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Safety and efficacy of AMG 714 in adults with coeliac disease exposed to gluten challenge: a phase 2a, randomised, double-blind, placebo-controlled study

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Abstract

Background: Interleukin 15 (IL-15) is implicated in the pathophysiology of coeliac disease. AMG 714 is the first anti-IL-15 monoclonal antibody to be investigated for the treatment of coeliac disease. We aimed to investigate the effects of AMG 714 in patients with coeliac disease who underwent gluten challenge.

Methods: This randomised, double-blind, placebo-controlled, parallel-group, phase 2a trial was done at three clinical sites in Finland. Inclusion criteria included age 18-80 years, a confirmed diagnosis of coeliac disease, and adherence to a gluten-free diet for at least 12 months before screening. Patients

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were randomly assigned (1:1:1) to 150 mg AMG 714, 300 mg AMG 714, or placebo using permuted blocks and stratified by study site and sex. Patients and study staff were masked to treatment assignment. Treatments were administered by two subcutaneous injections every 2 weeks for 10 weeks (total six doses). Patients without severe villous atrophy at baseline received a gluten challenge (2-4 g daily) during weeks 2-12. Small bowel biopsy samples were obtained for histological assessments at baseline and week 12. The primary efficacy endpoint was the percentage change from baseline to week 12 in villous height-to-crypt depth (VHCD) ratio. Secondary endpoints were CD3-positive intraepithelial lymphocyte density; clinical symptoms measured by gastrointestinal symptom rating scale (GSRS), coeliac disease GSRS, and Bristol stool form scale (BSFS); and changes in anti-tTG and anti-DGP antibodies from baseline. The primary analysis was done in the per-protocol 1 population of patients who received at least one dose of study drug and who underwent the gluten challenge. Safety analyses were done in all patients who received at least one dose of study drug. This trial is registered at ClinicalTrials.gov, [NCT02637141](https://clinicaltrials.gov/ct2/show/study/NCT02637141) and EudraCT, 2015-003647-19.

Findings: Between April 13, 2016, and Nov 22, 2016, 64 patients were enrolled and randomly assigned to either the 150 mg AMG 714 group (n=22), the 300 mg AMG 714 group (n=22), or the placebo group (n=20). Two patients did not start treatment and two did not provide post-treatment biopsy samples. 49 patients underwent the gluten challenge (per-protocol 1 population) and 11 patients did not because of baseline villous atrophy. AMG 714 did not prevent mucosal injury due to gluten challenge. The least square mean difference in the relative change from baseline in VHCD ratio was -2.49% (95% CI -16.82 to 11.83; p=0.73) between 150 mg AMG 714 and placebo and 6.39% (-7.07 to 19.85; p=0.34) between 300 mg AMG 714 and placebo. Neither comparison was statistically significant. The density of CD3-positive intraepithelial lymphocytes increased in all groups, with smaller increases in the 300 mg group (-41.24% [95% CI -79.28 to -3.20] vs placebo, nominal p=0.03) but not the 150 mg group (-14.32% [-54.39 to 25.74], nominal p=0.47). Clinical symptoms were ameliorated with AMG 714 treatment between baseline and week 12, particularly diarrhoea as measured by the BSFS (nominal p=0.01 for 150 mg vs placebo, and nominal p=0.0002 for 300 mg vs placebo). Serum antibody titres for anti-tTG and anti-DGP antibodies increased in all three treatment groups, with no significant difference between AMG 714 and placebo. Treatment-emergent adverse events occurred in 21 (95%) patients in the 150 mg AMG 714 group, 0 (95%) in the 300 mg AMG 714 group, and 19 (100%) in the placebo group. The most common treatment-emergent adverse events were gastrointestinal disorders (17 [77%] participants in the 150 mg AMG 714 group, 16 [76%] in the

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300 mg AMG 714 group, and 13 [68%] in the placebo group). Injection site reactions were the most common individual adverse event, reported in eight (36%) patients in the 150 mg AMG 714 group, 11 (52%) in the 300 mg group, and five (26%) in the placebo group. No serious adverse events occurred.

Interpretation: The primary endpoint, change in VHCD ratio from baseline after 12 weeks of treatment in patients with coeliac disease undergoing gluten challenge, was not significantly different between placebo and AMG 714 at either 150 mg or 300 mg. Effects on intraepithelial lymphocyte density and symptoms suggest that further research of AMG 714 may be warranted in patients with non-responsive coeliac disease.

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