**A randomized, double blind, placebo-controlled, dose response, phase II, multicentre trial to evaluate the efficacy, safety and pharmacokinetics of oral CR6086 administered at the doses of 30, 90 or 180 mg bid for 12 weeks in combination with methotrexate, in DMARD-naïve patients with early rheumatoid arthritis**

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## SUMMARY OF RESULTS

**Background**: MTX is the first line treatment in early RA. There is robust evidence from cohort studies, but less from RCTs, that a "window of opportunity" exists over 12-16 weeks symptom duration. CR6086 is a selective prostaglandin EP4 receptor antagonist, with an immunomodulatory profile.

**Objective**: To test efficacy and safety of CR6086 added to MTX in early RA, DMARD-naïve patients.

**Methods**: Patients with RA (ACR/EULAR 2010 criteria), < 1 year from symptom onset and naïve to DMARDs were randomized to oral CR6086 30, 90, 180mg, or placebo bid and oral MTX for 13 weeks (NCT03163966). Primary endpoint was the ACR20 response rate: 240 patients were required to detect a difference among groups, with 50% responders on placebo and 70% on the 90mg CR6086 target dose. Pairwise comparisons of proportions were performed, with nonresponder imputation for withdrawals. A subgroup of patients underwent dynamic contrast-enhanced (DCE) MRI for quantification of synovitis at MCP and wrist joints, evaluated as DEMRIQ-ME and DEMRIQ-vol.

**Results**: The ITT population included all 244 randomized patients receiving at least one dose of study drugs (59 CR6086 30mg/MTX, 60 CR6086 90mg/MTX, 63 CR6086 180mg/MTX, 62 placebo/MTX). Safety was good with no increased rate of infections or other disorders; however, there were more minor upper GI adverse events (AEs) with CR6086, and increased withdrawals due to AEs with the 180mg dose (9/63, 14.3% vs 1.7-3.4% in other groups). There were more ACR20 responders with MTX monotherapy than predicted (59.7%) and thus the 10.3% difference with the 90mg target dose (70.0%) was not significant. The low 30mg dose was no better than placebo (55.9%), while the high 180mg dose did not provide additional benefit compared with 90mg (74.0% net of withdrawals). CR6086 90mg and 180mg groups showed a significant improvement in MRI, compared with placebo (Fig. 1). In a post-hoc analysis in patients < 6 months from symptom onset (ACR definition of early RA: 98/244, 40.2%), MTX monotherapy exerted a large 76% ACR20 response rate that precluded potentiation. Conversely, in patients of 6-12 months disease duration (146/244, 59.8%) ACR20 responders were 48.6% with MTX monotherapy vs 68.4% with 90mg, i.e. a 19.8% difference as postulated, with proportional differences in secondary endpoints (Tab. 1).

**Conclusion:** There was no benefit demonstrated for CR6086 added to MTX in the study cohort as a whole. However, in a post-hoc analysis, enhanced responses were observed with CR6086 90mg bid added to MTX in patients >6 months disease duration. This generated the hypothesis that addition of CR6086 90mg bid may benefit RA in patients initiating MTX after the window of opportunity, to be tested in further studies.

**Table 1. ITT outcomes at week 13**

| | Symptom onset <12 months (principal analysis) | | Symptom onset 6-12 months (post-hoc analysis)* | |
|---|---|---|---|---|
| | **Placebo +MTX (N=62)** | **CR6086 90mg +MTX (N=60)** | **Placebo +MTX (N=37)** | **CR6086 90mg +MTX (N=38)** |
| ACR20, % | 59.7% | 70.0% | 48.6% | 68.4% |
| ACR50, % | 33.9% | 38.3% | 29.7% | 39.5% |
| ACR70, % | 17.7% | 23.3% | 10.8% | 28.9% |
| DAS28 (CRP) <2.6, % | 12.9% | 20.0% | 8.1% | 18.4% |
| CDAI ≤2.8, % | 8.1% | 11.7% | 5.4% | 15.8% |
| SDAI ≤3.3, % | 6.5% | 10.0% | 2.7% | 15.8% |
| Boolean-based remission, % | 6.5% | 6.7% | 2.7% | 10.5% |

*In patients with symptom onset <6 months, MTX monotherapy exerted a large 76% ACR20 response, and correspondingly high secondary efficacy parameters, precluding potentiation in this subset

**Figure 1. Change in MRI (DEMRIQ-ME#) after 13 weeks**