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Secukinumab shows high efficacy irrespective of HLA-Cw6 status in patients with moderate-to-severe plaque-type psoriasis: SUPREME study

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Conflict of Interest: Antonio Costanzo acted as paid speaker for Novartis, Abbvie, Celgene, Pfizer, Lilly and UCB. Giovanna Malara acted as paid speaker for Novartis, Abbvie, Celgene and Janssen. Luca Bianchi has acted as speaker and consultant for Abbvie, Celgene, UCB, Janssen and Pfizer. Maria Laura Flori Acted as paid speaker for Novartis. Luca Stingeni acted as speaker and consultant for Abbvie, Lilly, Novartis and Almirall. Marta Bartezaghi, Lorenzo Carraro, and Gabriella Castellino are Novartis employees.

What's already known about this topic?

HLA-Cw6 is associated with the phenotypic features of psoriasis and positive response to ustekinumab and is present in approximately 40%–80% of cases. Secukinumab is a fully human monoclonal antibody neutralizing IL-17A and it has demonstrated a rapid onset of action and sustained responses with a favourable safety profile in moderate-to-severe psoriasis, psoriatic arthritis, and ankylosing spondylitis.

What does this study add?

Although Cw6-POS and Cw6-NEG patients have distinct clinical features, the present study showed that secukinumab achieved similar clinical responses in both cohorts after 24 weeks of treatment. There was no difference in efficacy regarding Cw6 status.

Abbreviations: AE, adverse event; CI, confidence interval; Cw6-NEG, HLA-Cw6-negative; Cw6-POS, HLA-Cw6-positive; HR, hazard ratio; IGA, Investigator's Global Assessment; IL, interleukin; ITT, intent-to-treat; LOCF, last observation carried forward; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PASI 50/75/90/100, 50/75/90/100% improvement from baseline in Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation; TNF, tumour necrosis factor; TEAE, treatment-emergent adverse event

Abstract (word limit: 250 words, current count: 247 words)

Background: Understanding genetic variations is important in predicting the treatment response and forms the basis for identifying new pharmacogenetic and pharmacogenomic targets for the treatment of psoriasis. Limited data are available for the efficacy of secukinumab in relation to genetic markers.

Objective: To evaluate the efficacy and safety of secukinumab 300 mg in HLA-Cw6-positive (Cw6-POS) and HLA-Cw6-negative (Cw6-NEG) patients with moderate-to-severe chronic plaque-type psoriasis.

Methods: SUPREME was a 24-week, Phase 3b study with an extension period up to 72 weeks. The primary endpoint was Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks.

Results: Patients (434) were recruited: 185 (42.6%) were Cw6-POS, and 246 (56.7%) were Cw6-NEG (3 not assessed). The mean age was 45.2±13.2 years (Cw6-POS, 42.7±13.1; Cw6-NEG, 47.2±12.9). The baseline PASI score was comparable between the two cohorts (Cw6-POS, 20.7±8.99; Cw6-NEG, 21.5±9.99; p=0.7766). At Week 16, PASI 90 was achieved in 80.4% of Cw6-POS and 79.7% of Cw6-NEG patients (difference: 0.76; 95% confidence interval: −7.04, 8.23). No differences in the mean (standard deviation) absolute PASI at Week 16 (Cw6-POS, 1.36±3.58; Cw6-NEG, 1.18±2.29) were observed. The overall safety profile of secukinumab was consistent with that reported in earlier studies. No statistically significant difference was detected in the rate of treatment-emergent adverse events (Cw6-POS, 42.7%; Cw6-NEG, 49.6%; p=0.2955). A high PASI 90 response was achieved with secukinumab irrespective of the HLA-Cw6 status, with a fast reduction in absolute PASI.

Conclusion: Determination of the HLA-Cw6 status for secukinumab therapy is unnecessary, as it is highly effective regardless of the HLA-Cw6 status.

INTRODUCTION

Chronic plaque-type psoriasis is the most common form of plaque psoriasis and is characterised by increased proliferation of keratinocytes, hyperplasia of the epidermis, strong inflammatory infiltrate of the dermis and marked dilation of vessels in the papillary dermal region, leading to the formation of well-demarcated, red, raised, and scaly plaques [1-3]. Pathogenesis of plaque psoriasis involves a complex interaction of genetic, environmental, and immunological factors [1].

The understanding of the genetic variations is pivotal in predicting the treatment response and forms the basis for identifying new pharmacogenetic and pharmacogenomic targets for the treatment of psoriasis[4,5]. Genetic linkage and association studies have identified several chromosomal loci linked to psoriasis susceptibility[6,7]. A recent meta-analysis of psoriasis genetic predisposition identified 52 different PSORiasis Susceptibility (PSORS) loci associated with increased risk of developing the disease [8]. Among these, PSORS1, located within the major histocompatibility complex on chromosome 6p21, is associated with the greatest risk for early-onset (type 1) psoriasis. The most likely PSORS1 gene is HLA-Cw6 which is associated with the phenotypic features of psoriasis and present in approximately 40%–80% of cases [1,7,9-12]. HLA-Cw6 is associated with more severe and early-onset psoriasis, and Caucasian patients who are carriers of this allele have about a 10-fold increased risk of developing psoriasis [13].

Recent studies have shown that biological drugs approved for treating psoriasis and psoriatic arthritis (PsA) are not effective in all patients, and that variations in the genome have been associated with different clinical responses or side effects[14-18]. For example, ustekinumab, a human monoclonal antibody against interleukin (IL)-12 and IL-23, has shown a superior and faster response in HLA-Cw6-positive (Cw6-POS) patients compared with HLA-Cw6-negative (Cw6-NEG) patients with moderate-to-severe psoriasis[17,19]. Secukinumab is a fully human monoclonal antibody neutralizing IL-17A and it has demonstrated a rapid onset of action and sustained responses with a favourable safety profile in moderate-to-severe psoriasis, PsA, and ankylosing spondylitis [20-27]. The efficacy of secukinumab has been established in different indications; however, little is known about the potential differences in response to secukinumab treatment between patients stratified for the presence of a genetic biomarker. SUPREME was a Phase 3b study (NCT02394561) conducted to explore the efficacy and safety profile of

secukinumab 300 mg in patients with moderate-to-severe chronic plaque-type psoriasis, stratified for the HLA-Cw6 status. Herein, we present the efficacy and safety results from the core study.

MATERIALS AND METHODS

Study Design

The SUPREME core study was a 24-week, Phase 3b, multicentre, prospective study conducted across 50 centres in Italy, with an extension period up to 72 weeks. The study consisted of four periods: a screening period consisting of two visits (pre-screening and screening), an induction period of 4 weeks, a maintenance period of 20 weeks, and an extension period of at least 12 weeks up to 48 weeks. There were 12 study visits (Weeks −4, −2, 0 [baseline], 1, 2, 3, 4, 8, 12, 16, 20, and 24). Patients were centrally assessed for Cw6 positivity or negativity at the pre-screening visit (Week −4 and Day −28) and stratified into two cohorts. Cw6 status was blinded for both the patients and the investigators. After the full screening visit (Week −2 and Day −14 to −7), eligible patients were treated with subcutaneous secukinumab 300 mg (two 150 mg injections) per week for the first 5 weeks (visits 3–7) starting at baseline (Week 0), followed by a maintenance period of 300 mg (two 150 mg injections) per month (visits 8–12). Psoriasis severity was evaluated at Week 16, and patients achieving at least a Psoriasis Area and Severity Index (PASI) 50 response were eligible to continue the study treatment for an additional 8 weeks up to 24 weeks. Patients reaching PASI 75 at the end of 24 weeks were eligible to enter the 48-week extension phase.

Patients

Male or female patients aged ≥18 years diagnosed with moderate-to-severe chronic plaque-type psoriasis for at least 6 months (including patients with concomitant nail, scalp, or PsA according to Classification Criteria for Psoriatic Arthritis criteria [CASPAR] criteria) were included in the study. Moderate-to-severe plaque-type psoriasis was defined at enrollment by: PASI score ≥10 or PASI score >5 but <10 and Dermatology Life Quality Index ≥10. As a consequence of the European Medicines Agency's (EMA) approval of secukinumab in February 2015, inclusion criteria were updated in order to guarantee treatment to systemic naïve patients, as per label, other than to patients naïve to or intolerant to or failing a previous biologic treatment with anti-tumour necrosis factor α (TNFα) therapy.

Key exclusion criteria included forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic, and guttate psoriasis), cyclosporine or methotrexate administration within 4 weeks prior to Day 1, previous exposure to any biologic drug for the treatment of psoriasis that is not anti-TNFα therapy

All patients provided written informed consent before enrollment into the study. The study protocol was approved by the institutional review board of each participating centre. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and in compliance with all federal, local, or regional requirements.

Study Endpoints

The primary endpoint was a PASI 90 response rate in Cw6-NEG and Cw6-POS patients after 16 weeks. The key secondary endpoints were comparison of the following parameters between the cohorts: proportion of responders to PASI 50/75/90/100 over time; mean changes from baseline in the Investigator's Global Assessment (IGA) mod 2011 over time; time to reach PASI 90 and PASI 75; and safety and tolerability for 24 weeks and for up to 72 weeks thereafter.

Assessments

Efficacy: The severity of psoriasis was measured using PASI, at each visit from Visit 2 to Visit 12. PASI combines the assessment of the severity of lesions and the area affected into a single score with a range of 0 (no disease) to 72 (maximal disease) [28]. PASI 50, PASI 75, and PASI 90 were defined as the achievement of ≥50%, ≥75%, and ≥90% improvement (reduction) in PASI score compared with baseline, respectively. PASI 100 was defined as the achievement of complete clearing of psoriasis (PASI = 0). The IGA mod 2011 scale was used to assess overall psoriatic disease on a 5-point scale ranging from 0 (no disease, "clear") to 4 ("very severe") [29].

Safety: Haematology and clinical chemistry assessments were performed at Visits 2 and 3 and then at each visit starting from Visit 7. Urinalysis was performed at Visits 2, 10, and 12. Electrocardiogram (ECG) and chest X-ray were performed at Visit 2 (baseline). All reported adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology and were recorded by severity (mild, moderate, or severe), relationship to the study drug, duration, and outcome.

DNA extraction and Genotyping

Cw6 status was determined as previously described[17, 18]. Briefly, venous blood for genotyping was collected in ethylenediamine tetraacetic acid (EDTA) tubes and stored at −70°C. DNA was extracted from whole blood using DNAeasy blood and tissue kit (Qiagen, Inc., Hilden, Germany). HLA-Cw6 allele was detected by standard polymerase chain reaction using allele-specific primers (For 5' TACTACAACCAGAGCGAGGA-3'; Rev 5'-GGTCGCAGCCATACATCCA-3').

Statistical Analysis

The primary endpoint was the proportion of PASI 90 after 16 weeks of treatment. Assuming to enrol a rate of 60% of Cw6-POS patients, a one-sided alpha level of 0.025 and a power of 80%, 365 patients (219 Cw6-POS and 146 Cw6-NEG) are sufficient to evaluate if the response in terms of PASI 90 in the Cw6-NEG cohort is not less than 12% compared with the Cw6-POS cohort. The full analysis set includes all the enrolled patients (N = 434). The safety set includes all enrolled patients who were given at least one dose of the study drug (N = 434). The intent-to-treat (ITT) set includes all patients in the safety population with at least one post-baseline efficacy assessment and Cw6 assessment (N = 430). The primary and secondary objectives were evaluated on the ITT population, and all safety evaluations were performed on the safety population. The proportion of patients who reached PASI 90 at 16 weeks was presented with a one-tailed 97.5% confidence interval (CI) of the Cw6-POS – Cw6-NEG difference. For subjects who prematurely discontinued the study for any reason or subjects with missing visits (after baseline), PASI was imputed using the Last Observation Carried Forward (LOCF) approach. Non-responder imputation analysis was also performed. If all PASI post-baseline efficacy values were missing, then these missing values were not imputed, and this subject was removed from the analysis. A regression analysis was performed taking into account the patients' baseline characteristics, in order to balance the two cohorts. Differences in baseline characteristics between cohorts were explored. A Cox proportional hazard regression model was used to analyse time to reach PASI 90/75.

All statistical analyses were performed using SAS software 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient Demographics and Disease Characteristics

In total, 533 patients were screened, and 434 were enrolled in the study (**Figure 1**). Of these, 185 (42.6%) patients were Cw6-POS, and 246 (56.7%) were Cw6-NEG; Cw6 was not assessed for 3 patients. Overall 402 (92.6%) patients completed the core phase (24 weeks), in particular 172 (93.0%) Cw6-POS and 227 (92.3%) Cw6-NEG patients. The main reasons for discontinuation were AEs (overall, 3.7%; Cw6-POS, 3.8%; Cw6-NEG, 3.7%) and lack of efficacy (overall, 1.6%; Cw6-POS, 0.5%; Cw6-NEG, 2.4%).

The baseline demographics and disease characteristics, by overall study population and cohorts, are shown in **Table 1**. The mean (standard deviation [SD]) age of the overall study population was 45.2 ± 13.2 years, Cw6-POS patients were significantly younger than Cw6-NEG patients (42.7 ± 13.1 vs 47.2 ± 12.9 respectively; $P = 0.0004$). No significant difference was observed in gender, 71.7% were males (Cw6-POS, 67.6%; Cw6-NEG, 74.8%; $P = 0.0856$). Cw6-NEG patients had a significantly higher mean (SD) weight (83.97 ± 17.74 vs 76.67 ± 15.04 kg; $P = 0.0002$), body mass index (28.33 ± 5.62 vs 25.89 ± 4.29 kg/m^2; $P \leq 0.0001$) and waist circumference (99.33 ± 15.26 vs 92.61 ± 13.77 cm; $P = 0.0007$) compared with Cw6-POS patients. The mean age at diagnosis of psoriasis was significantly lower ($P = 0.0016$) in Cw6-POS patients (23.7±12.9 years) compared with Cw6-NEG patients (30.3±14.2 years). In total, 16.2% Cw6-POS and 22.4% Cw6-NEG patients had concomitant PsA ($P = 0.4989$). The baseline PASI was comparable between the two cohorts (Cw6-POS, 20.7 ± 8.99; Cw6-NEG, 21.5 ± 9.99; $P = 0.7766$). Most of the patients had a baseline IGA mod 2011 score ≥3, in particular 54.4% with 3 and 42.6% with 4, indicating moderate or severe disease, respectively.

Efficacy

At Week 16, PASI 90 (primary variable) was achieved in 80.4% (n = 148) of Cw6-POS and 79.7% (n = 196) of Cw6-NEG patients (Odds Ratio [OR]: 0.753; 95% CI: 0.44, 1.28; $P = 0.2932$) considering the non-responder imputation approach (**Figure 2A**). The proportion of patients with a PASI 90 response at Week 16 assessed using the LOCF approach was equivalent to non-responder imputation analysis. In particular, considering the LOCF approach, the non-adjusted difference between cohorts was −1.3 with

the one-tailed 97.5% CI of −8.8, confirming that proportion of Cw6-NEG patients who achieved PASI 90 is not less than the one observed in the Cw6-POS cohort. In both cohorts, no differences were observed in the mean (SD) absolute PASI at Week 16 (Cw6-POS, 1.36 ± 3.58; Cw6-NEG, 1.18 ± 2.29) and Week 24 (Cw6-POS, 1.15 ± 3.34; Cw6-NEG, 1.27 ± 2.90 (**Figure 2B**). The repeated measure analysis of absolute change from baseline in PASI total score over time showed that there was no significant difference in the PASI changes between the two cohorts at all time points (**Figure 3**), in particular at Week 16 the Least-sqaures (LS) mean of the difference [SE] = −0.08 [1.15] (*P* = 0.9439), and 0.15 [1.17] at Week 24 (*P* = 0.8982). Secukinumab showed a rapid onset of action with a mean PASI score reduction from baseline of −75.6 ± 21.1% and −73.2 ± 22.3% at Week 4 in the Cw6-POS and Cw6-NEG cohorts, respectively.

The clinical response to secukinumab was assessed by measuring the 50/75/90/100% improvement from baseline in PASI (PASI 50, PASI 75, PASI 90, and PASI 100) and IGA mod 2011. The proportion of PASI 50/75/90/100 responders was similar across the cohorts with numerically comparable results throughout the 24 weeks of treatment (**Figure 4**). PASI 75 was achieved in 92.9% of Cw6-POS and 92.7% of Cw6-NEG patients (OR: 0.706; 95% CI: 0.31, 1.62; *P* = 0.4119) at Week 16, and these responses remained stable until Week 24. The largest difference between the cohorts (6.39%; 95% CI: −3.09, 15.65) was observed for PASI 100 at 16 weeks (Cw6-POS, 59.2%; Cw6-NEG, 52.8%). At Week 24, PASI 100 responses were numerically similar in both cohorts (Cw6-POS, 62.0%; Cw6-NEG, 61.0%; difference: 0.98%; 95% CI: −8.31, 10.12).

Differences between the cohorts in IGA mod 2011 0/1 responses varied from −1.98% to 4.03%. By Week 16, >80% patients achieved IGA mod 2011 0/1 scores in both cohorts (Cw6-POS, 84.8%; Cw6-NEG, 85.4%; difference −0.58; 95% CI: −7.64, 6.10), and the efficacy was maintained until Week 24. The mean (SD) IGA mod 2011 scores were similar for both cohorts at Week 16 (Cw6-POS, 0.5 ± 0.84; Cw6-NEG, 0.6 ± 0.78) and Week 24 (Cw6-POS, 0.5 ± 0.82; Cw6-NEG, 0.5 ± 0.90).

The median time to reach PASI 90 was 57 days for the Cw6-POS cohort and 58 days for the Cw6-NEG cohort (hazard ratio [HR]: 1.086; 95% CI: 0.89, 1.33; *P* = 0.4286). The median time to reach PASI 75 was 29 days for both Cw6-POS and Cw6-NEG patients (HR: 1.025; 95% CI: 0.84, 1.25; *P* = 0.8066).

Safety

In total, 202 (46.5%) patients experienced at least one treatment-emergent adverse event (TEAE). The overall summary of TEAEs is shown in **Table 2**. The most commonly reported TEAEs in the overall population (incidence ≥2%) were hypertension (4.4%), pruritus (3.0%), headache (2.8%), arthralgia (2.5%), influenza (2.3%), and increased blood creatine phosphokinase (2.3%). Among the cohorts, 79 (42.7%) Cw6-POS patients and 122 (49.6%) Cw6-NEG patients experienced TEAEs (*P* = 0.2955). Serious TEAEs were reported in 7 (3.8%) and 14 (5.7%) patients in the Cw6-POS and Cw6-NEG cohorts, respectively. One patient in the Cw6-NEG cohort died of cardiac circulatory arrest during the study. Among the TEAEs of special interest, 2 cases of neutropenia and 1 case of candida infection were reported in the Cw6-NEG cohort. No clinically relevant changes were observed in vital signs and electrocardiographic findings.

DISCUSSION

The results of this study demonstrated the efficacy of secukinumab in patients with moderate-to-severe plaque-type psoriasis, irrespective of HLA-Cw6 status. In this study population, Cw6-POS patients were younger and had a significantly lower age at diagnosis compared with Cw6-NEG patients as previously reported [13,30-32]. A high PASI 90 response was achieved with secukinumab 300 mg irrespective of the HLA-Cw6 status, with a fast reduction in absolute PASI. This is in contrast to the results reported by other studies, wherein ustekinumab has shown higher PASI 90 and 75 response rates in Cw6-POS patients with moderate-to-severe psoriasis compared with Cw6-NEG patients[17-19,33,34]. In our study, PASI 75 was achieved in >90% in both cohorts by Week 16. More than half of the patients had complete skin clearance (PASI 100) by Week 16 in both cohorts. These results are in agreement with the CLEAR study, wherein up to 50% of patients treated with secukinumab 300 mg achieved PASI 100 by Weeks 12 and 20 [22]. The absolute PASI scores were reduced to a similar extent in both Cw6-POS and Cw6-NEG patients throughout the study period. These results show the consistent efficacy of secukinumab in both cohorts. A retrospective study in 18 patients, stratified for HLA-Cw6 allele, treated with secukinumab showed no

significant difference in average PASI improvement between the two groups (Cw6-POS: 74.2%, Cw6-NEG:62.4%, *P* = 0.397). These results are in agreement with our study with larger cohort of patients[35].

Consistent with the high PASI results, approximately 85% of patients had achieved IGA 0/1 scores (clear/almost clear skin) at Week 16, and the scores were comparable across the two cohorts. These results are clinically meaningful, since most of the patients had moderate-to-severe disease at baseline, and show that secukinumab provides a high level of skin clearance irrespective of HLA-Cw6 status. Secukinumab showed a rapid onset of action; by Week 4, a PASI score reduction of almost 75% with respect to baseline was observed in both cohorts. The median time to reach PASI 90 and PASI 75 was similar for both cohorts, even if Cw6-POS patients had a shorter time of clearance during the initial 8-week period, and there was minimal difference beyond 2 months. These results are relevant since more than half of the patients in this study were Cw6-NEG. The safety profile of secukinumab was similar to that reported in previous studies [22,23,36,37]. No statistically significant difference was detected in the rate of TEAEs in both cohorts. No new or unexpected safety signals were reported in the study.

In conclusion, secukinumab demonstrated efficacy and safety in patients with moderate-to-severe plaque psoriasis. Although Cw6-POS and Cw6-NEG patients have distinct clinical features, the present study showed that secukinumab achieved similar clinical responses in both cohorts after 24 weeks of treatment. Determination of the HLA-Cw6 status for secukinumab therapy is unnecessary, as it is highly effective regardless of the HLA-Cw6 status.

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REFERENCES

1 Alwan W, Nestle FO. Pathogenesis and treatment of psoriasis: exploiting pathophysiological pathways for precision medicine. *Clin Exp Rheumatol* 2015; **33**: S2-6.
2 Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. *Ann Rheum Dis* 2005; **64 Suppl 2**: ii30-6.
3 Martin DA, Towne JE, Kricorian G *et al.* The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. *J Invest Dermatol* 2013; **133**: 17-26.
4 Burlando M, Cozzani E, Campisi C *et al.* Different Responses to Ustekinumab of Two HLA-Cw6-positive Homozygous Twins with Psoriasis. *Acta Derm Venereol* 2016; **96**: 858-9.
5 Caldarola G, Sgambato A, Fanali C *et al.* HLA-Cw6 allele, NFkB1 and NFkBIA polymorphisms play no role in predicting response to etanercept in psoriatic patients. *Pharmacogenet Genomics* 2016; **26**: 423-7.
6 Mabuchi T, Ota T, Manabe Y *et al.* HLA-C*12:02 is a susceptibility factor in late-onset type of psoriasis in Japanese. *J Dermatol* 2014; **41**: 697-704.
7 Nair RP, Stuart P, Henseler T *et al.* Localization of psoriasis-susceptibility locus PSORS1 to a 60-kb interval telomeric to HLA-C. *Am J Hum Genet* 2000; **66**: 1833-44.
8 Tsoi LC, Stuart PE, Tian C *et al.* Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. *Nat Commun* 2017; **8**: 15382.
9 Bowcock AM, Cookson WO. The genetics of psoriasis, psoriatic arthritis and atopic dermatitis. *Hum Mol Genet* 2004; **13 Spec No 1**: R43-55.
10 Gudjonsson JE, Karason A, Antonsdottir A *et al.* Psoriasis patients who are homozygous for the HLA-Cw*0602 allele have a 2.5-fold increased risk of developing psoriasis compared with Cw6 heterozygotes. *Br J Dermatol* 2003; **148**: 233-5.
11 Lowes MA, Suarez-Farinas M, Krueger JG. Immunology of psoriasis. *Annu Rev Immunol* 2014; **32**: 227-55.
12 Allen MH, Ameen H, Veal C *et al.* The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis. *J Invest Dermatol* 2005; **124**: 103-6.
13 Gudjonsson JE, Karason A, Antonsdottir AA *et al.* HLA-Cw6-positive and HLA-Cw6-negative patients with Psoriasis vulgaris have distinct clinical features. *J Invest Dermatol* 2002; **118**: 362-5.
14 Galluzzo M, Boca AN, Botti E *et al.* IL12B (p40) Gene Polymorphisms Contribute to Ustekinumab Response Prediction in Psoriasis. *Dermatology (Basel, Switzerland)* 2016; **232**: 230-6.

15 Ovejero-Benito MC, Prieto-Perez R, Llamas-Velasco M *et al.* Polymorphisms associated with etanercept response in moderate-to-severe plaque psoriasis. *Pharmacogenomics* 2017; **18**: 631-8.
16 Prieto-Perez R, Llamas-Velasco M, Cabaleiro T *et al.* Pharmacogenetics of ustekinumab in patients with moderate-to-severe plaque psoriasis. *Pharmacogenomics* 2017; **18**: 157-64.
17 Talamonti M, Botti E, Galluzzo M *et al.* Pharmacogenetics of psoriasis: HLA-Cw6 but not LCE3B/3C deletion nor TNFAIP3 polymorphism predisposes to clinical response to interleukin 12/23 blocker ustekinumab. *Br J Dermatol* 2013; **169**: 458-63.
18 Talamonti M, Galluzzo M, Chimenti S *et al.* HLA-C*06 and response to ustekinumab in Caucasian patients with psoriasis: Outcome and long-term follow-up. *J Am Acad Dermatol* 2016; **74**: 374-5.
19 Chiu HY, Wang TS, Chan CC *et al.* Human leucocyte antigen-Cw6 as a predictor for clinical response to ustekinumab, an interleukin-12/23 blocker, in Chinese patients with psoriasis: a retrospective analysis. *Br J Dermatol* 2014; **171**: 1181-8.
20 Baeten D, Sieper J, Braun J *et al.* Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. *N Engl J Med* 2015; **373**: 2534-48.
21 Blauvelt A, Prinz JC, Gottlieb AB *et al.* Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). *Br J Dermatol* 2015; **172**: 484-93.
22 Blauvelt A, Reich K, Tsai TF *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. *J Am Acad Dermatol* 2017; **76**: 60-9 e9.
23 Langley RG, Elewski BE, Lebwohl M *et al.* Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med* 2014; **371**: 326-38.
24 McInnes IB, Mease PJ, Kirkham B *et al.* Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015; **386**: 1137-46.
25 Mease PJ, McInnes IB, Kirkham B *et al.* Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. *N Engl J Med* 2015; **373**: 1329-39.
26 Paul C, Lacour JP, Tedremets L *et al.* Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). *J Eur Acad Dermatol Venereol* 2015; **29**: 1082-90.
27 Thaci D, Blauvelt A, Reich K *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol* 2015; **73**: 400-9.
28 Weisman S, Pollack CR, Gottschalk RW. Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. *J Dermatolog Treat* 2003; **14**: 158-65.
29 Langley RG, Feldman SR, Nyirady J *et al.* The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatolog Treat* 2015; **26**: 23-31.
30 Enerback C, Martinsson T, Inerot A *et al.* Evidence that HLA-Cw6 determines early onset of psoriasis, obtained using sequence-specific primers (PCR-SSP). *Acta Derm Venereol* 1997; **77**: 273-6.
31 Gudjonsson JE, Karason A, Runarsdottir EH *et al.* Distinct clinical differences between HLA-Cw*0602 positive and negative psoriasis patients--an analysis of 1019 HLA-C- and HLA-B-typed patients. *J Invest Dermatol* 2006; **126**: 740-5.
32 Ikaheimo I, Tiilikainen A, Karvonen J *et al.* HLA risk haplotype Cw6,DR7,DQA1*0201 and HLA-Cw6 with reference to the clinical picture of psoriasis vulgaris. *Arch Dermatol Res* 1996; **288**: 363-5.

33 Li K, Huang CC, Randazzo B *et al.* HLA-C*06:02 Allele and Response to IL-12/23 Inhibition: Results from the Ustekinumab Phase 3 Psoriasis Program. *J Invest Dermatol* 2016; **136**: 2364-71.
34 van Vugt LJ, van den Reek J, Coenen MJH *et al.* A systematic review of pharmacogenetic studies on the response to biologics in patients with psoriasis. *Br J Dermatol* 2018; **178**: 86-94.
35 Anzengruber F, Drach M, Maul JT *et al.* Therapy response was not altered by HLA-Cw6 status in psoriasis patients treated with secukinumab: a retrospective case series. *J Eur Acad Dermatol Venereol.* 2018.
36 Mrowietz U, Leonardi CL, Girolomoni G *et al.* Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE). *J Am Acad Dermatol* 2015; **73**: 27-36 e1.
37 Papp KA, Langley RG, Sigurgeirsson B *et al.* Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. *Br J Dermatol* 2013; **168**: 412-21.

Table 1. Baseline demographic and disease characteristics

	Cw6-POS (n = 185)	Cw6-NEG (n = 246)	*P* value[1]	Overall (N = 434)[2]
Age, years	42.7 (13.1)	47.2 (12.9)	0.0004	45.2 (13.2)
Sex, n (%)				
Male	125 (67.6)	184 (74.8)	0.0856	311 (71.7)
Female	60 (32.4)	62 (25.2)		123 (28.3)
Race, n (%)				
Caucasian	184 (99.5)	241 (98.0)	0.5469	428 (98.6)
Weight, kg, mean (SD)	76.7 (15.0)	83.97 (17.7)	0.0002	80.9 (17.0)
Body mass index, kg/m^2, mean (SD)	25.9 (4.3)	28.3 (5.6)	<0.0001	27.3 (5.3)
Waist circumference, cm, mean (SD)	92.6 (13.8)	99.3 (15.3)	0.0007	96.6 (15.1)
Age at diagnosis of psoriasis, years, mean (SD)	23.7 (12.9)	30.3 (14.2)	0.0016	27.4 (14.0)
Number of patients with PsA, n (%)	30 (16.2)	55 (22.4)	0.4989	86 (19.8)
Time since first diagnosis of psoriasis, years, mean (SD)	19.6 (12.5)	17.5 (11.3)	0.015	18.4 (11.9)
Baseline PASI score, mean (SD)	20.7 (8.99) n = 184	21.5 (9.99) n = 246	0.7766	21.2 (9.6) n = 433
Baseline IGA mod 2011 score, n (%)				
0 = Clear	0 (0.0)	0 (0.0)		0 (0.0)
1 = Almost clear	0 (0.0)	0 (0.0)		0 (0.0)
2 = Mild disease	4 (2.2)	8 (3.3)		12 (2.8)
3 = Moderate disease	103 (55.7)	132 (53.7)		236 (54.4)
4 = Severe disease	77 (41.6)	106 (43.1)	0.0729	185 (42.6)
Missing	1 (0.5)	0 (0.0)		1 (0.2)

[1]*P* values for categorical variables are calculated using the logistic model and for continuous variables are calculated using analysis of covariance; [2]Three patients with missing Cw6 assessment are included under the "Overall" column.

Cw6-NEG, Cw6-negative; Cw6-POS, Cw6-positive; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation

Table 2. Summary of AEs (safety set)

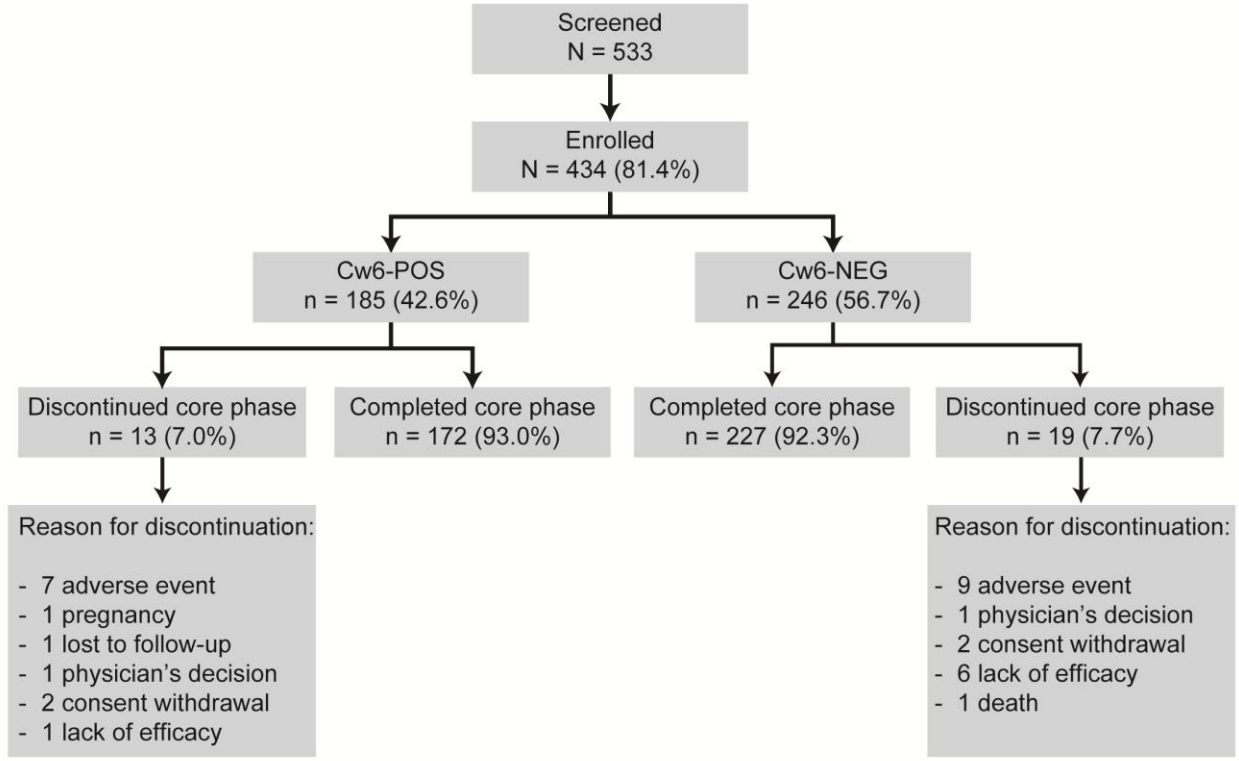
	Cw6-POS (N = 185) n (%)	Cw6-NEG (N = 246) n (%)	Overall (N = 434)[1] n (%)
Number of patients with TEAEs	79 (42.7)	122 (49.6)	202 (46.5)
Number of patients with serious TEAEs	7 (3.8)	14 (5.7)	21 (4.8)
Number of patients with TEAEs related to the study drug	22 (11.9)	42 (17.1)	64 (14.7)
Number of patients with TEAEs leading to discontinuation of the study drug	7 (3.8)	11 (4.5)	18 (4.1)
Deaths	0 (0.0)	1 (0.4)	1 (0.2)
TEAEs of special interest			
Any TEAE	0 (0.0)	3 (1.2)	3 (0.7)
Neutropenia	0 (0.0)	2 (0.8)	2 (0.5)
Candida infection	0 (0.0)	1 (0.4)	1 (0.2)

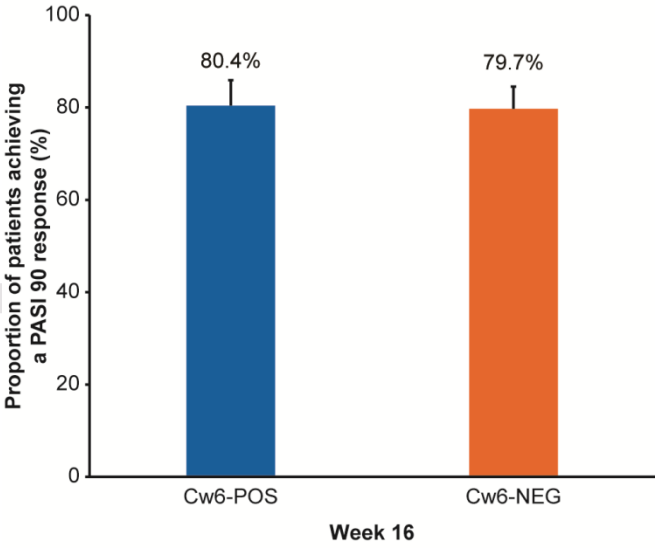
N = number of patients in the safety set, n = number of patients with at least one adverse event in the category.

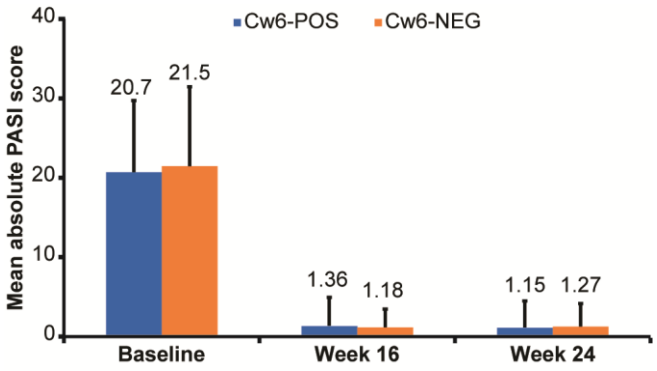
A patient with multiple AEs is counted only once in the "Any TEAE" row. A patient with multiple AEs within a system organ class is counted only once for that system organ class. A patient with multiple AEs with the same preferred term is counted only once for that preferred term.

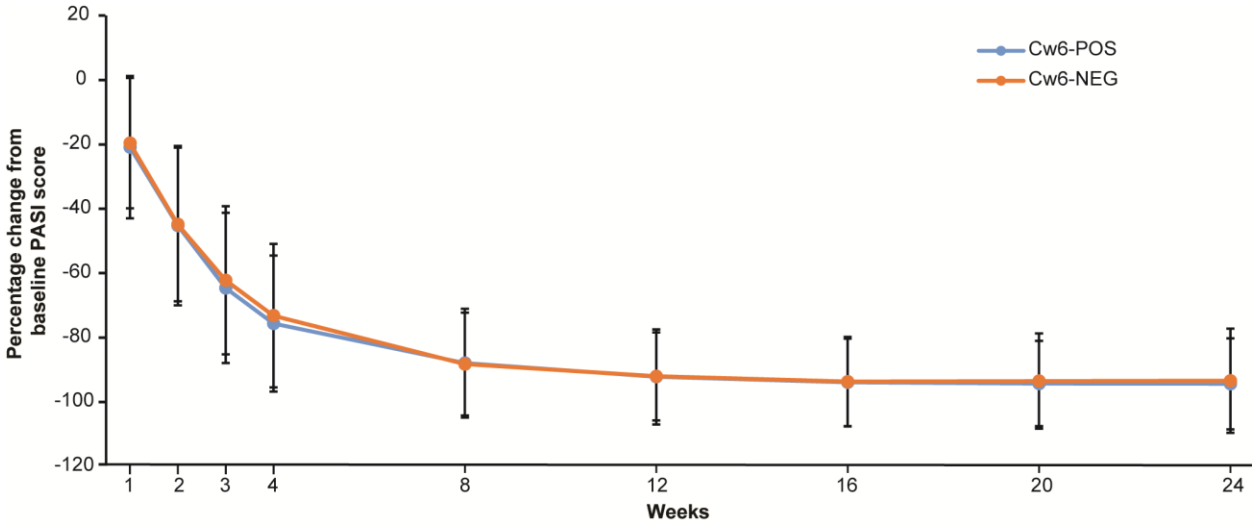
[1]Three patients with missing Cw6 assessment are included under the "Overall" column.

AE, adverse event; Cw6-NEG, Cw6-negative; Cw6-POS, Cw6-positive; TEAE, treatment-emergent adverse event









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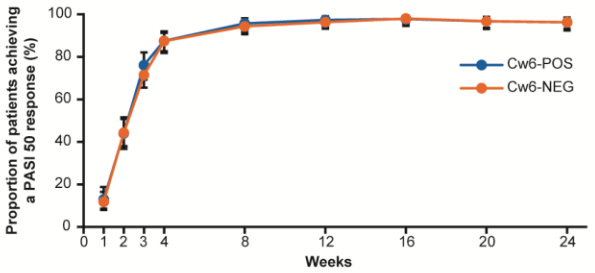
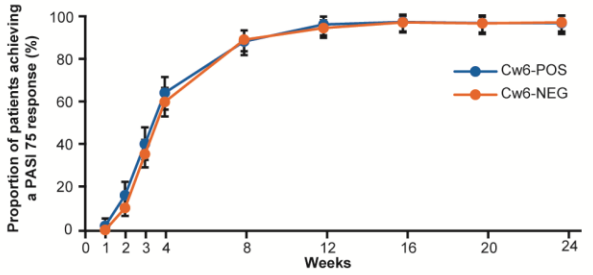


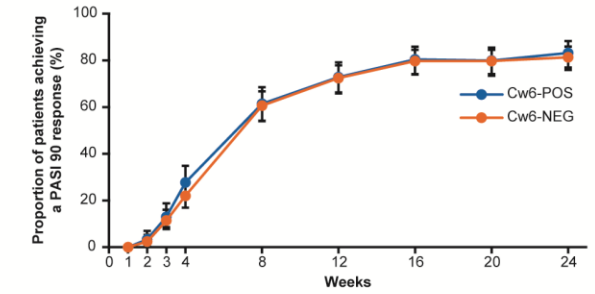
Week	1	2	3	4	8	12	16	20	24
Cw6-POS	13.0	44.0	76.1	87.5	95.7	97.3	97.8	96.7	96.2
Cw6-NEG	11.8	44.3	71.5	87.4	94.3	96.3	98.0	96.7	96.3
δ POS vs. NEG	1.25	−0.29	4.54	0.1	1.34	0.94	−0.14	−0.01	−0.15

B



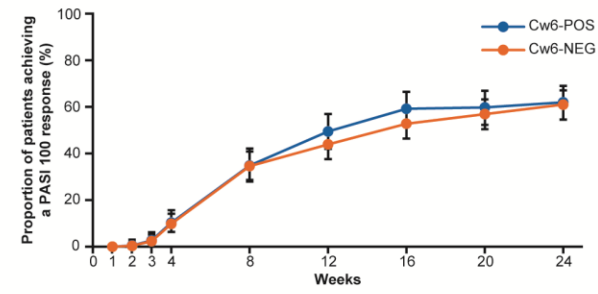
Week	1	2	3	4	8	12	16	20	24
Cw6-POS	2.2	15.8	38.6	61.4	84.2	91.8	92.9	92.4	92.4
Cw6-NEG	0.4	10.2	34.1	57.3	85.0	90.2	92.7	92.3	92.7
δ POS vs. NEG	1.77	5.60	4.44	4.10	−0.72	1.60	0.25	0.11	−0.29

C



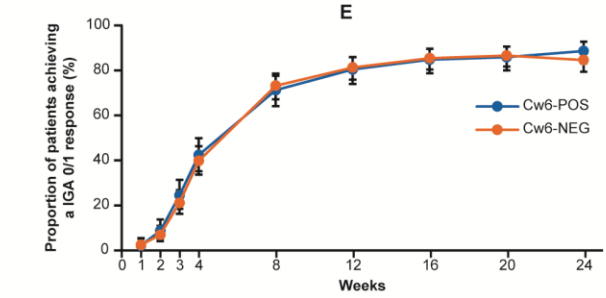
Week	1	2	3	4	8	12	16	20	24
Cw6-POS	0.0	3.3	13.0	27.7	61.4	72.8	80.4	79.9	83.2
Cw6-NEG	0.0	2.4	11.4	22.0	60.6	72.4	79.7	79.7	81.3
δ POS vs. NEG	-	0.82	1.66	5.77	0.84	0.47	0.76	0.22	1.85

D



Week	1	2	3	4	8	12	16	20	24
Cw6-POS	0.0	0.5	2.7	10.3	34.8	49.5	59.2	59.8	62.0
Cw6-NEG	0.0	0.4	2.4	9.8	34.6	43.9	52.8	56.9	61.0
δ POS vs. NEG	-	0.14	0.28	0.57	0.23	5.55	6.39	2.87	0.98

E



Week	1	2	3	4	8	12	16	20	24
Cw6-POS	2.2	8.7	24.5	42.4	71.2	80.4	84.8	85.9	88.6
Cw6-NEG	2.4	6.9	21.1	39.8	73.2	81.3	85.4	86.6	84.6
δ POS vs. NEG	−0.27	1.79	3.32	2.55	−1.98	−0.87	−0.58	−0.72	4.03

Figure 1. Patient disposition

Cw6-NEG, Cw6-negative; Cw6-POS, Cw6-positive

Figure 2. (a) Proportion of Cw6-POS and Cw6-NEG patients achieving PASI 90 response at Week 16 (non-responder imputation analysis, intent-to-treat set); (b) Absolute PASI scores at baseline, Weeks 16 and 24 in Cw6-POS and Cw6-NEG patients (LOCF approach, ITT set)

CI, confidence interval; Cw6-NEG, Cw6-negative; Cw6-POS, Cw6-positive; ITT, intent-to-treat; LOCF, last observation carried forward; PASI, Psoriasis Area and Severity Index

Figure 3. Percentage change from baseline PASI score overtime (LOCF approach, ITT set)

Cw6-NEG, Cw6-negative; Cw6-POS, Cw6-positive; ITT, intent-to-treat; LOCF; last observation carried forward; PASI, Psoriasis Area and Severity Index

Figure 4. The proportion of Cw6-POS and Cw6-NEG patients achieving a (a) 50% improvement in PASI from baseline (PASI 50); (b) PASI 75 response; (c) PASI 90 response; (d) PASI 100 response (e) IGA mod 2011 0/1 scores following secukinumab treatment (non-responder imputation analysis, ITT set)

Error bars represent 95% CI

CI, confidence interval; Cw6-NEG, Cw6-negative; Cw6-POS, Cw6-positive; IGA, Investigator's Global Assessment; ITT, intent-to-treat; PASI, Psoriasis Area and Severity Index