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Rheumatoid arthritis – biological DMARDs

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EFFICACY AND SAFETY OF E6011, AN ANTI-FRACTALKINE MONOCLONAL ANTIBODY, IN MTX-IR PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Fractalkine (CX3CL1, designated as FKN hereafter) is the sole member of the CX3C-chemokine which leads to dual actions, chemotaxis and cell adhesion for leukocytes expressing the cognate receptor, CX3CR1, during their migration. We have conducted clinical trials of E6011, a novel humanized anti-FKN monoclonal antibody, for patients with rheumatoid arthritis (RA) in Japan¹. This is the first report of efficacy and safety results of E6011 from a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study in RA patients inadequately responding to methotrexate (NCT02960438).

Objectives: To evaluate efficacy and safety of three dose of E6011 compared with placebo.

Methods: During the 24-week double-blind period, patients with moderately to severely active RA of inadequate response to MTX were randomly assigned to E6011 100 mg, 200 mg, 400/200 mg, or placebo groups at a 1:2:2:2 ratio. In the E6011 100 mg, 200 mg, and placebo groups, subjects received 100 mg, 200 mg, or placebo at Weeks 0, 1, 2, and every 2 weeks subsequently. In the E6011 400/200 mg group, subjects received 400 mg at Weeks 0, 1, 2, 4, 6, 8, 10 and then 200 mg every 2 weeks subsequently.

Results: A total of 190 subjects (54 in the placebo group, 28 in the 100 mg group, 54 in the 200 mg group, 54 in the 400/200 mg group) received study drug. Of the 190 subjects, 169 completed and 21 discontinued study treatment prematurely during the 24-week double-blind period. The ACR20 response rate at Week 12 (non-responder imputation), the primary endpoint, was 37.0% in the placebo group, 39.3% in the 100 mg group, 48.1% in the 200 mg group, and 46.3% in the 400/200 mg group (not statistically significant), and statistically significant difference from placebo in ACR20 response rate was found in the 200 mg and 400/200 mg groups at Week 24 (35.2% for placebo, 39.3% for 100 mg, 53.7% for 200 mg, 57.4% for 400/200 mg). In addition, we focused on CD16+ monocytes which highly expressing FKN receptor/CX3CR1 as a blood biomarker that linked to the clinical response to E6011. The whole patient population was divided into 2 groups according to the median value of baseline CD16+ monocyte percentage (Median: 10.35%). Much clearer ACR20 response was observed in a dose dependent manner in the subjects who showed higher baseline CD16+ monocytes over the median at Week 24 (NRI) (30.0% for placebo, 46.7% for 100 mg, 57.7% for 200 mg, and 69.6% for 400/200 mg) although such fashion was obscure in the subjects below the median value. Adverse events that occurred in ≥5% of subjects in any E6011 group were nasopharyngitis, upper respiratory tract infection, stomatitis, bronchitis, back pain, pharyngitis, and dental caries. As a results, E6011 was well tolerated with no notable safety concerns at doses of 100, 200, and 400/200 mg when administered subcutaneously for 24 weeks.

Conclusion: E6011 provided clinical improvements with a good safety profile in RA patients with inadequately responding to MTX. Especially, a higher efficacy of E6011 was suggested in patients with higher baseline CD16+ monocytes (%).

This is the world-first evidence suggesting that a novel approach to target FKN/CX3CR1 interaction could be beneficial for RA.

REFERENCES:

- [1] Tanaka Y, et al., *Mod Rheumatol* (2018) 28, 58-65

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