ORIGINAL ARTICLE

Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial

Diamant Thaçi, MD,[a] Andrew Blauvelt, MD, MBA,[b] Kristian Reich, MD,[c] Tsen-Fang Tsai, MD,[d] Francisco Vanaclocha, MD,[e] Külli Kingo, MD, PhD,[f] Michael Ziv, MD, BSc,[g] Andreas Pinter, MD,[h] Sophie Hugot, MSc,[i] Ruquan You, MSc,[j] and Marina Milutinovic, MD[i]

Lübeck, Göttingen, and Frankfurt, Germany; Portland, Oregon; Taipei, Taiwan; Madrid, Spain; Tartu, Estonia; Afula, Israel; Basel, Switzerland; and Shanghai, China

Background: Secukinumab, a fully human anti-interleukin-17A monoclonal antibody, has shown superior efficacy to etanercept with similar safety in moderate to severe plaque psoriasis (FIXTURE study).

Objective: We sought to directly compare efficacy and safety of secukinumab versus ustekinumab.

Methods: In this 52-week, double-blind study (NCT02074982), 676 subjects were randomized 1:1 to subcutaneous injection of secukinumab 300 mg or ustekinumab per label. Primary end point was 90% or more improvement from baseline Psoriasis Area and Severity Index (PASI) score (PASI 90) at week 16.

Results: Secukinumab (79.0%) was superior to ustekinumab (57.6%) as assessed by PASI 90 response at week 16 ($P < .0001$). The 100% improvement from baseline PASI score at week 16 was also significantly greater with secukinumab (44.3%) than ustekinumab (28.4%) ($P < .0001$). The 75% or more improvement from baseline PASI score at week 4 was superior for secukinumab (50.0%) versus ustekinumab (20.6%) ($P < .0001$). Percentage of subjects with the Dermatology Life Quality Index score 0/1 (week 16) was significantly higher with secukinumab (71.9%) than ustekinumab (57.4%) ($P < .0001$). The safety profile of secukinumab was comparable with ustekinumab and consistent with pivotal phase III secukinumab studies.

From the Comprehensive Center for Inflammation Medicine, University Hospital Schleswig-Holstein, Lübeck[a]; Oregon Medical Research Center[b]; Dermatologikum Hamburg and Georg-August-University Göttingen[c]; National Taiwan University Hospital, National Taiwan University College of Medicine[d]; Hospital 12 de Octubre, Av de Córdoba, Madrid[e]; Clinic of Dermatology, Tartu University Hospital, Department of Dermatology, University of Tartu[f]; Department of Dermatology, Ha'Emek Medical Center, Afula[g]; University of Frankfurt[h]; Novartis Pharma AG, Basel[i]; and Beijing Novartis Pharma Co. Ltd, Shanghai.[j]

Novartis Pharma AG (Basel, Switzerland) supported this study.

Disclosure: Dr Thaçi has served as a consultant, served as an advisory board member, and/or received honoraria for lecturing for AbbVie, Amgen, Biogen-Idec, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, MSD, Novartis, Pfizer, Regeneron, and Sanofi. Dr Blauvelt has served as a scientific consultant and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen Ortho Biotech, Merck, Novartis, Pfizer, and Sandoz. Dr Reich has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Eli Lilly, Forward Pharma, GSK, Janssen-Cilag, Leo Pharma, Medac, MSD, Novartis, Pfizer, Vertex, Takeda, and Xenoport. Dr Tsai has served as consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Galderma, Novartis, and Pfizer. Dr Kingo has served as a principal investigator in clinical studies sponsored by Celgene, Mitsubishi Pharma Corporation, Novartis, and Sandoz. Dr Pinter has served as a clinical study investigator and/or scientific consultant and/or paid speaker for AbbVie, Amgen, Biogen-Idec, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Merck, Novartis, Pfizer, and Regeneron. Dr Ziv has served as a paid speaker/consultant/clinical trials investigator for AbbVie, Coherus Biosciences, Janssen-Cilag, Novartis, and Pfizer. Dr Vanaclocha has served as a principal investigator in clinical studies sponsored by Celgene, Janssen, Merck, and Novartis. Ms Hugot, Mr You, and Dr Milutinovic are employees of and/or own stock in Novartis.

Accepted for publication May 10, 2015.

Correspondence to: Diamant Thaçi, MD, Comprehensive Center for Inflammation Medicine, University Hospital Schleswig-Holstein, Ratzeburger Allee 160, 23538 Lübeck, Germany. E-mail: diamant.thaci@uksh.de.

Published online June 16, 2015.

0190-9622

http://dx.doi.org/10.1016/j.jaad.2015.05.013

Limitations: The study was not placebo-controlled and of short-term duration.

Conclusions: Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe psoriasis and improving health-related quality of life with a comparable safety profile over 16 weeks. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.05.013.)

Key words: clear or almost clear skin; clinical trial; head to head; plaque psoriasis; secukinumab; superiority; ustekinumab; 90% or more improvement in baseline Psoriasis Area and Severity Index.

CAPSULE SUMMARY

- Secukinumab previously demonstrated superior efficacy to etanercept in psoriasis, with similar safety.
- CLEAR study demonstrates secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis and improving quality of life with comparable safety.
- These head-to-head results are important to inform treatment decisions for psoriasis.

Targeted biologic therapies—such as tumor necrosis factor (TNF)-α inhibitors infliximab, etanercept, and adalimumab and the interleukin (IL)-12/IL-23 antagonist ustekinumab—have greatly improved the treatment of moderate to severe plaque psoriasis. In randomized controlled trials, approximately 50% to 80% of subjects receiving these biologics achieved 75% or more improvement from baseline Psoriasis Area and Severity Index (PASI) score (PASI 75) after 10 to 16 weeks of treatment.[1-8] A 90% improvement from baseline PASI score, however, is now defined as the threshold of treatment success per the European Medicines Agency[9] and a "measure of optimal response" by the American Academy of Dermatology.[10] Of note, 90% or more improvement from baseline PASI score (PASI 90) response was only achieved by approximately 20% of patients treated with etanercept,[1,2] and approximately 40% to 50% with infliximab,[3,4] adalimumab,[5,6] and ustekinumab.[7,8]

Achieving PASI 90 response in patients with psoriasis is highly clinically relevant, given the direct relationship between PASI score improvement and health-related quality of life (HRQoL).[11-13] In 1 study, 44.3% of subjects achieving PASI 90 to less than 100% improvement from baseline PASI score response and 65.1% achieving 100% improvement from baseline PASI score (PASI 100) response at week 16 reported no impact of their skin problems on HRQoL, versus 24.3% of those with PASI 75 to less than PASI 90 response.[11] These results support the importance of achieving PASI 90 to PASI 100 responses in patients with psoriasis for the maximal improvement in HRQoL.

Secukinumab (Cosentyx, Novartis Pharma AG, Basel, Switzerland), recently approved for the treatment of adult patients with moderate to severe plaque psoriasis, is a fully human IgG1κ monoclonal antibody that selectively targets IL-17A.[14] IL-17A is a key pathogenic cytokine in psoriasis and acts directly on keratinocytes to stimulate the secretion of proinflammatory mediators; the action of IL-23 on keratinocytes is more remote but ultimately depends on inducing IL-17A.[15,16] The clinical benefit of TNF-α inhibition has been linked to the suppression of the IL-23/IL-17 axis.[16,17] The importance of IL-17A in psoriasis pathogenesis has been validated by the clinical efficacy of secukinumab in pivotal 52-week phase III trials; secukinumab was shown to be superior to placebo and to etanercept in achieving a strong and sustained response with a favorable safety profile.[18-22] PASI 90 responses were obtained by 70% to 72% of subjects treated with secukinumab 300 mg at week 16 and sustained in the majority of subjects at week 52.[18] The magnitude of improvement after 16 weeks of treatment with secukinumab[18] is higher than that reported in phase III studies for etanercept,[1,2] infliximab,[3,4] adalimumab,[5,6] and ustekinumab.[7,8]

Comparative efficacy among therapies is best evaluated in rigorous head-to-head randomized trials. CLEAR, the second head-to-head trial of secukinumab, directly compared the efficacy and safety of secukinumab with ustekinumab in subjects with moderate to severe plaque psoriasis. Ustekinumab is a human monoclonal antibody directed against cytokines IL-12 and IL-23, the latter of which, by activating T-helper 17 cells, functions upstream of IL-17A in driving psoriasis pathogenesis.[15,16] Like secukinumab, ustekinumab has shown superiority to etanercept in achieving PASI 75 responses in a phase III study.[23] The CLEAR study, presented here, was designed with the primary objective of demonstrating superiority of secukinumab to ustekinumab in achieving PASI 90 response, a high-threshold clinical response that to our knowledge has not been used as the primary end