Secukinumab is a fully human monoclonal antibody that selectively targets IL-17A and IL-17 is implicated in the pathogenesis of psoriasis and arthritis. Secukinumab has been shown to be effective in the treatment of plaque psoriasis in phase 3 studies (PASI 90 response ~70%). Among rheumatic diseases, secukinumab has shown early efficacy in PsA, AS and RA.

de Almeida et al. proposed that the shared epitope (SE) may play a functional role in arthritogenesis via Th17/IL-17 polarization in collagen-induced arthritis.

Background
- Secukinumab is a fully human monoclonal antibody that selectively targets IL-17A.
- IL-17A is implicated in the pathogenesis of psoriasis and arthritis.
  - Secukinumab has been shown to be effective in the treatment of plaque psoriasis in phase 3 studies (PASI 90 response ~70%).
  - Among rheumatic diseases, secukinumab has shown early efficacy in PsA, AS and RA.
- de Almeida et al. proposed that the shared epitope (SE) may play a functional role in arthritogenesis via Th17/IL-17 polarization in collagen-induced arthritis.

Scientific Rationale
- Post-hoc biomarker analysis of phase 2 secukinumab studies identified RA subgroups with differential response to anti-IL-17 treatment.
  - Exploratory phase 2 data analyses suggested differential response to secukinumab and placebo between:
    - HLA-DRB1*04 and SE carriers and non-carriers.
    - Subjects with high vs. low CRP at baseline.
  - Results informed the design of a dedicated biomarker study to reproduce these early findings in an independent cohort.

Study Objectives and Endpoints
- Key Objective:
  - To evaluate whether the association between HLA-DRB1*04 or SE and clinical response can be reproduced in an independent cohort of RA subjects.
- Primary Endpoint:
  - To assess whether the treatment effect of secukinumab vs. placebo at Week 12, measured by change from baseline in DAS28-CRP or ACR20 response, is associated with the presence/absence of the HLA-DRB1*04 allelic group in biologics-naive and DMARD-naive RA subjects.

Disclosures
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- Reviewing and consulting for public institutions, charities: Deutsche Forschungsgemeinschaft, BMBF, EULAR, Dutch Rheumafonds, Arthritis Research UK.
- No stocks.
Study Objectives and Endpoints II

Key Secondary Endpoints

• To assess whether the treatment effect of secukinumab vs. placebo measured by ACR50/ACR70 response rates is associated with the presence/absence of the HLA-DRB1*04 allelic group

• To assess whether the treatment effect of secukinumab vs. placebo is associated with other baseline biomarkers (presence/absence of HLA-DRB1*SE, presence/absence of other HLA-DRB1* alleles, OPG, hsCRP, ACPA, and RF)

ACPA, anti-cyclic citrullinated peptide antibodies; ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; DMARD, disease-modifying anti-rheumatic drug; hsCRP, high-sensitivity C-reactive protein; IR, incomplete responder; OPG, osteoprotegerin; RF, rheumatoid factor.

An International, Multicenter, Parallel-Group, Randomized, Placebo-Controlled Trial (CAIN457/F2208)

• Conducted in Belgium, Germany, Russia, and USA
• Biologics-naive (including TNFi-naive); both DMARD-naive and DMARD-IR eligible
• Fulfills ACR 2010 criteria for RA (ACPA or RF not required)
• CRP >10 mg/L (no ESR criterion)
• 6 single infusions of secukinumab 10 mg/kg i.v. or placebo q2w (Part 1)
• No stratification at enrollment for HLA-DRB1*04 and SE carriers, based on expected carrier frequencies

ESR, erythrocyte sedimentation rate; TNFi, tumor necrosis factor inhibitor.

Similar Baseline Characteristics Between Groups

Pharmacodynamic Set

Secukinumab 10 mg/kg i.v. (n = 64) Placebo (n = 32)

Disease duration (years), mean (SD) 6.1 (7.3) 6.5 (7.4)
DMARD-naive, n (%) 18 (28%) 8 (25%)
Concomitant DMARDs, n (%)a 46 (72%) 23 (72%)
Methotrexate, n (%) 43 (67%) 20 (63%)
Sulfasalazine, n (%) 6 (9%) 3 (9%)
Other, n (%) 2 (3%) 0
Concomitant steroids, n (%) 36 (56%) 12 (38%)
CRP (mg/L), median (range) 21.2 (1.8–132.9) 20.6 (2.4–85.6)
RF, U/mL, mean (SD) 149.3 (142.30) 136.0 (146.55)
ACPA (U/mL), median (range)** 133.0 (0–510) 126.5 (0–510)

ACR20 and ACR50 Responses Showed Rapid Onset and Significant Separation From Placebo

ACR20 response rates were significantly different between secukinumab and placebo groups as early as Week 2 (P < 0.05)
No Association of HLA-DRB1*04 Allelic Group and Secukinumab vs. Placebo for DAS28-CRP Responses

- Primary endpoint not met: similar DAS28-CRP reduction with secukinumab vs. placebo treatment for HLA-DRB1*04 carrier and non-carrier groups.

Adverse Events Through Week 12 (incidence by preferred term >3% in any group)

- There was a total of 2 serious AEs (in 2 secukinumab subjects), and neither was suspected to be related to study drug:
  - 1. necrotizing vasculitis (grade: severe)
  - 2. ovarian adenoma (grade: severe)

Summary

- Secukinumab induced rapid and significant DAS28 and ACR responses, particularly in subjects with high disease activity and elevated CRP at baseline.
- HLA-DRB1*SE and HLA-DRB1 position 11 V/L demonstrated statistically significant associations with change in DAS28-CRP for secukinumab vs. placebo (P = 0.007 for *SE; P = 0.004 for position 11 V/L, respectively). However, differences were mainly driven by the lack of placebo response in carriers.
- A significant signal was also seen with baseline RF for change in DAS28-CRP response.
- In line with the earlier results, findings suggest that SE non-carriers and ACPA seronegative RA subjects experience no added benefit from IL-17A neutralization, as no difference in the response between active and placebo-administered subjects in this subgroup.
  - This subgroup is excluded from the phase 3 program.
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