

## ORIGINAL ARTICLE

# Effects of secukinumab on metabolic and liver parameters in plaque psoriasis patients

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## Abstract

**Background** Psoriasis is associated with metabolic, liver and cardiovascular comorbidity. Secukinumab, a fully human monoclonal antibody that selectively neutralizes interleukin-17A, has shown significant and sustained efficacy in the treatment of moderate to severe psoriasis.

**Objectives** This was an exploratory *post hoc* analysis of pooled data from three phase 3 studies in plaque psoriasis patient populations. The objective was to show the course of metabolic and liver parameters under secukinumab, etanercept or placebo treatment over time. A further objective was to assess the impact of selected comorbidities and metabolic characteristics on high-sensitivity C-reactive protein (hs-CRP), as a surrogate marker of systemic inflammation.

**Methods** Data from the phase 3 randomized controlled trials [FIXTURE (NCT01358578), ERASURE (NCT01365455) and SCULPTURE (NCT01406938);  $n = 3010$ ] were included in this analysis. Patients were treated with secukinumab 150 mg or 300 mg, placebo or etanercept 50 mg (FIXTURE only) as active comparator. A set of metabolic and liver parameters was longitudinally assessed over 52 weeks. Multivariate regression analyses assessed the impact of selected comorbidities and metabolic characteristics on hs-CRP levels at baseline and under treatment.

**Results** Secukinumab treatment reduced hs-CRP levels. Body weight and uric acid levels tended to decrease over 52 weeks with secukinumab. Secukinumab showed a neutral effect on fasting plasma glucose, lipid parameters and liver enzymes. Psoriatic arthritis, metabolic syndrome, obesity, impaired glucose metabolism, and hyperuricemia were each associated with increased hs-CRP levels at baseline. Concomitant obesity attenuated the decline in hs-CRP under treatment.

**Conclusions** These analyses suggest neutral to favourable long-term trends in metabolic and liver parameters under secukinumab treatment. Metabolic comorbidities were associated with increased hs-CRP levels, reflecting the role of systemic inflammatory processes in their pathophysiology.

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## Conflicts of interest

SG has been an advisor and/or received speakers' honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott/AbbVie, Almirall-Hermal, Amgen, Baxalta, Bayer Health Care, Biogen Idec, Bioskin, Boehringer-Ingelheim, Celgene, Centocor, Dermira, Eli Lilly, Foamix, Forward Pharma, Galderma, Hexal AG, Isotechnika, Janssen-Cilag, Leo Pharma, Medac, Merck Serono, Mitsubishi Tanabe, MSD, Novartis, Pfizer, Polichem SA, Regeneron Pharmaceutical, Sandoz Biopharmaceuticals, Sanofi-Aventis, Schering-Plough, Takeda, Teva, UCB Pharma, VBL therapeutics and Wyeth Pharma. AP is a speaker for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Celgene, Eli Lilly, Galderma, Janssen, LEO Pharma, Medac, Novartis, Pfizer and UCB Pharma, an advisor for AbbVie, Almirall-Hermal, Amgen, Celgene, Eli Lilly, Janssen, LEO Pharma, and Novartis and has participated in clinical trials funded by AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer-Ingelheim, Celgene, GSK, Eli Lilly, Galderma, Hexal, Janssen, LEO Pharma, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Schering-Plough and UCB Pharma. CP is an employee of Novartis Pharma AG. MR is an employee of Novartis Pharma GmbH.

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## Introduction

Psoriasis is a chronic T cell-mediated inflammatory disorder characterized by skin and joint manifestations, with localized keratinocyte hyperproliferation and elevated type 1 T helper cell (Th1) and type 17 T helper cell (Th17) cytokines. Psoriasis is associated with a range of inflammatory and metabolic comorbidities, including obesity, diabetes, dyslipidemia, hyperuricemia and psychiatric conditions, and is associated with increased cardiovascular risk.<sup>1</sup> The exact aetiology of comorbidity in psoriasis remains a topic of current research, but a state of systemic low-grade inflammation induced by dysregulated Th1 and Th17 activation may contribute to the development of (pre)diabetes, obesity, non-alcoholic fatty liver disease (NAFLD) and atherosclerosis.<sup>2–6</sup>

Psoriasis is linked to obesity, and a reduction of body weight is known to improve skin symptoms and response to systemic treatment.<sup>7</sup> Psoriasis patients are also at increased risk of metabolic syndrome (MetS), which may be related to an increase in circulating adipocytokines,<sup>8,9</sup> mediating systemic pro-inflammatory effects.<sup>10</sup> The metabolic and cardiovascular comorbidity of psoriasis is characterized by inflammatory processes as key parts of their pathophysiology, such as adipose tissue inflammation in obesity, insulin resistance and diabetes; liver tissue inflammation in NAFLD; or vascular inflammation in coronary artery disease.<sup>6,11–14</sup> This is also reflected by the growing number of compounds and clinical trials targeting inflammation in diabetes or coronary artery disease,<sup>15</sup> such as the successful proof of concept for anti-inflammatory treatment of coronary artery disease with canakinumab, anti-interleukin (IL)-1-beta-directed monoclonal antibody.<sup>16</sup>

In this context, it is of high interest to examine the metabolic and liver effects of systemic psoriasis treatments. Markers of systemic inflammation decrease with a range of systemic treatments for psoriasis and other inflammatory conditions; however, impact on metabolic and liver parameters, including weight, is more diverse.<sup>17</sup> Different metabolic effects have been described for existing treatment options. Anti-tumour necrosis factor-alpha (anti-TNF-alpha) biologic agents may be associated with weight gain in psoriasis and psoriatic arthritis (PsA) patients.<sup>18,19</sup> Although distinct from the psoriasis population, an increased risk of elevated liver enzymes was observed with etanercept treatment in ankylosing spondylitis (AS) patients, which was exacerbated by increasing body mass index (BMI).<sup>20</sup> Similarly, elevation of liver enzymes was seen in rheumatoid arthritis patients treated with infliximab, adalimumab and etanercept.<sup>21</sup>

A study of systemic and biologic anti-inflammatory drugs in psoriasis patients showed limited impact on lipid profiles, with an overall rise in low-density lipoprotein (LDL) cholesterol.<sup>22</sup>

Secukinumab is a fully human monoclonal antibody that selectively neutralizes IL-17A, a key cytokine involved in the development of psoriasis.<sup>23</sup> Secukinumab has shown efficacy and safety in the complete spectrum of psoriasis manifestations, including PsA.<sup>24–27</sup> Here, the effects of secukinumab on a range of metabolic and liver parameters were examined in a pooled analysis of three phase 3 studies of secukinumab in moderate to severe plaque psoriasis patients.

## Methods

### Study design and patients

This is a *post hoc* analysis of pooled metabolic and liver data from FIXTURE (NCT01358578), ERASURE (NCT01365455) and SCULPTURE (NCT01406938): three phase 3 randomized controlled trials of secukinumab in moderate to severe plaque psoriasis. The total pooled population of all three studies includes 3010 patients (see Table S1 for baseline characteristics). The design and populations of FIXTURE, ERASURE and SCULPTURE were previously reported in detail.<sup>24,28</sup> Briefly, in FIXTURE, patients received secukinumab 300 mg at Weeks 0, 1, 2, 3 and 4 and then once every 4 weeks until Week 52, etanercept 50 mg twice weekly for 12 weeks and then once weekly until Week 52 or placebo to Week 16. In ERASURE, patients were treated with secukinumab 300 mg at Weeks 0, 1, 2, 3 and 4 and then once every 4 weeks until Week 52 or placebo to Week 16. In the SCULPTURE study, patients received secukinumab 300 mg at Weeks 0, 1, 2, 3 and 4 and then once every 4 weeks, with Psoriasis Area and Severity Index (PASI) 75 responders at Week 12 re-randomized to either fixed interval (FI) or retreatment as needed (RAN) regimens.

All patients were aged  $\geq 18$  years with moderate to severe plaque psoriasis [defined as PASI  $\geq 12$ , Investigator's Global Assessment (IGA) mod 2011 score 3/4 and body surface area (BSA) affected  $\geq 10\%$ ] and a history of the disease for at least 6 months prior to inclusion, and who were therefore candidates for systemic therapy. Key exclusion criteria were previous exposure to study drug, active ongoing inflammatory or infectious diseases, evidence of tuberculosis infection or use of prohibited concomitant treatments. ERASURE, FIXTURE and SCULPTURE were conducted in accordance with the ethical principles of the declaration of Helsinki, and written informed consent was obtained from each patient.

Out of the total pooled population, patients treated with secukinumab 300 mg (as this is the approved dose) under a FI, etanercept or placebo (for the first 12 weeks only) were selected for the longitudinal analyses of treatment effects. Patients who received secukinumab 150 mg in the ERASURE, FIXTURE or SCULPTURE study were excluded from the analyses of the treatment effects since 150 mg is not the approved dose for psoriasis treatment. Patients who received secukinumab RAN in the SCULPTURE study were also excluded from these analyses since the treatment interruptions, which occurred during RAN regimen, would heavily hamper the interpretation of any effects of drug treatment. Body weight, fasting plasma glucose (FPG), uric acid, liver enzymes [aspartate transaminase (GOT) and alanine transaminase (GPT)], hs-CRP, triglycerides, cholesterol, high-density lipoprotein (HDL), LDL, lipoprotein, apolipoprotein A1 and apolipoprotein B were assessed.

Furthermore, the impact of selected comorbidities (MetS, PsA) and metabolic parameters (BMI, FPG, uric acid) on hs-CRP levels at baseline as well as under treatment with secukinumab/etanercept was assessed by applying multivariate regression analyses. Since this part of the analysis was completely independent of any treatment or treatment effects only looking at baseline values, the total pooled population was evaluated here. MetS was defined as being present in patients who fulfilled  $\geq 3$  out of the following five criteria at baseline according to the International Diabetes Federation, American Heart Association and the National Heart, Lung, and Blood Institute consensus criteria:<sup>29</sup> elevated blood pressure, defined as systolic blood pressure  $\geq 130$  and/or diastolic BP  $\geq 85$  mmHg OR ongoing antihypertensive drug treatment; elevated FPG, defined as FPG  $\geq 100$  mg/dL OR ongoing glucose-lowering drug treatment; reduced HDL, defined as HDL  $< 40$  mg/dL in men/ $< 50$  mg/dL in women OR ongoing drug treatment for low HDL; elevated triglycerides, defined as triglycerides  $\geq 150$  mg/dL OR ongoing drug treatment for elevated triglycerides; and waist circumference above ethnicity specific cut-offs (see Appendix S1). The following categories were applied for BMI, FPG and uric acid: BMI ( $\text{kg/m}^2$ ): normal weight  $\geq 18.5$ – $< 25$ , overweight  $\geq 25$ – $< 30$ , obesity class 1  $\geq 30$ – $< 35$ , obesity class 2  $\geq 35$ – $< 40$  and obesity class 3  $\geq 40$ ; FPG (mg/dL): normal  $< 100$ , prediabetes  $\geq 100$ – $\leq 125$  and diabetes  $\geq 126$ ; and uric acid (mg/dL): normal  $\leq 7.0$  in male/ $\leq 6.0$  in female subjects and hyperuricemia  $> 7.0$  in male/ $> 6.0$  in female subjects. These ranges represent clinically accepted categories for all three parameters.<sup>30–33</sup>

### Study objectives

Due to the association of psoriasis with various metabolic and liver comorbidities described above, it is of clinical relevance to know the impact of psoriasis treatments on metabolic and liver parameters. This was an exploratory *post hoc* analysis with the objective to show the course of metabolic and liver parameters under secukinumab, etanercept or placebo treatment over time in a descriptive manner.

As outlined above, systemic inflammation is highly involved in the pathophysiology of metabolic comorbidities and of PsA. In this context, it was of further interest to assess the impact of the comorbidities PsA and MetS, and the metabolic characteristics BMI, FPG and uric acid on hs-CRP, which is a surrogate marker of systemic inflammation.

### Statistical analysis

All analyses were performed on the safety set of patients. All data are presented as observed; no imputation of missing data was performed. Descriptive time course data (unadjusted means) are presented for each variable. Descriptive time course data (unadjusted means) are presented for each variable. No statistical testing was performed on the longitudinal time course data of metabolic and liver parameters, as this analysis was purely of a *post hoc* nature. Multivariate linear regression analysis was applied to assess the impact of the predictors PsA, MetS, BMI, FPG and uric acid on the dependent variable hs-CRP levels at baseline while simultaneously adjusting for all other predictors in the same model (Table 1). One model included the comorbidities PsA and MetS, while the other included the metabolic parameters BMI, FPG and uric acid. A third unified model was applied to assess the impact of all predictors on the decline in hs-CRP under treatment (between baseline and week 52). Parameter estimates were obtained from the model and reported with 95% confidence intervals, *P*-values and  $R^2$  values. In the two models looking at baseline hs-CRP levels, the dependent variable hs-CRP was transformed and analysed on the  $\log_e$  scale; therefore, exponential parameter estimates are shown in addition. The independent variables BMI, FPG and uric acid were treated as ordered categorical variables with clinically accepted categories described above. PsA, MetS and treatment with secukinumab/etanercept were treated as indicator variables.

### Results

Key baseline population characteristics of this total pool are given in Table S1. Mean baseline PASI was  $23.3 \pm 10.0$ , reflecting a patient population with moderate to severe disease.

#### Impact of secukinumab on body weight

Secukinumab treatment was associated with a slight reduction in body weight over 52 weeks of treatment. In comparison, etanercept showed a trend towards an increase in body weight (Fig. 1).

#### Impact of secukinumab on fasting plasma glucose (FPG)

In the overall population, secukinumab treatment had a neutral effect on FPG, with stable levels observed over 52 weeks (Fig. S1a). In patients with FPG  $> 125$  mg/dL at baseline (Fig. 2a), a diagnostic criterion for diabetes according to current guidelines,<sup>34</sup> secukinumab treatment showed a trend towards lowering FPG levels compared with placebo treatment during the first 12 weeks. This trend was consistent in patients with

**Table 1** Assessment of the impact of selected comorbidities and metabolic parameters on hs-CRP levels at baseline assessed by multivariate regression analysis

Variable	Level	Parameter estimates (SE)	95% CI	Exponential (parameter estimate)	P-value	R <sup>2</sup>
Metabolic syndrome	Presence of disease	0.52 (0.04)	(0.43, 0.60)	1.68	<0.0001	0.0789
Psoriatic arthritis	Presence of disease	0.55 (0.06)	(0.44, 0.66)	1.73	<0.0001	
BMI, kg/m <sup>2</sup>	≥18.5–<25	N/A	N/A	–	N/A	0.1401
	≥25–<30	0.35 (0.05)	(0.24, 0.45)	1.41	<0.0001	
	≥30–<35	0.63 (0.06)	(0.50, 0.75)	1.87	<0.0001	
	≥35–<40	0.88 (0.08)	(0.72, 1.04)	2.41	<0.0001	
	≥40	1.36 (0.10)	(1.17, 1.54)	3.88	<0.0001	
FPG, mg/dL	<100	N/A	N/A	–	N/A	
	≥100–≤125	0.12 (0.052)	(0.02, 0.22)	1.13	0.0207	
	≥125	0.37 (0.075)	(0.22, 0.52)	1.45	<0.0001	
Uric acid, mg/dL	≤7.0 in males or ≤6.0 in females	N/A	N/A	–	N/A	
	>7.0 in males or >6.0 in females	0.28 (0.05)	(0.19, 0.37)		<0.0001	

Two individual regression models were applied, one to assess the impact of the comorbidities psoriatic arthritis and metabolic syndrome on hs-CRP (comorbidity model) and a second one to assess the impact of the metabolic parameters BMI, FPG and uric acid (metabolic parameter model). The parameter estimate represents the expected change in log (e) hs-CRP in patients who are within the respective predictor level when compared to the reference level category; the exponential parameter represents the expected change in hs-CRP. In the comorbidity model, absence of disease was the reference level. Variables as well as hs-CRP levels were assessed at baseline. R<sup>2</sup> for the comorbidities. BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; SE, standard error.

medical history of diabetes (Fig. S1b). A similar trend was observed for etanercept.

#### Impact of secukinumab on lipid parameters

Levels of triglycerides, cholesterol, HDL and LDL remained stable over 52 weeks of secukinumab treatment with no consistent pattern of increase or decrease (Fig. S2a–d). No consistent changes were seen in lipoprotein, apolipoprotein A1 or apolipoprotein B over 52 weeks of treatment with secukinumab (Fig. S2e–g).

#### Impact of secukinumab on uric acid levels

Uric acid levels tended to decrease over 52 weeks treatment with secukinumab, both in the overall population (Fig. S3), and to a

more pronounced degree in patients with elevated baseline uric acid, >6.0 in females/7.0 mg/dL in males, which are common cut-off values for hyperuricemia (Fig. 2b).

#### Impact of secukinumab on hs-CRP levels

In the overall population and in patients with concomitant PsA, treatment with secukinumab and etanercept caused a rapid decrease in hs-CRP levels, which was maintained at low levels (Fig. 2c and Fig. S4).

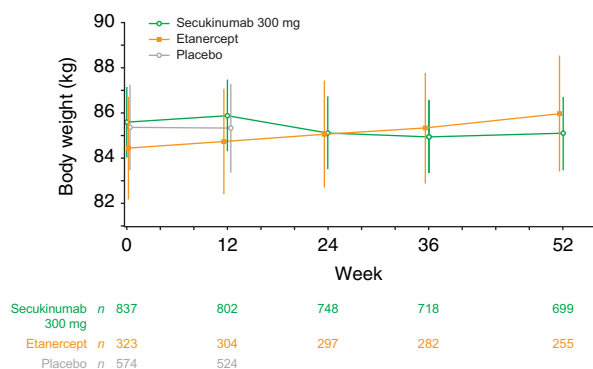
#### Impact of secukinumab on liver enzymes

Over 52 weeks of treatment with secukinumab, stable levels of GOT and GPT were observed (Fig. 3a,b). In contrast, an increase in levels of these enzymes was apparent with etanercept over 52 weeks, starting from Week 16.

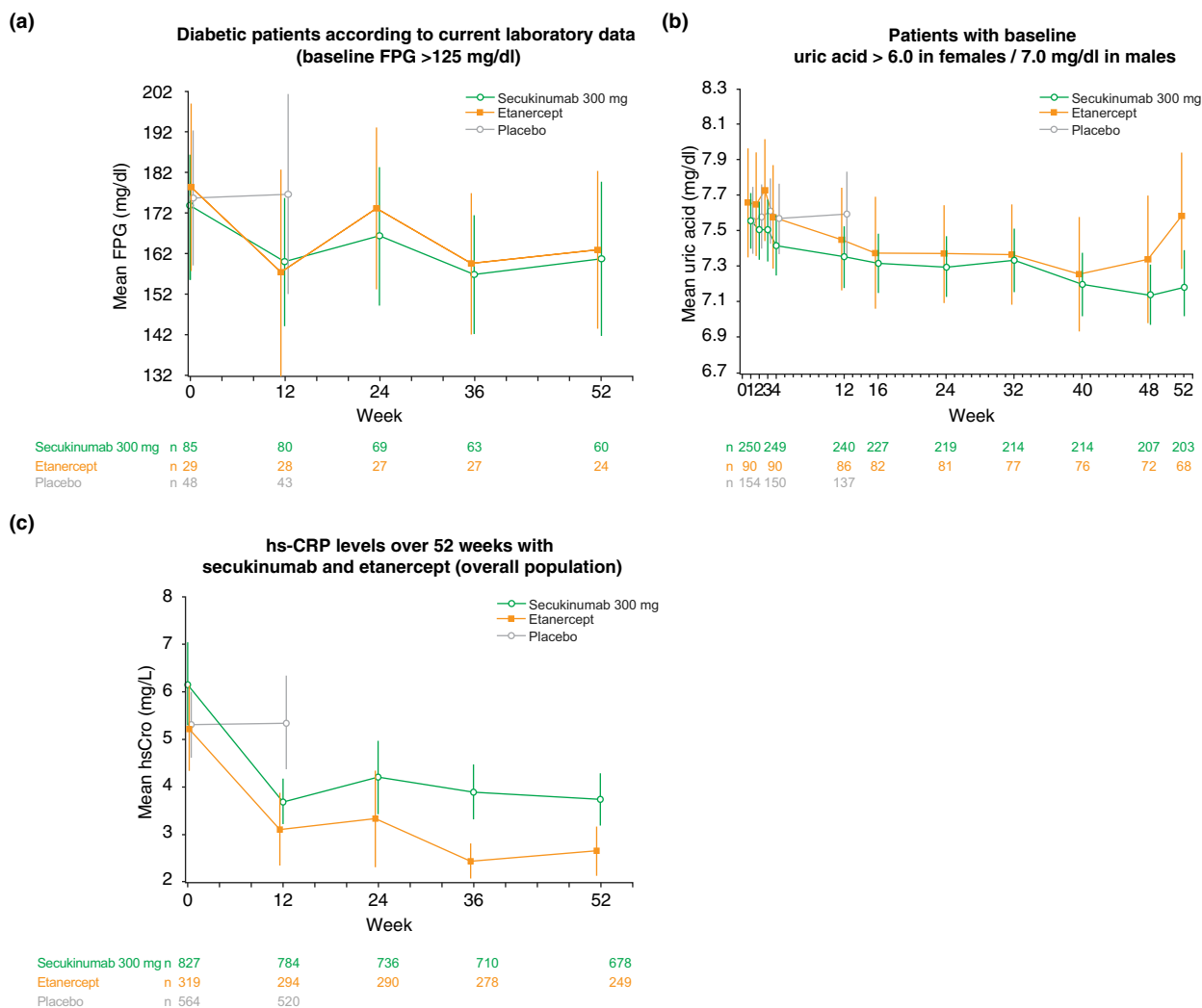
#### Impact of metabolic characteristics and comorbidities on hs-CRP at baseline and under treatment

In the comorbidity model (Table 1), MetS showed a significant impact on hs-CRP levels at baseline, compared with the impact of PsA (exponential parameter estimates: MetS: 1.68, PsA: 1.73). In the metabolic characteristics model (Table 1), overweight (BMI ≥25–<30 kg/m<sup>2</sup>) and all obesity classes showed a clear and significant impact on hs-CRP levels at baseline, with increasing strength of association for increasing BMI categories. Elevated FPG levels also showed significant impact on hs-CRP, with diabetes being a stronger predictor than prediabetes. Furthermore, hyperuricemia was a significant predictor of hs-CRP levels.

Since we could show that treatment with secukinumab and etanercept led to a decrease in hs-CRP levels (Fig. 2c) and that



**Figure 1** Effect of secukinumab and etanercept treatment on body weight over 52 weeks. Etanercept, orange; secukinumab, green; placebo, grey. As observed, unadjusted mean with 95% confidence intervals.



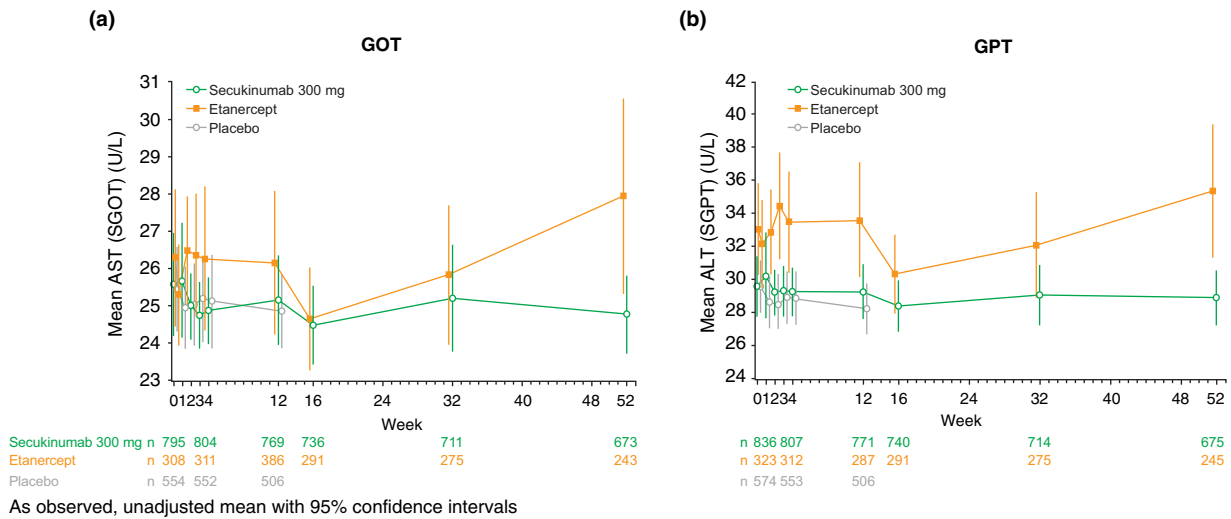
**Figure 2** Effect of secukinumab and etanercept treatment on laboratory parameters of metabolism and inflammation over 52 weeks. (a) Mean FPG levels over time. (b) Mean uric acid levels over time. (c) Mean hs-CRP levels over time.

selected metabolic characteristics and comorbidities exhibit a significant impact on hs-CRP levels at baseline, we assessed the impact of these characteristics and comorbidities on the decrease in hs-CRP under treatment with secukinumab/etanercept (Table S2): The presence of concomitant overweight/obesity significantly attenuated the treatment-induced decline of hs-CRP levels between baseline and week 52 in a dose-dependent manner, meaning the higher the BMI the smaller the decline in hs-CRP under treatment. In contrast to that, the presence of concomitant PsA did not attenuate the decrease in hs-CRP under treatment (it even significantly increased it, however to a very small, clinically irrelevant extent). Furthermore, the higher hs-CRP levels are at baseline, the higher the decrease that occurs

under treatment (Table S2). There was no significant difference in the decline of hs-CRP under secukinumab vs. etanercept.

### Discussion

Psoriasis is associated with cardiovascular and metabolic comorbidities including atherosclerosis, obesity, diabetes, hyperuricemia, NAFLD and MetS.<sup>4,6,35,36</sup> Genetic studies suggest only a modest association between psoriasis and cardiovascular or metabolic diseases.<sup>37–39</sup> The links between psoriasis and cardiovascular and metabolic conditions may therefore be mediated through systemic inflammation and/or metabolic dysregulation associated with inflammation, rather than shared genetic architecture. Therefore, the impact of psoriasis treatment on systemic



**Figure 3** Effect of secukinumab and etanercept treatment on liver enzymes over 52 weeks. (a) Mean AST (SGOT) over time. (b) Mean ALT (SGPT) over time.

inflammation and metabolic parameters is of interest in terms of long-term treatment and safety, and with regard to improving, or at least not exacerbating, known metabolic and liver comorbidities of psoriasis.

In this pooled *post hoc* analysis of data from the ERASURE, FIXTURE and SCULPTURE studies, patients treated with secukinumab showed a slight downward trend in body weight, distinct from the gradual rise observed with etanercept, consistent with previous studies of anti-TNF-alpha agents.<sup>18,19</sup> In addition to bringing overall cardiovascular and metabolic benefits, weight loss may increase the effectiveness of psoriasis treatments. For example, ustekinumab treatment was found to be less effective in patients with higher BMI.<sup>40</sup> FPG remained stable in the overall population and showed a trend towards a decrease in the diabetic population. This suggests a neutral, or in patients with pre-existing diabetes, a neutral to minimally lowering effect on FPG levels. Furthermore, the trend towards a decrease in the diabetic population observed for both active compounds, but not for placebo, might be a sign of reduced systemic inflammation, which is known to contribute to insulin resistance.<sup>9,14</sup>

Uric acid levels decreased over 52 weeks of treatment with secukinumab, both in the overall population and in patients with elevated baseline levels of uric acid. In recent years, it was shown that hyperuricemia is associated with a risk for cardiovascular and metabolic diseases, with inflammatory response regarded as a potential pathogenic mechanism of the vascular effects of uric acid.<sup>41–43</sup> Uric acid is one of the signals involved in the activation of NLRP3 inflammasome, which then mediates its pro-inflammatory effects by triggering the release of pro-inflammatory cytokines such as IL-1-beta.<sup>41</sup> High levels of uric

acid are frequently observed in psoriasis patients, probably reflecting the higher cell turnover rate in psoriatic skin.<sup>36</sup> In view of this, it seems plausible that successful psoriasis treatment could potentially lower uric acid levels via normalizing cell turnover rates.<sup>44</sup>

Liver enzymes GPT and GOT were stable over 52 weeks of treatment with secukinumab, in contrast to etanercept, which elevated these enzymes after Week 16, consistent with previous studies of anti-TNF-alpha agents.<sup>20</sup> Secukinumab had a neutral impact on lipid parameters, including triglycerides, cholesterol, HDL and LDL. Dyslipidemia, in particular elevated triglycerides, is a key component of MetS and contributes to cardiovascular risk and metabolic comorbidity in psoriasis.<sup>8</sup>

Hs-CRP as a marker of systemic inflammation has been shown to decrease with psoriasis treatment, as observed here with secukinumab and etanercept.<sup>17</sup>

The regression analysis on the impact of selected metabolic characteristics and comorbidities on baseline hs-CRP levels confirmed an impact of PsA on hs-CRP levels, as observed in previous studies of inflammatory biomarkers in PsA versus psoriasis patients without PsA.<sup>45</sup> This suggests that joint involvement leads to a higher systemic inflammatory burden compared to skin involvement only. Furthermore, it revealed an impact of obesity, disorders of glucose metabolism and hyperuricemia on hs-CRP, with all of them being predictors for hs-CRP elevations. The same was the case for the presence of concomitant MetS. This reflects that not only PsA but also metabolic diseases such as obesity, MetS, diabetes or hyperuricemia are characterized by systemic inflammatory processes, such as adipose tissue inflammation. Interestingly, the effect of MetS on hs-CRP levels was

comparable to the one observed for PsA, underlining the pro-inflammatory character of MetS. The regression analysis on the impact of selected metabolic characteristics and comorbidities on the decrease of hs-CRP levels under treatment with secukinumab/etanercept revealed an interesting phenomenon (Table S2): as outlined above, similar to PsA, overweight and obesity also significantly increase baseline hs-CRP levels. However, when looking at the impact of these comorbidities on hs-CRP levels under 52 weeks of treatment they show a differential effect: overweight and obesity significantly attenuate the decline of hs-CRP under treatment, whereas the presence of concomitant PsA does not affect this decline to a relevant extent. This interesting differential response might reflect that the additional systemic inflammatory burden caused by concomitant PsA is more responsive to anti-IL17A/anti-TNF-alpha treatment than the inflammatory processes caused by overweight/obesity, which seem to be more resistant.

In this context, it is of interest to consider that metabolic patient characteristics such as obesity, MetS, diabetes or hyperuricemia can further drive systemic inflammation in psoriasis patients. It is under current investigation whether weight loss can improve secukinumab treatment efficacy in patients with concomitant MetS by reducing systemic inflammation (METABOLYX study, CAIN457ADE08, NCT03440736).

The correlation between hs-CRP and cardiovascular risk is well described, with recent data proving a relationship between lower hs-CRP and reduced cardiovascular risk.<sup>46</sup> However, the validity of hs-CRP as a biomarker of cardiovascular risk is partly limited by certain factors. During states of systemic inflammatory response, which occur during infections (pneumonia, sepsis etc.), hs-CRP levels are primarily driven by the systemic inflammatory response and less by vascular inflammation. Therefore, hs-CRP levels cannot be interpreted as a cardiovascular risk factor during a state of systemic inflammatory response, e.g. in a patient with ongoing infection.

There are limited data available on the impact of systemic psoriasis treatments on metabolic and cardiovascular parameters. A study of adalimumab in 21 patients demonstrated a decrease at 12 weeks in E-selectin and IL-22,<sup>47</sup> but no impact on vascular inflammation was seen with adalimumab in an FDG-PET imaging study.<sup>48</sup> Ixekizumab, which also targets IL-17A, showed a neutral impact on metabolic parameters.<sup>49</sup> Preliminary results of a study examining the effects of secukinumab throughout 6 months on a set of adipocytokines (resistin, chemerin, adiponectin and CRP) in 28 patients with PsA showed no significant effect on any of these biomarkers.<sup>50</sup> The decrease in hs-CRP under secukinumab and etanercept treatment reported in the present publication (Fig. 2c) stands in contrast to what was shown in the publication by Fassio *et al.*,<sup>50</sup> which showed no effect on hs-CRP. A difference between the studies that should be mentioned in this context is that Fassio *et al.* enrolled PsA patients only, whereas the

present study included psoriasis patients, with only 18.6% of them having concomitant PsA (Table S1). However, when analysing only psoriasis patients with concomitant PsA, there is still a trend towards decreasing hs-CRP under secukinumab and etanercept (Fig. S4).

The current analyses are primarily limited by their *post hoc* nature. Another limitation is that the data are presented as observed without any imputation; therefore, the patient number decreases at each visit. Furthermore, it cannot be excluded that treatment with other medications affecting cardiometabolic parameters was started or dose adjusted during the study; however, this applies to all treatment arms including placebo, which limits the potential bias. Although it restricts long-term comparisons, a duration of 12 weeks for the placebo treatment arm is the current standard in psoriasis phase 3 trials, since longer placebo treatments are ethically very difficult to justify in moderate to severe psoriasis patients. Furthermore, the number of patients was relatively low for some analyses that focused on preselected subgroups, such as patients with baseline FPG >125 mg/dL.

Further prospective evaluation of cardiovascular and metabolic parameters with secukinumab treatment is needed to confirm the observed trends, such as the VIP-S study (NCT02690701), CARIMA (NCT02559622) or the METABOLYX trial. In conclusion, these analyses suggest stable long-term trends in metabolic parameters under secukinumab treatment, with potential improvement in some factors such as body weight.

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### Supporting information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Effect of secukinumab on fasting plasma glucose in the overall population (a) and in patients with a medical history of ongoing diabetes (b) Secukinumab treatment and fasting plasma glucose.

**Figure S2.** Effect of secukinumab treatment on lipid parameters.

**Figure S3.** Impact of secukinumab and etanercept treatment on uric acid levels over 52 weeks: Overall population.

**Figure S4.** hs-CRP levels over 52 weeks with secukinumab ( $n = 153$ ) and etanercept ( $n = 44$ ) in patients with psoriatic arthritis.

**Table S1.** Analysis population baseline characteristics.

**Table S2** Multiple linear regression analysis to assess the impact of selected comorbidities and metabolic parameters on the change of hs-CRP levels under treatment.

**Appendix S1.** Supplementary methods, tables, and results.