A NOVEL FORMULATION OF CT-P13 (INFliximAB BIOSIMILAR) FOR SUBCUTANEOUS ADMINISTRATION: 1-YEAR RESULTS FROM A PART 1 OF PHASE III, RANDOMIZED CONTROLLED TRIAL IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

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Background: Efficacy and safety of a new subcutaneous (SC) formulation (CT-P13 SC) up to Week 30 were comparable with intravenous (IV) formulation (CT-P13 IV) in both patients with rheumatoid arthritis (RA) [1] and Crohn's disease [2].

Objectives: This report is to further investigate pharmacokinetics, efficacy and overall safety of CT-P13 SC in patients with RA throughout the 1-year treatment period.

Methods: Patients with active RA [presence of 6 or more swollen and tender joints [of 28 assessed], and serum C-reactive protein [CRP] concentration >0.6 mg/dL] were treated with CT-P13 IV at Weeks 0 and 2, and were randomized for continuation with CT-P13 IV or SC administration at Week 6. The IV cohort received CT-P13 IV 3 mg/kg every 8 weeks and the SC cohorts received CT-P13 SC 90 mg, 120 mg or 180 mg, respectively, every 2 weeks up to Week 54. Pharmacokinetics blood samples were collected before study drug administration at each visit and drug levels were determined by electrochemiluminescent assay. Efficacy parameters including DAS28 and ACR criteria and overall safety were evaluated.

Results: A total of 50 patients were enrolled, of whom 48 patients were randomly assigned at Week 6 into 4 cohorts (1:1:1:1 ratio). The mean trough (pre-dose serum concentration of CT-P13 before next dose injection) of SC cohorts throughout the study visits were higher than those of IV cohort after randomization at Week 6. Trough levels increased with SC dose and were generally comparable to those of IV cohort after randomization at Week 6 in SC cohorts were generally comparable to those of IV cohort and appeared similar to those previously reported for IV infliximab [3]. All injection site reactions were grade 1 or 2. No malignancy or death was reported (Table 1).

Conclusion: The results from 1-year treatment suggest similar efficacy and safety of CT-P13 SC to CT-P13 IV in RA. The mean serum concentration in all SC cohorts consistently exceeded the threshold of target therapeutic concentration. These results show that the novel SC formulation of CT-P13 may enhance treatment options for use of infliximab biosimilar by providing high consistency in drug exposure.

REFERENCE:
1 Westhovens et al., Annals of the Rheumatic Disease 2018;77:315.
2 Schreiber et al., Gastroenterology 2018;154(6):S-1371.
3 Yoo et al., Arthritis Research 18:22.


Rheumatoid arthritis – non biological treatment

THE BTK INHIBITOR, FENEBRUTINIB, EFFECTIVELY MODULATES B AND MYELOID CELL BIOLOGY IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Bruton's tyrosine kinase (BTK) plays an essential role in B cell development. BTK acts downstream of the B cell receptor in B cells, and FC receptor signalling in myeloid cells, pathways thought to be involved in the pathogenesis of RA. Fenebrutinib (FEN) is a non-covalent small molecule inhibitor of BTK with greater than 100-fold selectivity relative to other kinases [1].

Objectives: To characterize the mechanistic effects of FEN on B and myeloid cell biology and determine the potential of biomarkers to predict response to FEN treatment in patients with RA.

Methods: The ANDES study included RA patients (pts) on background methotrexate (MTX) with inadequate response to MTX (n=480, Cohort 1, MTX-IR) or anti-TNFs (n=98, Cohort 2, TNF-IR). Cohort 1 pts were randomized to receive PBO, adalimumab (ADA) 40 mg Q2W, or FEN 50 mg QD, 150 mg QD or 200 mg BID. Cohort 2 pts were randomized to receive PBO or FEN 200 mg BID. Clinical efficacy was assessed based on the proportion of pts achieving ACR50 at week 12. Pts for whom samples were available were assessed for levels of rheumatoid factor (RF), total IgM and IgG, CCL4, CXCL13, CRP and IL6.

Results: Primary study results are reported separately. Overall, treatment with FEN caused significant reductions in RF (by week 12) and total IgM and IgG (at weeks 4-12) relative to PBO (Table 1). Early and sustained reductions of the B cell chemokine CXCL13 and the myeloid-enriched biomarker CCL4 were observed with FEN or ADA relative to PBO by week 1. CRP levels were significantly reduced with 200 mg BID FEN by week 8, and with ADA by week 2 relative to PBO. By week 12, there was a trend toward lower IL6 levels with FEN treatment relative to PBO, whereas ADA significantly reduced IL6 levels by week 1 relative to PBO in MTX-IR pts. In TNF-IR patients, IL6 was significantly reduced by FEN treatment by week 12 relative to PBO. PK-PD relationships were observed for multiple B and myeloid cell biomarkers. No single biomarker at baseline was associated with clinical response (at 12 weeks) in MTX-IR and TNF-IR pts. However, greater baseline RF titers were associated with increased FEN clinical response in TNF-IR pts.

Conclusion: FEN treatment resulted in strong pharmacodynamic effects on the biomarkers of B and myeloid cell biology in RA. This included reductions in total IgM and IgG that were not observed with ADA. Conversely, ADA reduced IL6 and CRP faster than FEN, highlighting key mechanistic differences between FEN and ADA. Baseline RF titer was associated with FEN clinical response in the more refractory TNF-IR
ppts. These data provide mechanistic insights into the efficacy of FEN in RA patients.

REFERENCE:

Table 1. FEN Treatment Causes Changes in B and Myeloid Cell Biomarkers (median±

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
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<tbody>
<tr>
<td>FEN</td>
<td>50 mg</td>
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</tr>
<tr>
<td>FEN</td>
<td>100 mg</td>
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</tr>
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<tr>
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<td>40 mg</td>
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<td>(n=103)</td>
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<tr>
<td>BID</td>
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</table>

RF 71 63 58 87 66 56 120
IGM 88* 86* 84* 100 103 78* 96
IGG 100 96* 91* 100 100 89* 99
CCL4 83* 88* 77* 96 64* 79* 112
IL-1α 63 63 60 76 43* 60* 83
CRP 66 64 59* 81 37* 42* 98

*significant versus PBO (p-value ≤ 0.05 FDR adjusted; Kruskal-Wallis test


FR10130

RELATIONSHIP BETWEEN DEPRESSION AND DISEASE ACTIVITY IN US VETERANS WITH EARLY RHEUMATOID ARTHRITIS RECEIVING METHOTREXATE

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Background: Depression is common in rheumatoid arthritis (RA) patients and exacerbates disease activity and may reduce response to first-line disease-modifying antirheumatic drugs.

Objectives: To determine whether depression affects disease activity in patients with early RA treated with methotrexate (MTX).

Methods: Patients in the Veterans Affairs Rheumatoid Arthritis registry with early RA (onset <2 years) receiving MTX were selected (n=268). Depression was assessed at baseline using International Classification of Diseases codes (296.2-296.39, 300.4, 311). Disease activity was measured using the 28 joint count disease activity score (DAS-28), tender and swollen joint counts (TJC and SJC), patient and provider global assessment (PTGA and PRGA), patient-reported pain, multidimensional health assessment questionnaire (MDHAQ), and erythrocyte sedimentation rate (ESR). Baseline confounders included sociodemographics, anthropometrics, comorbid treatments, and other clinical characteristics. Propensity score weights were used to equate the depressed and non-depressed partici- pants on baseline confounders. Generalized linear survey models were used to compare disease activity trajectories between depressed (n=48) and non-depressed (n=220) patients over two years. Standardized causal mean outcome differences were estimated at 6 months and 1- and 2- years follow-up.

Results: Depression was associated with significantly greater DAS-28 at 6 months (β=0.36, 95% CI: 0.03, 0.69) but not at 1- or 2-years follow-up (Table 1). Associations for DAS-28 components were smaller in magnitude, decreased over time, and not statistically significant. Depression was also associated with significantly greater pain at both 6 months (β=0.47; 95% CI: 0.11, 0.82) and 1-year (β=0.42; 95% CI: 0.03, 0.82) follow-up but not the PRGA or MDHAQ at any assessed time interval.

Table 1. Causal mean differences in standardized disease activity measure at 6 months and 1- and 2-years follow-up comparing those with depression to those without baseline.

<table>
<thead>
<tr>
<th>Measure</th>
<th>6 Months(β, 95% CI)</th>
<th>1 Year(β, 95% CI)</th>
<th>2 Years(β, 95% CI)</th>
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<tr>
<td>DAS-28</td>
<td>0.36 (0.03, 0.69)</td>
<td>0.11 (-0.29, 0.51)</td>
<td>-0.20 (-0.75, 0.35)</td>
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<tr>
<td>SJC</td>
<td>0.24 (0.01, 0.50)</td>
<td>0.03 (-0.28, 0.34)</td>
<td>0.03 (-0.49, 0.54)</td>
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<tr>
<td>TJC</td>
<td>0.29 (0.02, 0.61)</td>
<td>0.12 (-0.22, 0.47)</td>
<td>-0.16 (-0.75, 0.43)</td>
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<tr>
<td>PTGA</td>
<td>0.30 (0.06, 0.56)</td>
<td>0.27 (0.08, 0.61)</td>
<td>0.00 (0.45, 0.60)</td>
</tr>
<tr>
<td>ESR</td>
<td>0.17 (0.23, 0.57)</td>
<td>0.07 (-0.47, 0.33)</td>
<td>-0.15 (0.72, 0.41)</td>
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<tr>
<td>PRGA</td>
<td>0.14 (0.16, 0.43)</td>
<td>0.15 (0.20, 0.50)</td>
<td>-0.33 (-1.00, 0.34)</td>
</tr>
<tr>
<td>Pain</td>
<td>0.47 (0.11, 0.82)</td>
<td>0.42 (0.03, 0.82)</td>
<td>0.20 (-0.35, 0.75)</td>
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FR10131

ELUCIDATING THE MECHANISM UNDERLYING CREATINE PHOSPHOKINASE UPREGULATION WITH UPADACITINIB

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Background: JAK inhibitors, including Upadacitinib (UPA), have been associated with increased serum levels of creatine phosphokinase (CPK) in patients with inflammatory disorders, but not in patients with myeloproliferative disease or in healthy subjects treated for a limited duration (1). While CPK increases can be indicative of muscle damage, there are no other indicators of muscle pathology observed with JAK inhibitors, including Upadacitinib (UPA), have been associa-
ted with increased serum levels of creatine phosphokinase (CPK) in patients with inflammatory disorders, but not in patients with myeloproliferative disease or in healthy subjects treated for a limited duration (1). While CPK increases can be indicative of muscle damage, there are no other indicators of muscle pathology observed with JAK inhibitors, suggesting that there may be another mechanism behind the increased CPK levels. Inflammatory diseases including rheumatoid arthritis are often associated with reduced muscle mass (sarcopenia), a process reversed with disease control (2).

Objectives: We hypothesized that one or more cytokines present in the inflammatory milieu may block differentiation of myoblasts into mature myocytes and that JAK inhibition restores differentiation and associated CPK expression. We focused on the gp130-mediated cytokines IL6, Oncostatin M (OSM), CNTF, and LIF as these have been shown to impair myoblast differentiation.

Methods: Human skeletal muscle myoblast (HSMM) cells were cultured in 10% fetal bovine serum, or were serum starved (2% horse serum) to induce differentiation into myocytes, with and without stimulation with OSM (1–100 ng/ml) and/or UPA (0.0007–1 μM) for up to 5 days. RNA was purified and expression of CPK (M-type) was determined by QPCR using GAPDH as a reference. QPCR expression was also measured following stimulation of HSMM cells with other JAK inhibitors (Baricitinib and Tofacitinib).