Safety and Efficacy of Oral Chemokine Receptor 1 Antagonist CCX354-C in a Phase 2 Rheumatoid Arthritis Study

Paul P. Tak, M.D., Ph.D., AMC/University of Amsterdam, Amsterdam, The Netherlands
Andra Balanescu, M.D., Ph.D., University of Medicine and Pharmacy, Bucharest, Romania
Vira Tseluyko, M.D., City Clinical Hospital, Kharkiv, Ukraine
Silvia Bojin, M.D., Spitalul Judetean de Urgenta "Dr. Fogolyan Kristof", Sf. Gheorghe, Romania
Edit Drescher, M.D., Veszprém Megyei Csolnoky Ferenc Kórház Nonprofit Zrt., Veszprém, Hungary
Dan Dairaghi, Ph.D., Shichang Miao, Ph.D., Vittorio Marchesin, CCRP, Juan Jaen, Ph.D., Pirow Bekker, M.D., Ph.D., and Thomas J. Schall, Ph.D., ChemoCentryx, Inc., USA

Disclosures

- **P.P. Tak**: Abbott Laboratories, Amgen, Arthrogen, AstraZeneca, Bristol Myers Squibb, ChemoCentryx, Johnson & Johnson, Merck, MerckSerono, Novartis, NovImmune, NovoNordisk, Pfizer, Roche/Genentech. After study completion, became an employee of GlaxoSmithKline, an alliance partner of the study sponsor ChemoCentryx for CCX354-C
- **D. Dairaghi, S. Miao, V. Marchesin, J. Jaen, P. Bekker, and T.J. Schall** are employees of ChemoCentryx, the study sponsor
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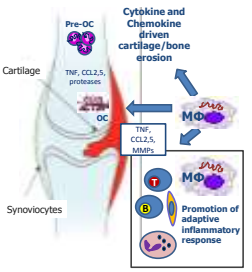
Effects of Chemokines in Inflammation

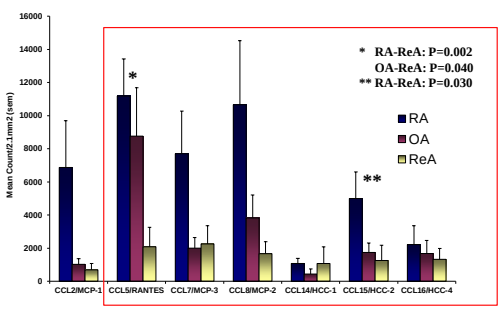
- Leucocyte recruitment and retention
- Neoangiogenesis
- Release of pro-inflammatory mediators, including cytokines

CCR1 Inhibition in Rheumatoid Arthritis: Scientific Rationale



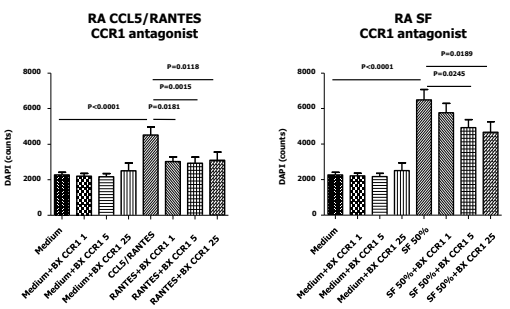
- **Blocks recruitment of activated macrophages to synovium**
  - CCR1 ligands actively secreted by inflammatory cells and synoviocytes
  - Macrophage is major producer of TNF/inflammatory cytokines, and proteases
- **Prevent bone destruction through effect on osteoclast maturation, mobility, and activity**

Abundant Expression of CCR1 Ligands in RA Synovium



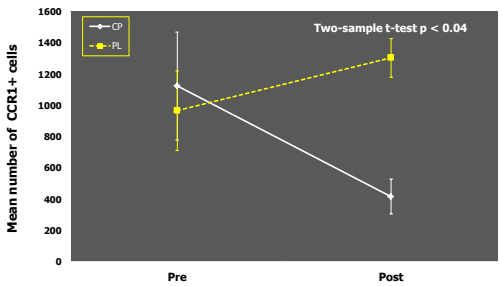
Haringman et al. Ann Rheum Dis 2006;65:294-300

CCR1 Antagonist Treatment Blocks Both CCL5/RANTES and Synovial Fluid-Induced RA Monocyte Migration



C Lebre et al. PLoS One. 2011;6:e21772

Decreased Number of Synovial CCR1+ Cells After CCR1 Blockade



Haringman et al. Ann Rheum Dis 2003;62:715-21

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The CCR1 Inhibitor CCX354-C

- Orally administered
- Highly specific
- Safe and well tolerated in 108 subjects in Phase 1 studies up to 300 mg dose

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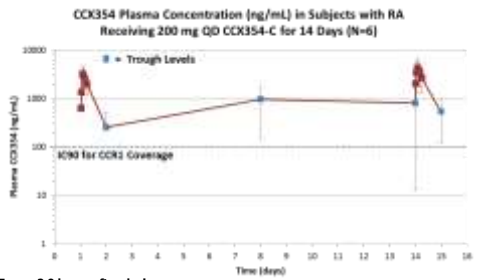
CARAT-1 Showed That 200 mg CCX354-C QD Provides >90% CCR1 Plasma Coverage



- T_{max} 2.0 hours after dosing
- $T_{1/2}$ 7 hours
- C_{max} 4590 ng/mL; C_{min} 540 ng/mL
- IC_{90} (A_{10}) for CCR1 coverage ~100 ng/mL , based on competitive Alexa-MIP1α binding assays

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CCR1 Antagonist in Rheumatoid Arthritis Trial-2 (CARAT-2)

- Study Objectives
  - Primary Safety: Evaluation of the safety and tolerability of CCX354-C in subjects with RA with inadequate response to MTX
  - Efficacy: Evaluation based on RA disease measurements: ACR, DAS28, CRP, ESR, bone turnover markers
- Study Design
  - Randomized, double-blind, placebo-controlled, parallel group study
  - Stratification based on previous biologics use, and current corticosteroid use

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CCR1 Antagonist in Rheumatoid Arthritis Trial-2 (CARAT-2)

- Subject Population
  - 160 adult subjects with RA, on stable dose of MTX
  - At least 8 swollen joints and 8 tender joints (based on 66/68 joint count)
  - CRP > 5 mg/L
- Treatment Groups
  - Placebo, 100 mg CCX354-C twice daily, and 200 mg CCX354-C once daily
- Study Duration
  - 12-week treatment period and 4-week follow-up period

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Recruitment by Country

Country	Number of Study Centers	Number of Subjects Enrolled
Belgium	3	4
Czech Republic	6	19
Germany	3	4
Hungary	6	20
The Netherlands	1	2
Poland	11	43
Romania	9	40
Ukraine	6	28
TOTAL	**45**	**160**

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Subject Groups Well Balanced at Baseline

Mean (SD)	Placebo (N=54)	100 mg BID CCX354-C (N=53)	200 QD CCX354-C (N=52)
Age (years)	55.5 (9)	54.9 (11)	54.0 (10)
Gender M/F (%)	13/87	19/81	17/83
BMI, kg/m^2	28 (5)	28 (6)	27 (5)
RA Duration, years	6 (0-42)	5 (0-26)	5 (0-36)
RF Positive (%)	67%	77%	79%
Methotrexate weekly dose in prior 8 weeks*	15 [7.5-25]	15 [7.5-25]	15 [7.5-25]
DAS28-CRP	5.9 (0.7)	6.0 (0.8)	6.1 (0.8)
Tender Joint Count (68)*	19.5 [8-60]	23.0 [10-64]	25.0 [7-60]
Swollen Joint Count (66)*	13 [8-29]	14 [8-39]	15 [8-40]
CRP (mg/L)*	17.2 [5.2-142.0]	13.8 [5.3-80.9]	14.2 [5.5-109.1]
* Median [range]			

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SAFETY PROFILE

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Overall Adverse Event Profile

System Organ Class Preferred Term Number of Subjects, n (%)	Placebo (N=53)	100 mg BID CCX354-C (N=53)	200 mg QD CCX354-C (N=54)
Subjects with any AE	26 (49%)	30 (57%)	21 (39%)
Subjects with AE leading to withdrawal	2 (4%)	7 (13%)	0
Subjects with Serious AEs	0	4 (8%)	0
Syncope (vasovagal reaction associated with blood draw)	0	1	0
Non-cardiac chest pain	0	1	0
Myocardial infarction	0	1	0
Temporal lobe epilepsy	0	1	0

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CCX354-C: Tolerability and Safety in CARAT-2

- The overall adverse event incidence was similar across dose groups
- Four SAEs observed in the CCX354-C 100 mg BID group were not considered related to CCX354-C treatment
- Most commonly observed AEs with CCX354-C were headache, nasopharyngitis and nausea
- No significant safety issues were observed regarding safety laboratory parameters including hepatic, renal, metabolic, and hematologic data
- Slight increases (0.6 mmol/L) in total cholesterol were observed with 200 mg QD CCX354-C treatment, consistent with anti-inflammatory activity
- No significant safety issues were evident based on review of vital signs, physical examination, and ECG data

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EFFICACY RESULTS

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Study Populations of Interest

- Intent-to-Treat Population
  - All subjects who were randomized and had at least 1 post-baseline DAS28-CRP measurement
- Day 1 Eligible Population
  - Subjects meeting CRP and Joint Count eligibility at Day 1 (baseline)
  - 81% of ITT population
- Biologics Naïve Population
  - Subjects not receiving biologics previously
  - 88% of ITT population
- Day 1 Eligible, Biologics Naïve Population
  - Subjects meeting CRP and Joint Count eligibility at Day 1 (baseline) and who did not receive biologics previously
  - 70% of ITT population

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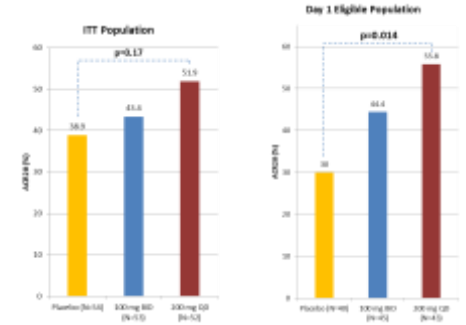
ACR20 Response Highest in 200 mg QD Group at Week 12



p–values for Cochran-Mantel-Haenszel chi-square test, incorporating the 2 baseline stratification factors

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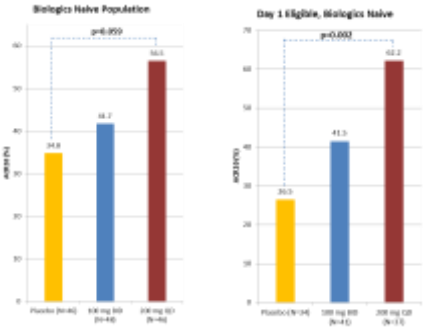
Biologics-Naïve Subjects Showed Higher ACR20 Response with 200 mg QD Dose



p–values for Cochran-Mantel-Haenszel chi-square test

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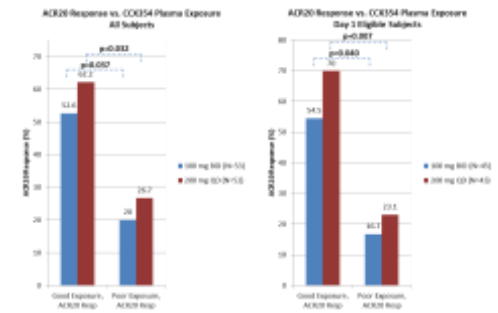
ACR20 Responders Typically Had Plasma CCX354 > 100 ng/mL (>90% CCR1 Coverage)



Good exposure defined as plasma CCX354 >100 ng/mL

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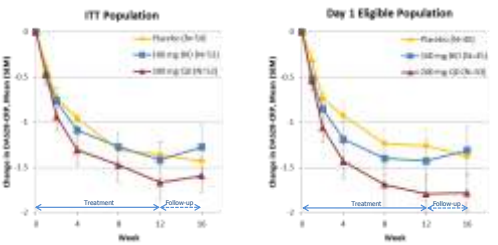
Larger Decrease in DAS28-CRP With 200 mg QD Dose



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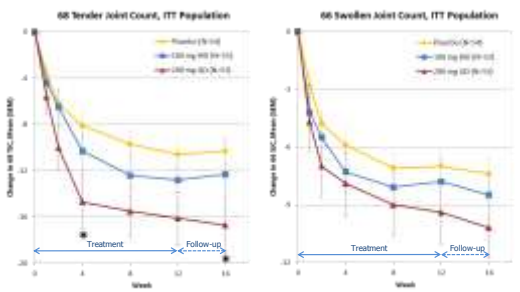
68 Tender Joint Count and 66 Swollen Joint Decreases More Pronounced with 200 mg QD



* p < 0.05 vs. Placebo, Wilcoxon Rank Sum Test

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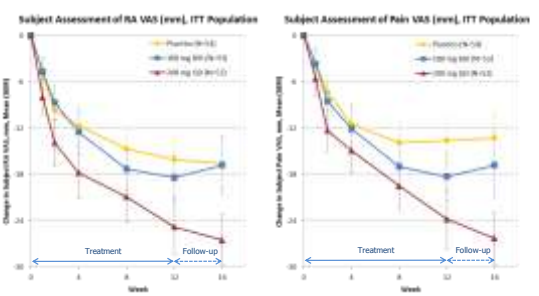
Subject Assessment of RA and Pain Decreases More Pronounced with 200 mg QD



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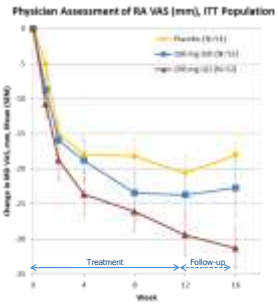
Physician Assessment of RA Decrease More Pronounced with 200 mg QD



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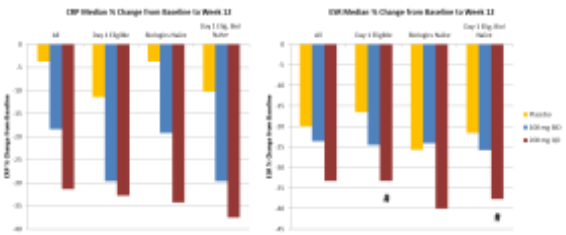
Decreases in CRP and ESR at Week 12 More Pronounced with 200 mg QD vs. Placebo



# p < 0.10 vs. Placebo, Wilcoxon Rank Sum Test

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Bone Turnover Markers

- Bone turnover markers measured commonly in clinical trials in bone disease include—
  - Serum C-telopeptide (CTx), a stable Type I collagen degradation product indicative of bone resorptive activity
  - Serum Procollagen Type I N-Terminal Propeptide (PINP), a molecule produced early in bone formation indicative of bone turnover
  - Serum osteocalcin, also produced during bone matrix formation, reflects bone turnover
- Levels of these markers decrease with bone antiresorptive drugs such as bisphosphonates and denosumab, resulting in an increase in bone mineral density and reduction in fracture incidence

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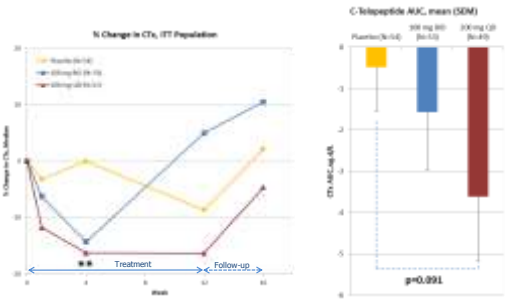
C-Telopeptide Decrease More Marked with 200 mg QD vs. Placebo



** p < 0.01 vs. Placebo (Wilcoxon Rank Sum Test)

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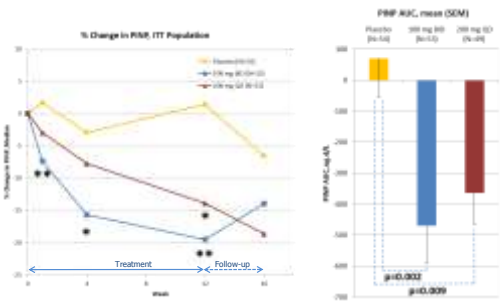
Procollagen Type I N-Terminal Propeptide (PINP) Decreases Statistically Significant for CCX354-C vs. Placebo



* p < 0.05 vs. Placebo
** p < 0.01 vs. Placebo (Wilcoxon Rank Sum Test)

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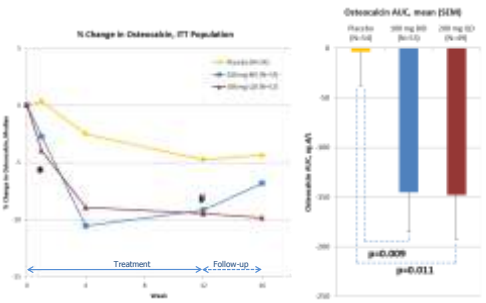
Osteocalcin Decreases More Pronounced with 200 mg QD vs. Placebo



# p < 0.10 vs. Placebo
* p < 0.05 vs. Placebo (Wilcoxon Rank Sum Test)

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Summary

- CCX354-C well tolerated and safe in this study
- CCX354-C 200 mg QD showed greatest efficacy based on ACR and DAS28 response measurements
- ACR20 responders typically had plasma CCX354 > 100 ng/mL (>90% CCR1 coverage)
- CCX354-C 200 mg QD decreased CRP significantly compared to placebo at Week 12
- Bone turnover markers CTx, PINP, and osteocalcin showed statistically significant treatment effects supporting the bone anti-resorptive efficacy of CCX354-C in RA
- CCX354-C shows promise as an orally delivered, CCR1-specific antagonist in the treatment of RA

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