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A phase 2 trial investigating the efficacy and safety of the mPGES-1 inhibitor vipoglanstat in systemic sclerosis-related Raynaud's

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Abstract

Objective: Our objective was to test the hypothesis, in a double-blind, placebo-controlled study that vipoglanstat, an inhibitor of microsomal prostaglandin E synthase-1 (mPGES-1), which decreases prostaglandin E_2 (PGE_2) and increases prostacyclin biosynthesis, improves RP.

Methods: Patients with SSc and ≥7 RP attacks during the last screening week prior to a baseline visit were randomized to 4 weeks treatment with vipoglanstat 120 mg or placebo. A daily electronic diary captured RP attacks (duration and pain) and Raynaud's Condition Score, with change in RP attacks/week as the primary end point. Cold challenge assessments were performed at baseline and end of treatment. Exploratory end points included patients' and physicians' global impression of change, Assessment of Scleroderma-associated Raynaud's Phenomenon questionnaire, mPGES-1 activity, and urinary excretion of arachidonic acid metabolites.

Results: Sixty-nine subjects received vipoglanstat ($n = 33$) or placebo ($n = 36$). The mean weekly number of RP attacks [baseline; vipoglanstat 14.4 (S.D. 6.7), placebo 18.2 (12.6)] decreased by 3.4 (95% CI –5.8; –1.0) and 4.2 (–6.5; –2.0) attacks per week ($P = 0.628$), respectively. All patient-reported outcomes improved, with no difference between the groups. The mean change in recovery of peripheral blood flow after the cold challenge did not differ between the study groups. Vipoglanstat fully inhibited mPGES-1, resulting in 57% reduction of PGE_2 and 50% increase of prostacyclin metabolites in the urine. Vipoglanstat was safe and well tolerated.

Conclusion: Although vipoglanstat was safe, and well tolerated in a dose achieving full inhibition of mPGES-1, it was ineffective in SSc-related RP. Further development and evaluation of vipoglanstat will therefore be in other diseases where mPGES-1 plays a pathogenetic role.

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Trial registration: ClinicalTrials.gov, https://www.clinicaltrials.gov, NCT0474420.

Keywords: clinical trial, microsomal prostaglandin E synthase-1, vipoglanstat, Raynaud's phenomenon, systemic sclerosis.

Rheumatology key messages

- Vipoglanstat inhibits microsomal prostaglandin E synthase-1 (mPGES-1), decreasing prostaglandin E_2 (PGE_2) and increasing prostacyclin biosynthesis.
- A randomized, double-blind, placebo-controlled parallel group study of vipoglanstat in SSc-related Raynaud's phenomenon is reported.
- Despite full mPGES-1 inhibition, treatment with vipoglanstat did not improve Raynaud's or finger blood flow.

Introduction

Almost all patients with SSc experience RP [1], episodic colour change of the extremities (most noticeably the fingers) in response to cold exposure or emotional stress. Attacks of RP are often painful and disabling, and SSc-related RP has a major impact on quality of life: the results of a survey of almost 2000 patients with SSc suggested that RP was the 'organ' complication that had the most impact on daily life [2]. Current treatments are only partially effective (if at all). Therefore, new, effective therapies are required.

One way to improve blood supply to the fingers in patients with SSc is via supplementation of the prostacyclin pathway, as in the treatment of pulmonary arterial hypertension [3]. I.v. iloprost has been shown to reduce frequency and severity of RP attacks in patients with SSc [4, 5], and to improve temperature recovery to the fingers after a cold challenge [6], but has the disadvantage of requiring hospitalization. Oral therapies would be advantageous. However, studies of oral prostanoid therapy have been disappointing [4, 5]. The most recent randomized controlled trial of oral prostanoid therapy in SSc was primarily a study of digital ulceration, with limited assessment of RP [7]: treprostinil conferred no benefit compared with placebo as measured by a visual analogue scale (VAS) for interference of RP with daily activities, although there was some RP benefit in terms of the 'patient assessment of change' questionnaire. The prostacyclin receptor agonist selexipag conferred no benefit in a placebo-controlled trial in patients with SSc-related RP [8].

A novel way of augmenting the prostacyclin pathway is through inhibition of microsomal prostaglandin E_2 synthase-1 (mPGES-1), which is a terminal enzyme converting the unstable cyclooxygenase-derived PGH_2 to prostaglandin E_2 (PGE_2). Other synthases convert PGH_2 to prostacyclin, thromboxane and other metabolites in the arachidonic acid cascade (Fig. 1). By inhibition of mPGES-1, PGH_2 is shunted towards other metabolites, and increased prostacyclin synthesis has been demonstrated in mouse peritoneal macrophages [9] and mPGES-1 knock-out mice [10, 11], as well as by pharmacological inhibition of mPGES-1 in humans [12, 13]. Shunting of PGH_2 towards biosynthesis of prostacyclin might be beneficial in patients with SSc-related RP.

Vipoglanstat (also known as GS-248 and BI 1029539) is a selective inhibitor of mPGES-1. The compound is highly potent, with IC_{50} in *ex vivo* human whole blood estimated to be $\leq$0.5 nmol/l in a phase 1 study in healthy volunteers [12]; vipoglanstat at doses fully inhibiting mPGES-1 was safe and well tolerated, and urinary analyses showed decreased levels of PGE_2 and increased levels of prostacyclin metabolites.

This study aimed to test the hypothesis that, in patients with SSc, treatment with vipoglanstat increases endogenous production of prostacyclin and decreases the RP attack frequency and severity. Other specific objectives were to evaluate the safety and efficacy of vipoglanstat on peripheral blood flow in response to cold challenge, inhibition of mPGES-1 activity and excretion of arachidonic acid metabolites in urine. The correlation between change in Assessment of Scleroderma-associated Raynaud's Phenomenon (ASRAP) questionnaire score and patient global impression of change was explored in a *post hoc* analysis.

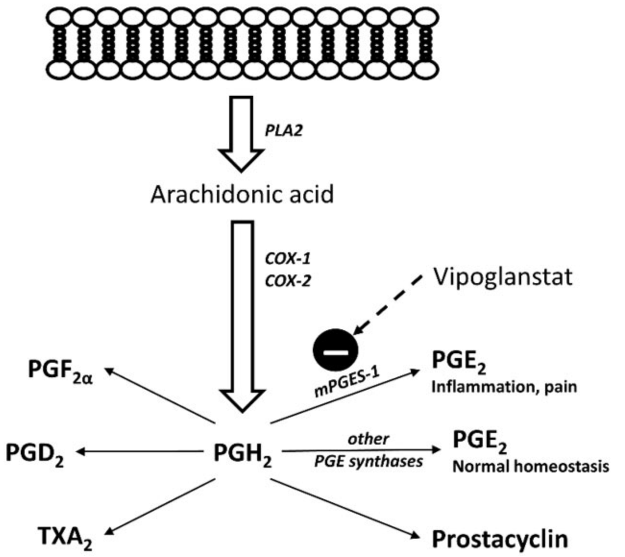

Figure 1. Arachidonic acid metabolism. Arachidonic acid, released from the cell membrane by phospholipase A2 (PLA2), is by cyclooxygenases (COX-1 and COX-2) metabolized to the unstable PGH_2, which by different terminal synthases is converted to different prostaglandins. The inducible enzyme prostaglandin E_2 synthase-1 (mPGES-1) is associated with inflammation and pain, while other PGE synthases maintain normal homeostasis. PLA2: phospholipase A2; PGE_2: prostaglandin E_2; PGI_2: prostacyclin; TXA_2: thromboxane A_2; PGD_2: prostaglandin D_2; $PGF_{2\alpha}$: prostaglandin F_2alpha; PGH_2: prostaglandin H_2

Material and methods

Study design

This was a Phase 2, randomized, double-blind, placebo-controlled, parallel group study (ClinicalTrials.gov, NCT0474 4207) with a 1:1 allocation of participants to either three capsules of 40 mg (total dose 120 mg) vipoglanstat, or corresponding identical placebo capsules, for oral intake once daily in the morning for 4 weeks. The blinding was maintained throughout the study. Patients were enrolled by the investigator at each study site. Patients were scheduled to have five visits: initial screening (2–3 weeks before randomization), randomization and start of treatment (baseline visit), safety assessments (2 weeks after randomization), end of treatment (4 weeks after randomization), and an end-of-study visit (2–3 weeks after last treatment) (Supplementary Fig. S1, available at *Rheumatology* online). The allocation codes were masked and not broken until declaration of a clean file, which kept patients, investigators and outcome assessors blinded throughout the study. The study was approved by appropriate independent ethics committees, and informed consent was obtained from all patients.

Eligibility criteria

Male and female non-smoking patients were eligible for recruitment if they fulfilled the EULAR/ACR 2013 criteria for SSc [14], with a disease duration of ≤120 months from first non-Raynaud's manifestation, were aged 18–75 years and had a typical frequency of RP attacks of ≥7 times per week during the 4 weeks prior to screening, despite background medication [calcium channel blockers or phosphodiesterase type 5 (PDE-5) inhibitors]. To be eligible for randomization, patients were required to have ≥7 RP attacks during the last week of the run-in period, with no >2 days without RP attacks. During the 4 weeks prior to screening, patients should not have changed dose or initiated treatment with vasodilating substances. The use of calcium channel blockers or PDE-5 inhibitors in a stable dose was allowed throughout the study. Further, the patients should not have been treated with prostacyclin receptor agonists, systemic CSs or immunosuppressive therapy other than stable doses of MMF, and they should not have had an active digital ulcer within 4 weeks prior to screening. The full eligibility criteria are presented in the Supplementary Material, available at *Rheumatology* online.

Primary and key secondary end points

From screening to end of treatment, the patients completed a daily electronic diary, including number of Raynaud's attacks, the length (min) and pain [Numerical Rating Scale (NRS) 0–10] of each RP attack, and daily assessment of the Raynaud's Condition Score (RCS) (NRS 0–10).

The primary end point was defined as the mean change in number of Raynaud's attacks from the last 7 days of screening to the last 7 days of treatment, as assessed by the electronic diary. The diary also included assessments for the key secondary end points, which were defined as: mean change from baseline to week 4 in (i) pain experience during RP attacks, (ii) RCS Score, (iii) cumulative duration of RP attacks (log-transformed), and (iv) mean duration of RP attacks (log-transformed).

Thermography and cold challenge

Thermographic end points at Visit 2 and Visit 4 were evaluated only at selected sites, based on the researcher's experience in the methodology. All measurements were performed in a temperature-controlled (23 ± 2°C) or temperature-monitored room. Patients were requested to wear light clothing and refrain from vigorous exercise, caffeine and alcohol for at least 4 h prior to the assessment. Upon arrival, patients were seated comfortably in the temperature-controlled (or temperature-monitored) room for 20 min and acclimatized. At Visit 2 assessments were performed before and 180 min after study drug administration, and at Visit 4 immediately before study drug administration.

The temperature of the dorsum of each hand and all eight distal phalanges (excluding thumbs) was measured. The distal dorsal difference (DDD), defined as the difference in measurements between the dorsum and distal phalanx, was calculated for each finger. For comparison between the treatment groups, the mean finger temperature and DDD for all eight fingers was calculated.

The cold challenge involved a 1 min exposure to 15°C water for both hands to the MCP joints and rewarming at ambient temperature. Immediately prior to the cold challenge, a baseline image of both hands was taken with the thermal camera, with the subject's hands placed on a thermally insulated surface. Rewarming of the fingers after the cold challenge was imaged with 4 frames per min over 15 min following hand removal from the water, and the averaged areas under the curve (AUC) and maximum (MAX) values for all eight fingers were calculated [15].

The mean change from Visit 2 (pre study drug assessments) to Visit 4 were predefined as secondary end points, and the change between the two assessments at Visit 2 as exploratory end points.

mPGES-1 activity and urinary excretion of arachidonic acid metabolites

Inhibition of the target enzyme (mPGES-1) was assessed on blood samples drawn prior to study drug administration on Visit 2 and Visit 4, and analysed by a qualified whole-blood assay, with the results expressed as percentage change. Quantification of the urinary excretion of metabolites derived from PGE_2 (PGEM), prostacyclin (PGIM) and thromboxane (TXM) was performed on the morning urine at Visit 2 and Visit 4, with the results expressed as percentage change after normalization to urinary creatinine (for details on the methods, see the supplementary methods, available at *Rheumatology* online).

Other exploratory end points

Other exploratory end points included patients' and physicians' global impression of change (PaGIC and PhGIC) assessed at end of treatment, and the mean change from baseline to end of treatment in the ASRAP questionnaire total score [16, 17]. The ASRAP questionnaire was assessed at baseline (Visit 2) and all subsequent visits using the preliminary 39-item beta version, and scores were *post hoc* calculated using the algorithm for the final 27-item version [16, 17].

Nailfold capillaroscopy

At baseline, patients underwent nailfold capillaroscopy, and the investigator classified the pattern as normal/early/active/late [18], with the results expressed as either the 'majority' verdict across all fingers, or in the case of a tie the worst grade. Frames (usually four per finger) were quantitatively assessed automatically regarding capillary density and width (after manual identification of the location of the capillary apices) as previously described [19]. Giant capillaries were defined as present if the maximal capillary width was >50 µm in any finger.

Safety assessments

Evaluation of safety was a pre-defined secondary objective. All adverse events, serious and non-serious, reported from the first day of study treatment up until and including 7 days after the last dose of the study treatment were considered treatment-emergent adverse events (AEs). At all study visits haematological, blood chemistry and urine analyses were performed. ECGs were recorded at inclusion, randomization,

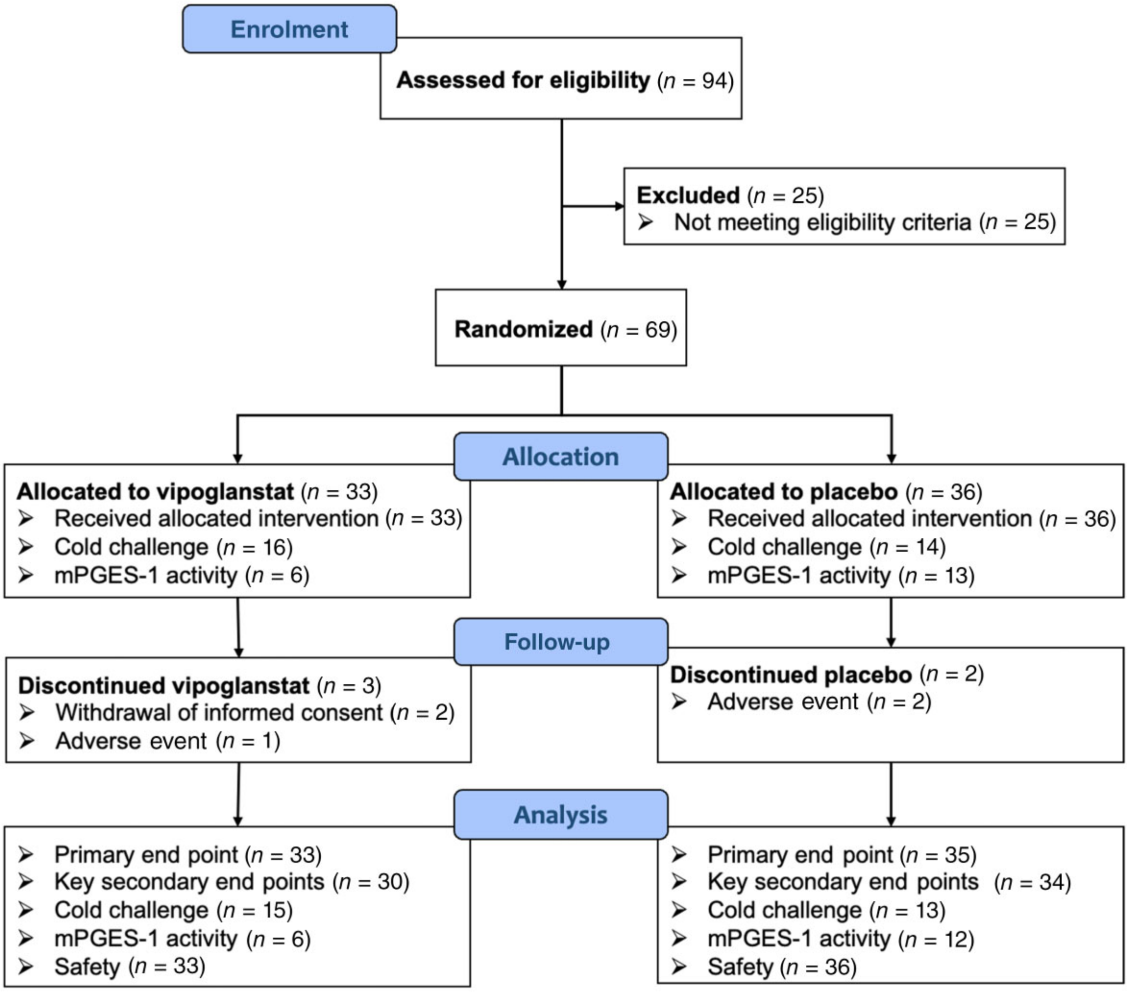

Figure 2. Patient disposition. Primary and key secondary end points were analysed for the FAS population, with missing data at week 4 for the primary end point replaced using the placebo multiple imputation (pMI) method. For one subject in the placebo group, the screening period was extended due to an intercurrent medical event, and the electronic diary could not capture a RP attack during the last week of the run-in period. Since this subject had fulfilled the screening criteria earlier during the run-in period, the subject was considered as eligible and was randomized into the study, but as data on RP attacks were not captured during the defined baseline period, the subject was excluded from the end point analyses on RP attacks. FAS: full analysis; mPGES-1: prostaglandin E synthase-1

2 weeks after start of treatment, and at the follow-up visit. An additional ECG was recorded at the assumed peak exposure 170 min after the first administration of the study drug.

Statistics

Sample-size calculation was done for the primary end point and based on a two-sided t test for independent samples with a type-I error rate of 0.05. Calculations assumed a mean change from baseline to week 4 of 12.0 attacks per week for the active treatment arm *vs* 4.0 for the placebo arm, and a common S.D. of 10.0, with a power of 80%. The calculations revealed that 26 patients per group were needed; to allow for dropouts, it was planned to randomize ∼80 patients into the study.

The random allocation sequence in blocks of four was generated by an independent statistician not involved in any other aspects of the study. Randomization was performed at a central site, with stratification based on background vasodilatory treatment (calcium channel blockers, PDE-5 inhibitors, or no background vasodilatory treatment).

The statistical analyses for the primary end point and all other continuous end points were performed using analysis of covariance (ANCOVA), including the stratification factor and treatment as fixed factors, and baseline levels as a covariate. Analysis was done for the full analysis (FAS) population, which consisted of all patients who were randomized and received at least one dose of investigational medicinal product (IMP). For the primary end point, missing data at week 4 was replaced using the placebo multiple imputation (pMI) method, i.e. imputing the placebo behaviour for missing data, utilizing multiple draws from the posterior predictive distribution estimated from the placebo arm. There was no imputation for missing data in other end points. Due to the skew distribution of Raynaud's attack duration (single attacks and cumulatively over a week) and temperature after cold challenge, these variables were analysed on log-transformed (natural logarithm) values. Categorical end points such as PaGIC and PhGIC at week 4 were analysed using the Cochran Mantel–Haenzel method, adjusted for the stratification factor. The change from baseline to end of treatment in mPGES-1 activity assessed by PGE_2 formation in the whole blood assay and urinary excretion of arachidonic acid metabolites was analysed by the Mann–Whitney *U* test.

The overall type I family-wise error rate for testing the primary and the key secondary efficacy end points was controlled at the type-I error rate of 0.05 using a serial gatekeeping multiple comparisons procedure. Following this multiple comparisons procedure, progression to the next end point only occurred if the null hypothesis was rejected. Since the null hypothesis was not rejected for the primary efficacy end point, all subsequent hypothesis tests were rejected, and the reported *P*-values should be regarded as nominal.

In a *post hoc* analysis, correlation between PaGIC and change in ASRAP score from baseline to end of treatment was estimated using the Spearman rank order correlation coefficient.

Results

The study was conducted from 29 December 2020 (first patient first visit) to 15 June 2022 (last patient last visit) at 14 sites in four European countries. No patients were enrolled between 20 April and 22 September 2021 to minimize the effect of warmer weather on the efficacy outcome variables. Recruitment was permanently halted when 69 patients were randomized, since the warmer summer months were approaching, and it was assumed, based on actual drop-out rate, that at least 26 patients had been allocated to each treatment arm as stipulated in the power calculations. The study over-ran by one winter season, mainly due to recruitment challenges during the COVID-19 pandemic. A total of 94 patients were enrolled for screening, of whom 25 failed the eligibility criteria. Out of the 69 randomized patients, 33 were allocated to vipoglanstat and 36 to placebo (Fig. 2). At pre-selected sites, patients were assessed by thermography, cold challenge, and whole-blood assay for mPGES-1 activity. Three patients in the vipoglanstat group and two patients in the placebo group withdrew during the treatment period. The baseline characteristics were comparable between the two groups (Table 1).

Table 1. Patient characteristics

	Treatment group	
	Vipoglanstat ($N = 33$)	Placebo ($N = 36$)
Females	27 [81.8%]	33 [91.7%]
Race		
– Asian	1 [3.0%]	0 [0.0%]
– White	30 [90.9%]	34 [94.4%]
– Not collected	2 [6.1%]	2 [5.6%]
Age (years)	49.0 (10.6)	50.6 (10.6)
Weight (kg)	74.5 (16.4)	68.9 (14.1)
BMI (kg/m^2)	26.1 (5.0)	25.1 (4.4)
Duration of RP (months)[a]	122.1 (135.1)	93.1 (68.6)
Duration of SSc from first non-RP manifestation (months)[b]	37.4 (33.5)	52.0 (32.4)
Capillaroscopy pattern[c]		
– Normal	3 [9.1%]	3 [8.3%]
– Early	9 [27.3%]	9 [25.0%]
– Active	11 [33.3%]	11 [30.6%]
– Late	10 [30.3%]	13 [36.1%]
Capillary dimensions[d]		
– Capillary density (per mm); mean 8 fingers	5.9 (2.3)	5.9 (1.8)
– Mean width (μm); mean 8 fingers	31.1 (7.5)	29.8 (6.3)
– Presence of giant capillaries	25 [86.2%]	26 [83.9%]
Autoantibodies		
– ANA positive	33 [100.0%]	35 [97.2%]
– ACA positive	16 [48.5%]	20 [55.6%]
– Anti-Scl-70 antibody positive	13 [39.4%]	12 [33.3%]
Background vasodilatory treatment		
– Calcium channel blockers	18 [54.6%]	19 [52.8%]
– PDE-5 inhibitors	9 [27.3%]	10 [27.8%]
– No vasodilatory treatment	6 [18.2%]	7 [19.4%]

Values are number [percentage] for categorical variables and mean (S.D.) for continuous variables.
[a] Placebo $N = 33$.
[b] Vipoglanstat $N = 32$, placebo $N = 31$.
[c] Majority verdict of eight fingers, or in the case of a tie the worst grade.
[d] Vipoglanstat $N = 29$, placebo $N = 31$.

Primary and key secondary end points (RP attacks and RCS)

There was no statistically significant difference between the vipoglanstat and placebo groups regarding the primary end point, mean change from baseline to week 4 in the number of RP attacks per week ($P = 0.628$). The mean change in number of attacks decreased in both the vipoglanstat and placebo groups by 3.4 and 4.2 attacks per week, respectively. Further, there were no statistically significant differences between the vipoglanstat and placebo groups on the key secondary end points (cumulative duration of and pain experienced during attacks, and RCS), which all improved in both the vipoglanstat- and placebo-treated groups (Table 2). The results were not influenced by use of background vasodilatory treatment (data not shown).

Thermography and cold challenge

There was no statistically significant difference between the vipoglanstat and placebo groups in peripheral blood flow in terms of DDD and mean finger temperature, as assessed by thermography, following the first study drug administration or from baseline to end of treatment (Table 2, Supplementary Table S1, available at *Rheumatology* online). The recovery of peripheral blood flow after the cold challenge did not change following the first administration of the study drug, or from baseline to end of treatment in either the vipoglanstat or the placebo groups (Table 2, Supplementary Table S1, available at *Rheumatology* online).

ASRAP and global impression of change

There was no statistically significant difference between the vipoglanstat and placebo groups in the mean change from baseline to week 4 in the ASRAP scores, which improved in both treatment groups (Table 2). Further, there was no statistically significant difference between the treatment groups for PaGIC or PhGIC, and physicians' and patients' ratings were very similar (Supplementary Table S2, available at *Rheumatology* online). *Post hoc* analysis showed high correlation between PaGIC and change in the ASRAP score from baseline to end of treatment (Spearman's rho $= 0.618$; $P < 0.001$) (Fig. 3).

Inhibition of mPGES-1 activity and excretion of arachidonic acid metabolites

The median change in mPGES-1–derived PGE_2 in the whole-blood assay from baseline to ∼24 h after dosing at end of treatment was –102.4% in the vipoglanstat group and –2.8% in the placebo group ($P < 0.01$), demonstrating full inhibition of the enzyme over the full dosing interval (Fig. 4). The median change from baseline to end of treatment in urinary excretion of the PGE_2 metabolite was –57.2% and +4.9% in the vipoglanstat

Table 2. Change from baseline to end of treatment in primary, secondary and exploratory end points

	Baseline (BL)		End of treatment (EoT)		LS mean change from baseline to end of treatment[a]			
	Vipoglanstat	Placebo	Vipoglanstat	Placebo	Vipoglanstat	Placebo	Vipoglanstat – Placebo	*P* value
Electronic diary	*N* = *33*	*N* = *35*	*N* = *30*	*N* = *34*				
Number of attacks per week	14.4 (6.7)	18.2 (12.6)	11.1 (9.5)	14.0 (12.8)	–3.41 [–5.83; –0.99]	–4.22 [–6.48; –1.96]	0.81 [–2.48: 4.10]	0.628
Cumulative duration of attacks (min)	525.5 (460.4)	480.6 (479.6)	450.4 (571.8)	356.0 (320.6)				
ln(cumulative duration of attacks)[b]	5.9 (0.82)	5.8 (0.81)	5.6 (1.04)	5.4 (1.20)	0.70 [0.51; 0.98]	0.61 [0.45; 0.82]	1.16 [0.75; 1.81]	0.506
Mean attack duration (min)	38.5 (36.0)	27.4 (19.2)	43.4 (51.5)	25.7 (14.6)				
ln(mean attack duration)[b]	3.4 (0.72)	3.1 (0.65)	3.4 (0.82)	3.1 (0.66)	1.06 [0.87; 1.29]	0.89 [0.74; 1.08]	1.18 [0.90; 1.56]	0.231
Mean pain during attack (NRS 0–10)	3.8 (2.0)	4.0 (2.1)	3.0 (2.0)	3.4 (2.3)	–0.65 [–1.16; –0.14]	–0.60 [–1.07; –0.13]	–0.05 [–0.74; 0.64]	0.891
RCS (NRS 0–10)	4.1 (2.2)	4.1 (2.1)	2.9 (2.2)	3.2 (2.2)	–0.99 [–1.54; –0.45]	–0.95 [–1.45; –0.46]	–0.04 [–0.78; 0.70]	0.918
Hand and finger temperature	*N* = *16*	*N* = *14*	*N* = *12*	*N* = *13*				
DDD (°C)	–1.58 (1.16)	–2.13 (1.89)	–1.53 (1.81)	–2.43 (1.85)	0.27 [–0.87; 1.40]	–0.05 [–1.19; 1.08]	0.32 [–1.23; 1.87]	0.671
Mean finger temperature (°C)	28.51 (2.56)	28.27 (3.44)	28.18 (3.07)	27.77 (3.28)	–0.15 [–2.22; 1.93]	–0.22 [–2.28; 1.85]	0.07 [–2.71; 2.85]	0.958
Finger temperature after cold challenge	*N* = *16*	*N* = *15*	*N* = *14*	*N* = *13*				
AUC (°C*sec)	22 670 (2961)	22 496 (2916)	23 083 (2008)	22 999 (3294)				
ln(AUC)[b]	10.02 (0.126)	10.01 (0.121)	10.04 (0.085)	10.03 (0.136)	1.05 [0.98; 1.13]	1.04 [0.97; 1.11]	1.01 [0.92; 1.11]	0.825
Max temperature (°C)	26.8 (4.17)	26.5 (4.03)	27.7 (3.61)	26.8 (4.36)				
ln(Max temperature)[b]	3.28 (0.151)	3.27 (0.143)	3.31 (0.129)	3.28 (0.154)	1.07 [0.97; 1.17]	1.03 [0.94; 1.13]	1.04 [0.92; 1.17]	0.559
Exploratory end point	*N* = *33*	*N* = *36*	*N* = *30*	*N* = *34*				
ASRAP	53.65 (6.04)	52.49 (5.69)	49.31 (8.71)	49.42 (7.81)	–4.38 [–6.35; –2.41]	–3.14 [–4.95; –1.32]	–1.24 [–3.82; 1.33]	0.338

[a] ANCOVA on comparison between treatments, including pMI imputations for RP attacks end points and RCS.
[b] For variables not normally distributed statistical analyses were performed on logarithmic values, and change was back transformed. Values are Mean (S.D.) and LS mean [95% CI]. LS: Least Square Mean; RCS: Raynaud's Condition Score; ANCOVA: analysis of covariance; ASRAP: Assessment of Scleroderma-associated Raynaud's Phenomenon; NRS: Numerical Rating Scale; DDD: distal dorsal difference; AUC: area under the curve.

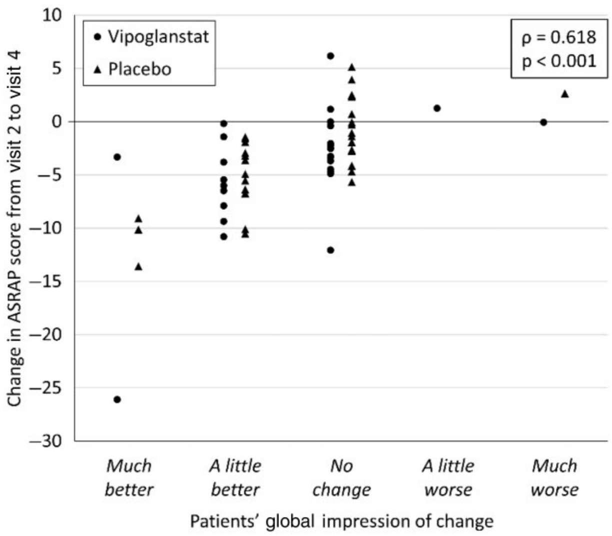

Figure 3. Correlation between Assessment of Scleroderma-associated Raynaud's Phenomenon (ASRAP) and Patients' Global Impression of Change (PaGIC). ρ = Spearman's rho

and placebo groups, respectively ($P < 0.001$). The corresponding values for the prostacyclin metabolite were +49.9% and –9.8% ($P < 0.01$) and for the thromboxane metabolite +48.4% and –5.0% ($P < 0.001$) (Fig. 4).

Safety

There were no deaths or serious AEs reported in vipoglanstat group. One subject in the placebo group experienced a serious AE, not considered related to treatment or study procedures, classified as a thermal burn (scalding with hot water), leading to hospitalization and complicated with sepsis caused by an unspecified intrahospital bacterium, leading to death.

All patients who had taken at least one dose of the study medication were included in the safety analyses: 33 and 36 patients in the vipoglanstat and placebo groups, respectively. The frequency of AEs was similar in the treatment groups, with 37 AEs in 16 patients (48.5%) in the vipoglanstat group and 45 AEs in 18 patients (50.0%) in the placebo group. AEs classified as possibly or probably related to treatment were reported by 10 (30.3%) patients in the vipoglanstat group and 11 (30.6%) patients in the placebo group. One subject from the vipoglanstat group and two patients from the placebo group experienced AEs that led to discontinuation from the study, and an AE of severe intensity was reported by one subject in each treatment group. The most frequently reported AEs (≥5% of patients in any treatment group) were headache (6 and 4), nausea (2 and 1), upper abdominal pain (2 and 0), arthalgia (0 and 3) and decreased white cell count (0 and 2), in the vipoglanstat and placebo groups, respectively. There were no clinically relevant changes in haematological, blood chemistry or urine analyses. Neither were there any changes in ECG recordings during the study or at the assumed maximal exposure.

Discussion

This is the first study investigating the effect of an mPGES-1 inhibitor in SSc-related RP. However, despite full inhibition of mPGES-1, leading to decreased systemic biosynthesis of pro-inflammatory PGE_2 and shunting to increased prostacyclin biosynthesis, no effect on RP-related outcomes or recovery after a cold challenge was observed.

Both the vipoglanstat and the placebo groups improved in RP-related end points, specifically frequency of, duration of and pain during attacks, RCS, ASRAP, PaGIC and PhGIC. This is in accordance with many studies in SSc-related RP [8, 20], and the level of decrease in frequency of RP attacks was similar to the assumptions for the power calculation. This phenomenon has been described as being likely to represent a regression towards the mean [21], but other explanations such as change in behaviour avoiding RP attack triggers during participation in a clinical study cannot be excluded. No improvement was observed in hand and finger temperature or rewarming following a cold challenge; a placebo effect on these assessments is unlikely, since these assessments provide an objective assessment of pathophysiology related to the underlying vasculopathy. The patients studied had well-established disease, with structural vascular abnormalities (as demonstrated by RP-duration and nailfold capillaroscopy findings) and were representative of patients with SSc most in need of effective treatment for RP.

The study provides further confirmation of the feasibility of recording RP attacks using electronic diaries in patients with SSc.

The ASRAP questionnaire is a novel patient-reported outcome (PRO) instrument for assessing the severity and impact of RP in patients with SSc. The instrument was developed by an international consortium of SSc experts and with direct input from patients with SSc throughout the process to achieve the goal of fully capturing the patient experience of SSc-RP [16, 17]. This was the first interventional clinical study including ASRAP as an end point, demonstrating the feasibility of the instrument in that setting. The observed improvement in ASRAP and the high correlation between PaGIC and change in ASRAP score provide useful additional responsiveness data in the validation of this PRO instrument.

Studies on mPGES-1 knock-out mice have demonstrated increases in plasma levels [10] and urinary excretion of prostacyclin metabolites [11]. A shift from the PGE_2 towards the prostacyclin pathway has also been demonstrated in humans by pharmacological inhibition of mPGES-1 in phase 1 studies with LY3023703 [13] and vipoglanstat [12], where full shunting was already observed during the first day of treatment (Gesynta data on file). The explanation for increased prostacyclin synthesis following mPGES-1 inhibition is a shunting of excess amounts of PGH_2 to other pathways in the arachidonic acid cascade. The importance of this increased prostacyclin production has been demonstrated in studies on human vessels *in vitro*, which have shown that mPGES-1 inhibitors reduce vasomotor tone under various conditions. Different mPGES-1 inhibitors reduced adrenergic vasoconstriction in resistance arteries obtained from abdominal s.c. fat biopsies, the internal mammary artery, and the saphenous vein [22–24]. Furthermore, acetylcholine-induced dilatation in the resistance arteries increased when exposed to mPGES-1 inhibitors [24].

Vipoglanstat efficiently inhibited mPGES-1, as demonstrated by complete inhibition in whole blood. Systemic PGE_2 production, measured as urinary PGE_2 metabolite excretion, was reduced by 57%, indicating that other PGE synthases, important for homeostasis, were less affected (because 43% of PGE_2 production was still observed). As mentioned above, prostacyclin analogues improve RP symptoms [4, 5]

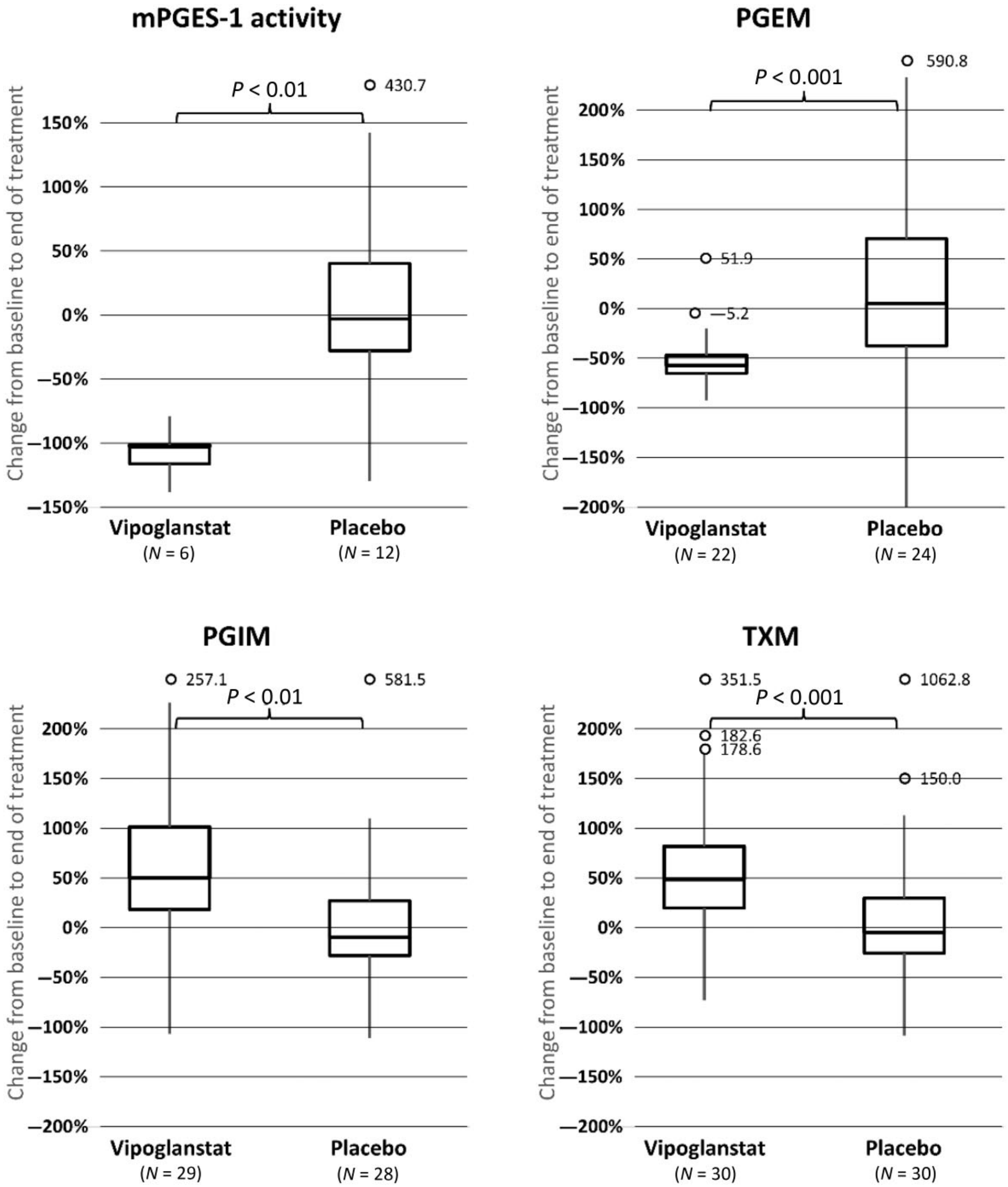

Figure 4. Change from baseline to end of treatment in prostaglandin E synthase-1 (mPGES-1) activity and excretion of arachidonic acid metabolites. mPGES-1 activity was assessed as prostaglandin E_2 (PGE_2) synthesis in a whole-blood assay. Urinary excretion of metabolites from PGE_2 (PGEM), prostacyclin (PGIM) and thromboxane (TXM) were analysed in morning urine before intake of study medication and was normalized to urinary creatinine concentration. For details, see material and methods section. Some samples could not be analysed for technical reasons; thus, the patient was excluded from metabolite analysis if either the visit 2 or visit 4 results were 'missing'. Box-whisker plot: The boxes indicate the intraquartile range (IQR) and the lines inside the boxes the median values. The whiskers indicate the range of values that are outside of the IQR in a distance $\leq 1.5 \times$ IQR. Any points outside the whiskers are considered to be outliers and are marked as circles. mPGES-1: prostaglandin E synthase-1; PGEM: metabolite derived from PGE_2; PGIM: metabolite derived from prostacyclin; TXM: metabolite derived from thromboxane

and rewarming after cold challenge [6] in patients with SSc. However, we could not observe any beneficial effects by increasing endogenous prostacyclin synthesis by 50%, as evaluated by urine metabolite excretion. The lack of effect could be due to levels of prostacyclin produced in the digital microvessels being too low. Prostacyclin has a biological half-life of about 1.5 min [25] and is thus active only at, or close to, the site of synthesis. Local levels of prostacyclin cannot be easily measured, and it is possible that the increased synthesis does not take place close enough to the finger microvessels. Although the treatment period was only 4 weeks, because of vipoglanstat's rapid onset of action any beneficial effect would have been expected to be observed within this timeframe. In conclusion, although vipoglanstat did not confer benefit in SSc-related RP, the study suggested that vipoglanstat was safe and well tolerated in a dose achieving full inhibition of mPGES-1, warranting its further evaluation in diseases where mPGES-1 plays a pathogenetic role.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The Sponsor will share de-identified individual participant data collected during the trial with researchers who provide a methodologically sound proposal.

Funding

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Consistent safety profile with over 8 years of real-world evidence, across licensed indications[1–3]

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8+ years of real-world evidence[1–3]

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Real-world evidence shows a consistent safety profile over 6 years[6,7]

No trend toward increased AE rates over time (pooled PsA, AS, PsO):†[6]

AEs of select interest (EAIR per 100 PY)	1 year	2 years	3 years	4 years	5 years	6 years	Cumulative rate
Serious infections	2.0	1.7	0.7	1.3	1.3	1.1	1.3
Cases	n=149	n=475	n=649	n=1,841	n=2,285	n=2,226	n=8,719
Malignant or unspecified tumours	0.2	0.2	0.2	0.3	0.3	0.3	0.3
Cases	n=15	n=50	n=225	n=422	n=520	n=573	n=1,896
MACE	0.2	0.1	0.2	0.2	0.2	0.1	0.2
Cases	n=15	n=39	n=151	n=238	n=264	n=287	n=1,031
Total IBD	0.2	0.2	0.2	0.3	0.2	0.1	0.2
Cases	n=12	n=46	n=185	n=340	n=312	n=261	n=1,291
Exposure (PY)	7450	28,549	93,744	137,325	182,024	212,636	680,470

Adapted from Novartis Data on File. 2021.[6]

No trend towards increased rates of malignancy, MACE or IBD over time[6]

The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[1,2] Refer to the prescribing information for a summary of adverse events.

Refer to the Cosentyx Summary of Product Characteristics for full details, dosing and administration, including special populations.

Cosentyx® (secukinumab) licensed indications in rheumatology: Cosentyx, alone or in combination with methotrexate, is indicated for the treatment of active **psoriatic arthritis** in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active **ankylosing spondylitis** in adults who have responded inadequately to conventional therapy; active **non-radiographic axial spondyloarthritis** with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active **enthesitis-related arthritis** in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate conventional therapy; active **juvenile psoriatic arthritis** in patients 6 years or older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[1,2]

Prescribing information, adverse event reporting and full indication can be found on the next page.

*Patients prescribed Cosentyx for any indication since launch.

†Successive time periods of PSUR shown with cumulative rate: 26 Dec 2014 to 25 Dec 2015; 26 Dec 2015 to 25 Dec 2016; 26 Dec 2016 to 25 Dec 2017; 26 Dec 2017 to 25 Dec 2018: 26 Dec 2018 to 25 Dec 2019; 26 Dec 2019 to 25 Dec 2020.[6]

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; EIAR, exposure-adjusted incidence rate; HCP, healthcare professional; IBD, inflammatory bowel disease; MACE, major adverse cardiac event; PsA, psoriatic arthritis; PsO, plaque psoriasis; PY, patient year.

References: 1. Cosentyx® (secukinumab) GB Summary of Product Characteristics; **2.** Cosentyx® (secukinumab) NI Summary of Product Characteristics; **3.** European Medicines Agency. European public assessment report. Available at: https://www.ema.europa.eu/en/documents/overview/cosentyx-epar-medicine-overview_en.pdf [Accessed February 2024]; **4.** Novartis Data on File. Secukinumab – Sec008. 2023; **5.** Novartis. Novartis Cosentyx® positive 16-week PREVENT results advance potential new indication for patients with axial spondyloarthritis. Available at: https://www.novartis.com/news/media-releases/novartis-cosentyx-positive-16-week-prevent-results-advance-potential-new-indication-patients-axial-spondyloarthritis [Accessed February 2024]; **6.** Novartis data on file. Cosentyx Periodic Safety Update Report (PSUR); 26 December 2019 – 25 December 2020. 22 February 2021; **7.** Deodhar A, et al. Arthritis Res Ther 2019;21(1):111.

NOVARTIS

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common* (≥1/10): Upper respiratory tract infection. *Common* (≥1/100 to <1/10): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions*: Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity*: Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** EU/1/14/980/005 - 150 mg pre-filled pen x2 £1,218.78; EU/1/14/980/010 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** May 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

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Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Cosentyx® (secukinumab) Great Britain Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 75mg and 150 mg pre-filled syringe and 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common (≥1/10):* Upper respiratory tract infection. *Common (≥1/100 to <1/10):* Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions*: Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity*: Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

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Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report.

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com