Secukinumab Reduces Endothelial Dysfunction in Subjects With Moderate-to-Severe Plaque Psoriasis Over 52 Weeks: Results of the Exploratory CARIMA Study

E von Stebut[1], K Reich[2], D Thaçi[3], W Koenig[4], A Pinter[5], A Körber[6], T Rassaf[7], A Waisman[1], V Mani[8], D Yates[9], J Frueh[10], C Sieder[11], N Melzer[11], T Gori[1]

[1]University Medical Center Mainz, Mainz, Germany; [2]Dermatologikum Hamburg and SCIderm Research Institute, Hamburg, Germany; [3]University Hospital Schleswig-Holstein, Lübeck, Germany; [4]University of Ulm Medical Center, Ulm, Germany, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; [5]University Hospital Frankfurt, Frankfurt, Germany; [6]University Hospital Essen, Essen, Germany; [7]West-German Heart and Vascular Center, University Hospital Essen, Essen, Germany; [8]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [9]Novartis Institutes for Biomedical Research, Cambridge, MA, USA; [10]Novartis Pharma AG, Basel, Switzerland; [11]Novartis Pharma GmbH, Nürnberg, Germany

ABSTRACT

- **Introduction:** An increased incidence of cardiovascular (CV) events has been reported in psoriasis subjects. Secukinumab, a fully human monoclonal antibody that selectively neutralizes IL-17A, has significant efficacy in moderate-to-severe psoriasis and psoriatic arthritis. CARIMA explored the effect of secukinumab on CV risk markers in psoriasis.
- **Methods:** CARIMA was a 52-week, multicenter, exploratory, randomized, double-blind, placebo-controlled trial (NCT02559622). Subjects with moderate-to-severe plaque psoriasis but without manifest CV diseases were eligible. The primary outcome measure was endothelial function, a marker of early atherosclerosis, measured by flow-mediated dilation (FMD).
- **Results:** 151 subjects (mean age 45 years, 68% male) were randomized. Of these, 48 and 54 subjects received 300 mg and 150 mg secukinumab, respectively and 26 and 23 subjects received placebo followed by 300 mg or 150 mg secukinumab, respectively. A baseline FMD (mean±SD) of 4.6% (±3.5), 4.6% (±4.6), 3.9% (±3.9), and 3.7% (±3.2) was observed for subjects assigned to 300 or 150 mg secukinumab or placebo followed by 300 mg or 150 mg secukinumab. At week 12, the baseline-adjusted FMD showed a numerically larger improvement in subjects receiving 300 mg secukinumab vs. the pooled placebo group (Δ = 1.2%, CI [-0.7; 3.1], *P*=0.223) than in subjects receiving 150 mg secukinumab vs. the pooled placebo group (Δ = 0.8%, CI [-1.0; 2.6], *P*=0.403). At week 52, FMD was increased by 2.1% in subjects receiving 300 mg secukinumab (CI [0.8; 3.3], *P*=0.002) and by 2.1% in subjects receiving 150 mg secukinumab (CI [0.7; 3.4], *P*=0.003) vs. baseline. There were no deaths and no myocardial infarctions in the study. There was one case of a cerebral infarction, which was not suspected to be related to study medication.
- **Conclusions:** Although subjects with established CV diseases were excluded, the comparably large CARIMA study population confirmed earlier findings of endothelial dysfunction associated with subclinical atherosclerosis in psoriasis. A numerical, clinically meaningful improvement of FMD was observed after 12 weeks (secukinumab 300 mg). The difference reached statistical significance after 52 weeks (150 and 300 mg). The safety profile of secukinumab was comparable to prior studies and there were no new safety signals. Secukinumab may improve endothelial function, which could help to prevent cardiovascular disease progression in psoriatic subjects.

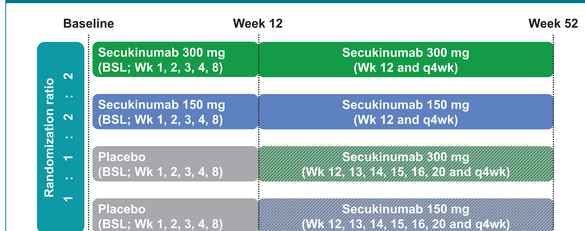
INTRODUCTION

- An increased incidence of CV events has been reported in psoriasis patients
- This comorbidity could be the result of a prolonged subclinical systemic inflammatory response
- Secukinumab, a fully human monoclonal antibody that selectively neutralizes interleukin (IL)-17A, has shown significant efficacy in the treatment of moderate-to-severe psoriasis and psoriatic arthritis, demonstrating a rapid onset of action and sustained response with a favorable safety profile[1]
- Previous studies have shown that a 1% increase in FMD corresponds to a 13% relative CV risk reduction[2]
- CARIMA aimed to explore the effect of secukinumab on CV risk markers in psoriasis patients

METHODS

- CARIMA was a multicenter, exploratory, interdisciplinary, randomized, double-blind, placebo-controlled trial (NCT02559622). Only subjects with moderate-to-severe plaque psoriasis and without known severe CV diseases were eligible
- They were randomized in a 2:2:1:1 ratio to 300 mg or 150 mg secukinumab until week 52 or to placebo until week 12 followed by 300 mg or 150 mg secukinumab until week 52. Placebo groups were pooled for week 12 comparisons
- The primary outcome measure was endothelial function, a marker of early atherosclerosis, measured by FMD
- Experienced sonographers were trained and certified to measure FMD using a standard protocol, equipment, and software. FMD values of 49 volunteers (not study subjects) were acquired twice on the same day to assess reproducibility
- The subject's arm was immobilized using a pneumatic pillow and brachial artery diameter was measured at rest (1 minute), during inflation of the distal cuff to 220 mmHg for 5 minutes and for 4 minutes following deflation. FMD was measured as the % maximal increase in diameter following deflation of the cuff
- Data were assessed by cardiologists at a reading center for quality control and blinded evaluation of results

Figure 1. CARIMA Study Design



BSL, baseline; q4wk, every 4 weeks; Wk, week.

RESULTS

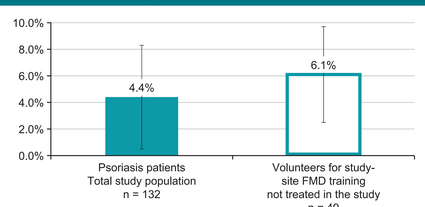
Table 1. Baseline Demographic and Disease Characteristics

Characteristic	A. SEC 300 mg (n = 48)	B. SEC 150 mg (n = 54)	C. PBO – SEC 300 mg (n = 26)	D. PBO – SEC 150 mg (n = 23)
Mean age, years (SD)	44.2 (12.9)	46.0 (14.4)	43.7 (11.4)	46.8 (13.1)
Male gender, n (%)	37 (77.1)	31 (57.4)	18 (69.2)	16 (69.6)
Body weight (kg), mean (SD)	86.5 (15.3)	84.4 (19.3)	95.4 (26.0)	89.8 (22.0)
BMI (kg/m²)	27.8	28.1	30.1	29.7
Baseline PASI, mean (SD)	19.3 (7.9)	21.7 (10.5)	17.5 (4.2)	19.5 (6.1)
Mean time since psoriasis diagnosis, years (SD)	20.6 (12.7)	20.8 (13.3)	18.9 (11.7)	20.3 (11.7)
Psoriatic arthritis reported, n (%)	12 (25.0)	15 (27.8)	4 (15.4)	4 (17.4)
Prior non-biologic, systemic therapy, n (%)	43 (89.6)	46 (85.2)	24 (92.3)	16 (69.6)
Prior biologic therapy, n (%)	15 (31.3)	20 (37.0)	8 (30.8)	9 (39.1)
Diabetes, n (%)	4 (8.3)	9 (16.7)	3 (11.5)	–
Dyslipidemia / hyperlipidemia, n (%)	3 (6.3)	3 (5.6)	5 (19.2)	1 (4.3)
Hypertension, n (%)	13 (27.1)	14 (25.9)	9 (34.6)	7 (30.4)
Smoking status, n (%) Never	19 (39.6)	21 (38.9)	11 (42.3)	9 (39.1)
Smoking status, n (%) Former	9 (18.8)	11 (20.4)	3 (11.5)	7 (30.4)
Smoking status, n (%) Current	20 (41.7)	22 (40.7)	12 (46.2)	7 (30.4)

BMI, body mass index; PASI, Psoriasis Area and Severity Index; PBO, placebo; SD, standard deviation; SEC, secukinumab

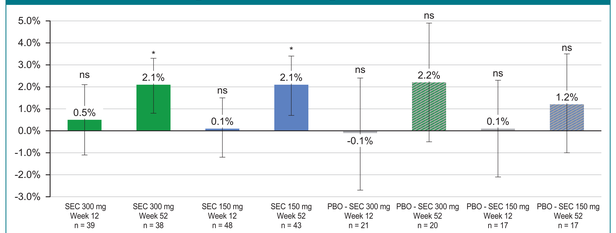
- At week 12, the baseline-adjusted FMD showed a numerically larger improvement in subjects receiving 300 mg secukinumab vs. the pooled placebo group (Δ = 1.2%, CI [-0.7; 3.1], p=0.223) than in subjects receiving 150 mg secukinumab vs. the pooled placebo group (Δ = 0.8%, CI [-1.0; 2.6], p=0.403)
- There were no deaths and no myocardial infarctions in the study up to week 52
- There was one case of a cerebral infarction after surgery for ovarian cancer in a 67-year-old hypertensive subject who had received 150 mg secukinumab for 94 days, which was not suspected to be related to the study medication

Figure 2. Baseline FMD



Mean +/- standard deviation
FMD, flow-mediated dilation

Figure 3. FMD Change vs. Baseline



Adjusted mean improvement vs. baseline +/- confidence interval. *p<0.01; ns: nonsignificant
FMD, flow-mediated dilation; PBO, placebo; SEC, secukinumab

CONCLUSIONS

- Although subjects with known severe CV diseases were excluded, the comparably large CARIMA study population confirmed earlier findings of endothelial dysfunction associated with subclinical atherosclerosis in psoriasis subjects
- The safety profile of secukinumab was comparable to prior studies and there were no new safety signals
- A numerical, but clinically meaningful, improvement in FMD (> 1%) was observed after 12 weeks (secukinumab 300 mg). The difference reached statistical significance after 52 weeks (150 and 300 mg)
- The CARIMA study results indicate that secukinumab may improve endothelial function, thereby reducing CV disease progression in psoriatic subjects

REFERENCES

1. Langley RG et al. *N Engl J Med*. 2014;371:326-338.
2. Inaba Y et al. *Int J Cardiovasc Imaging*. 2010;26:631-640.

DISCLOSURES

E von Stebut: Honoraria from Novartis. **K Reich:** Advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer-Ingelheim, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo, Lilly, Medac, Merck Sharp & Dohme Corp., Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, UCB Pharma, Xenoport. **D Thaçi:** Honoraria from AbbVie, Amgen, Almirall Biogen Idec, Celgene, Dignity, Lilly, Galapagos, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Maruho, Mitsubishi, MSD, Novartis, Pfizer, Regeneron, Sanofi, UCB, XenoPort. **W Koenig:** Honoraria from Pfizer, AstraZeneca, Novartis, The Medicines Company, DalCor, Sanofi, Berlin-Chemie, Kowa. Amgen: grants and nonfinancial support from Roche Diagnostics, Beckmann, Singulex, Abbott. All outside the submitted work. **A Pinter:** Honoraria from AbbVie, Amgen, Biogen-Idec, BMS, Celgene, Lilly, Janssen-Cilag, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, Roche. **A Körber:** Honoraria from Celgene, Lilly, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, Almirall, Grünenthal, AbbVie, MSD, UCB. **T Rassaf:** Honoraria from AstraZeneca and Bayer AG. **A Waisman:** Honoraria from Novartis. **V Mani:** Grant support from Aegerion, Amgen, Novartis, Daiichi Sankyo; honoraria from Aegerion; consultant for Tursiop Inc. and Medlion Inc. **D Yates**, **J Frueh**, **C Sieder**, and **N Melzer:** Employees of Novartis. **T Gori:** Honoraria from Novartis, Abbott Vascular/St Jude, Bayer, Daiichi-Sankyo, Boehringer-Ingelheim, Volcano, AstraZeneca, BMS, Stentys.

ACKNOWLEDGEMENTS

The authors thank the patients and their families and all investigators and their staff for participation in the study. Oxford PharmaGenesis, Inc., Newtown, PA, USA, provided assistance with layout and printing the poster; this support was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ. The authors had full control of the contents of this poster.

This research was sponsored by Novartis Pharma GmbH, Nuremberg, Germany.

Originally presented at: 26th Annual Congress of the European Academy of Dermatology and Venereology, Geneva, Switzerland; September 13–17, 2017.

Poster presented at: 13th Annual Winter Clinical Dermatology Conference, Maui, HI, USA; January 12–17, 2018.

Download document at the following URL:
http://novartis.medicalcongressposters.com/Default.aspx?doc=19d4f

And via Text Message (SMS)

Text: **Q19d4f**
To: **8NOVA (86682)** US Only
+18324604729 North, Central and South Americas; Caribbean; China
+447860024038 UK, Europe & Russia
+46737494608 Sweden, Europe

Scan to download a reprint of this poster