with at least one serious adverse event	5 (26%)	1 (11%)
Patients who discontinued because of adverse events	1 (5%)	0
Gastrointestinal disorders	7 (37%)	4 (44%)
Diarrhoea	3 (16%)	1 (11%)
Infections and infestations	12 (63%)	3 (33%)
Nasopharyngitis	8 (42%)	1 (11%)
Investigations	5 (26%)	2 (22%)
Eosinophil count increased	3 (16%)	0
Nervous system disorders	6 (32%)	4 (44%)
Headache	3 (16%)	0
Dizziness	0	3 (33%)

TEAE=treatment-emergent adverse event.

Table 5: **Summary of the most common TEAEs during the treatment period (intention-to-treat population)**

Discussion

To the best of our knowledge, this is the first industry-sponsored clinical trial of an experimental medication for the treatment of refractory coeliac disease type 2. The experimental treatment is an anti-IL-15 monoclonal antibody, AMG 714 (also known as PRV-015). Although treatment with AMG 714 did not achieve a significant

improvement compared with placebo for the primary endpoint—ie, the change in aberrant intraepithelial lymphocytes assessed by flow cytometry—the results showed improvement in an important biological endpoint (T-cell receptor clonality) and, most relevant, a clinical endpoint (diarrhoea), with nominal p values of less than 0·05. Additionally, 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 refractory coeliac disease type 2—ie, patients with clonal intraepithelial lymphocytes—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 refractory coeliac disease type 2 endpoints, whereas several patients with polyclonal intraepithelial lymphocytes responded to topical corticosteroids in endpoints such as aberrant intraepithelial lymphocytes and histology (data not shown). This differential response to background topical corticosteroids might have led to improvement and decreased effects of AMG 714.

The totality of the data, particularly the meaningful differences between AMG 714 and placebo in T-cell receptor clonality, confirm in vivo the purported role of IL-15 as a driving factor in the pathophysiology of refractory coeliac disease type 2. This finding was also supported by a clinical endpoint—fewer patients reported at least one episode of diarrhoea as measured by BSFS after receiving AMG 714. No validated symptom measures exist in refractory coeliac disease type 2, and the BSFS results should be interpreted with caution. Although 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.

Off-label treatment options for refractory coeliac disease type 2 are scarce and include chemotherapy (cladribine and alkylating drugs), haemopoietic stem-cell transplantation, 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 poor efficacy in eliminating all malignant clones in many patients. The patients in this study had failed previous treatment approaches (stem-cell transplantation, cladribine, azathioprine, and steroids). Pending further evidence, AMG 714 might address the medical needs of patients with this difficult-to-treat disease. Although data on long-term efficacy endpoints such as progression and survival are not yet available, this study has provided evidence that might 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 refractory coeliac disease type 2 study, patients were more severely ill and immune suppressed by previous treatment with haemopoietic stem-cell transplantation and chemotherapy, as well as by concomitant treatment with corticosteroids. Thus, the higher number of adverse events reported in the refractory coeliac disease type 2 study was anticipated. Overall, the incidence of adverse events was similar between the AMG 714 group and the 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 nasopharyngitis, which accounted for eight of 12 patients with presumed infections in the AMG 714 group, compared with one of three patients in the placebo group. Decrease in splenic size and function (hyposplenism) associated with refractory coeliac disease type 2, although not assessed in this study, might also have led to higher susceptibility to infection and bacteraemia.[25] Increased susceptibility to infections is not specifically expected with AMG 714, as it does not affect natural killer 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 had serious adverse events of mild functional balance disorder and cerebellar syndrome, which were likely to be due to the underlying coeliac disease, because AMG 714 was re-introduced in one of the patients and the balance symptoms improved while the patient was on the 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.

This study was necessarily limited by the small sample size given the low prevalence of refractory coeliac disease type 2, contributing to modest imbalance in some 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 percentage of aberrant intraepithelial lymphocyte, VHCD ratio, symptoms, and T-cell receptor clonality. This might have reduced any apparent effect of AMG 714. Additionally, the use of budesonide as background therapy during study treatment probably affected the efficacy results. Concomitant use of budesonide was allowed in both groups for ethical reasons but might have reduced the effect of AMG 714 compared with placebo, particularly in the per-protocol population. These findings suggest that future studies should stratify randomisation on the basis of baseline disease severity and corticosteroid use.

Another important limitation of this study was its short duration. The chronically inflamed environment of the gut with pre-existing effector memory cells might provide signals other than IL-15 that allow aberrant intraepithelial

lymphocytes to survive. However, treatment with AMG 714 was associated with symptomatic improvement and prevented the expansion and increased clonality of intraepithelial lymphocytes in the relatively short treatment duration of 10 weeks. Longer durations of AMG 714 treatment for 6–12 months might clarify its effects on these immunological, histological, and clinical outcomes and allow analysis of progression-free survival, possible refractory coeliac disease type 2 disease regression, and the prevention of enteropathy-associated T-cell lymphoma.

Furthermore, patients who had been treated for refractory coeliac disease type 2 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 might have contributed to the modest clinical benefit observed.

Despite the centralised training for study personnel, some variation among study sites in the intraepithelial lymphocyte enumeration could not be ruled out in locally conducted flow cytometry.

Data from this study provide further evidence to support the role of IL-15 in the pathophysiology of refractory coeliac disease type 2 (pre-enteropathy-associated T-cell lymphoma). There was no significant difference between groups in terms of the primary endpoint of aberrant intraepithelial lymphocyte reduction. However, AMG 714 (PRV-015) was associated with symptom improvement and reduction in clonal progression. Further study of AMG 714 in refractory coeliac disease type 2 is warranted.

Contributors

CC, FL, EB, OH, and CJM designed the study. GB, TvG, SK, GM, LC, PC, PHRG, SEC, and CJM 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. NC-B contributed to the study design and flow cytometry.

Declaration of interests

EB was a paid consultant to Celimmune during the conduct of the study. CC reports non-financial support from Amgen outside the submitted work. NC-B reports fees from Celimmune during the conduct of the study. OH reports grants and personal fees from AB Science and grants from Celgene, Novartis, and INatherys, outside the submitted work. SK reports fees from Celimmune during the conduct of the study. FL was the chief executive and medical officer of Celimmune during the conduct of the study and was a consultant for Amgen; is chief scientific officer of and owns stocks in Provention Bio, which is in a partnership with Amgen to develop AMG 714/PRV-015; he owned stock in Biomedal during the conduct of the study and has a pending patent for methods and compositions for the treatment of coeliac disease, non-coeliac gluten sensitivity, and refractory coeliac disease. EM reports fees from Celimmune during the conduct of the study; and has a patent 10185204.4-2402 with royalties paid to Euro-Clonality group of the European Scientific foundation of Laboratory Hematology. JRP is an employee of Amgen. WT reports grants and personal fees from and owns stock in Amgen and personal fees and other from Celimmune during the conduct of the study and outside the submitted work; and he has a patent: methods and compositions for the treatment of coeliac disease, non-coeliac gluten sensitivity, and refractory coeliac disease. PHRG declares stock options in ImmusanT and participation in a scientific advisory board for Janssen and ImmunogenX. All other authors declare no competing interests.

Data sharing

There is a plan to share data. This might include de-identified individual patient data for variables necessary to address the specific research question in an approved data-sharing request as well as related data dictionaries, study protocol, statistical analysis plan, informed consent form, or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and after this product and indication (or other new use) have been granted marketing authorisation in both the USA and Europe or after clinical development discontinues and the data will not be submitted to regulatory authorities. No end date exists 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 or 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 might include anonymised individual patient data or available supporting documents containing fragments of analysis code where provided in analysis specifications. Further details are available on the Amgen website.

For the **Amgen clinical trial data sharing request policy** see http://www.amgen.com/datasharing

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