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## 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

Christophe Cellier <sup>1</sup>, Gerd Bouma <sup>2</sup>, Tom van Gils <sup>2</sup>, Sherine Khater <sup>3</sup>, Georgia Malamut <sup>3</sup>, Laura Crespo <sup>4</sup>, Pekka Collin <sup>5</sup>, Peter H R Green <sup>6</sup>, Sheila E Crowe <sup>7</sup>, Wayne Tsuji <sup>8</sup>, Eric Butz <sup>8</sup>, Nadine Cerf-Bensussan <sup>9</sup>, Elizabeth Macintyre <sup>10</sup>, Jane R Parnes <sup>11</sup>, Francisco Leon <sup>12</sup>, Olivier Hermine <sup>10</sup>, Chris J Mulder <sup>2</sup>; RCD-II Study Group Investigators

Collaborators, Affiliations

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### Abstract

**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.

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**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](https://clinicaltrials.gov/ct2/show/study/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

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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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