



BRIEF REPORT

# Nail Involvement as a Predictor of Differential Treatment Effects of Secukinumab Versus Ustekinumab in Patients with Moderate to Severe Psoriasis

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## ABSTRACT

**Introduction:** Patients with plaque psoriasis may experience varying levels of treatment response to different biologics, based on phenotypic characteristics and underlying genetic factors. Nail psoriasis is a common manifestation of psoriasis (approx. 50% of patients) and has been linked to the human leukocyte antigen-C\*0602 (HLA-C\*0602) allele, which in turn has been associated with differential treatment responses to certain drugs. Here we investigate whether nail involvement in patients with psoriasis can predict differential skin responses to two biologics with different modes of action, namely secukinumab (anti-interleukin-17A) and ustekinumab (anti-interleukin-12/23), to ultimately guide treatment choice.

**Methods:** Data were pooled from the CLEAR and CLARITY studies and stratified post hoc by

nail involvement status at baseline. Psoriasis Area and Severity Index (PASI) 75 and 90 responses over 52 weeks and absolute PASI  $\leq 3$ ,  $\leq 1$ , and 0 values at weeks 16 and 52, were assessed.

**Results:** Based on the medical history, 30.4% (269/886) of the patients in the secukinumab arm and 29.7% (265/891) of patients in the ustekinumab arm presented with nail involvement. Nail involvement status had little to no impact on the efficacy of secukinumab, as comparable responses were achieved for patients with and without nail involvement in terms of PASI 75/90,  $\leq 3$ , and 0 responses; slightly lower PASI  $\leq 1$  responses were achieved in patients with nail involvement. In the ustekinumab arm, patients with nail involvement achieved lower responses across all endpoints.

**Conclusions:** These findings indicate that nail involvement can serve as an observable prognostic factor for efficacy in skin psoriasis treatment and guide the choice between secukinumab and ustekinumab.

**Trial Registration:** CLEAR: NCT02074982; CLARITY: NCT02826603.

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**Keywords:** Psoriasis; Secukinumab;  
Ustekinumab; Nail involvement; Prognostic  
factor

## Key Summary Points

### Why carry out this study?

Evidence in the literature suggests that human leukocyte antigen-C\*0602 (HLA-C\*0602)-negative patients with psoriasis are less responsive to certain treatment and that nail psoriasis is a common manifestation of psoriasis and is linked to the HLA-C\*0602 allele.

Our aim was to determine whether nail involvement, which is associated with the HLA-C\*0602 allele, might be used to predict therapy response with secukinumab and ustekinumab using the pooled data from the phase 3b CLEAR and CLARITY trials.

### What has been learned from the study?

Secukinumab demonstrated overall higher efficacy than ustekinumab in psoriasis and nail involvement status had no significant impact on the efficacy of secukinumab, as comparable responses were achieved for patients with and without nail involvement in terms of Psoriasis Area and Severity Index (PASI) 75/90,  $\leq 3$ , and 0 responses; patients with nail involvement achieved lower responses across all endpoints in the ustekinumab arm.

Nail involvement can serve as an observable indicator to predict treatment responses and could help to guide decision-making on the choice of future treatment with secukinumab or ustekinumab.

## INTRODUCTION

Psoriasis is a chronic, T cell-mediated inflammatory skin disease. Plaque-type psoriasis, its most prevalent form, manifests as well-demarcated erythematous-squamous plaques on the skin [1]. The introduction of biologics for the therapeutic management of psoriasis has led to significant improvement in treatment responses. However, patients with psoriasis may respond differently to different biologics based on their phenotypic presentation, clinical characteristics, involvement areas, involved immune pathways and underlying genetic factors [2–4]. The human leukocyte antigen (HLA)-C\*0602 allele, which lies within the major histocompatibility complex (MHC) on chromosome 6, has been established as a psoriasis risk allele [5]. It impacts the disease course, phenotypic features, disease severity, associated comorbidities and treatment response [2]. Previous studies have demonstrated that HLA-C\*0602-negative patients are less responsive to methotrexate and ustekinumab [2, 6]. In contrast, a phase 3b, multicentre, prospective study demonstrated that secukinumab achieved similar clinical responses in both HLA-C\*0602-positive and HLA-C\*0602-negative patients, rendering determination of the HLA-C\*0602 status unnecessary for secukinumab [7].

Nail psoriasis, a common manifestation of psoriasis, is associated with functional impairment, psychosocial disability and reduced quality of life. It occurs in up to 50% of patients with psoriasis and in 70–80% of patients with psoriatic arthritis (PsA). It serves as a predictive factor for the development of PsA [8–10]. Interestingly, nail psoriasis is more common in HLA-C\*0602-negative patients [2, 8].

Therefore, with the aim of improving outcomes in psoriasis patients, we assessed the hypothesis of whether nail involvement, with its negative association with the HLA-C\*0602 allele, could act as an observable indicator to predict treatment response. This information could help to clinically stratify patients and provide informed treatment selection between the two commonly used biologics, secukinumab and ustekinumab.

## METHODS

### Study Design and Patients

CLEAR and CLARITY were phase 3b trials designed as 52-week, randomised, double-blind, active-controlled, parallel-group, superiority studies. In both studies, patients were randomised (1:1) to receive secukinumab 300 mg or ustekinumab 45 or 90 mg (according to body weight at baseline). Patients received secukinumab at baseline and weeks 1, 2, and 3, then every 4 weeks from weeks 4 to 48, or ustekinumab at baseline and week 4, and then every 12 weeks from weeks 16 to 40. Patient eligibility criteria, primary and secondary objectives, assessments, statistical analysis and results of both studies have been published [11, 12].

### Assessments

Data from patients were pooled from both studies, and demographics and disease characteristics, including psoriasis severity, as measured by the Psoriasis Area and Severity Index (PASI), were assessed at baseline. Nail involvement in patients was identified from the case report form (CRF) that included information on ongoing and previous occurrence of nail psoriasis. Patients were included based on the nail involvement status declared in their medical history regardless of active nail involvement at study entry.

Efficacy in the pooled dataset was evaluated by the number (%) of patients with reduction from baseline PASI  $\geq 75\%$  (PASI 75) and  $\geq 90\%$  (PASI 90), as well as the number (%) of patients achieving an absolute (total score) PASI of  $\leq 3$ ,  $\leq 1$ , and 0. PASI 75 and 90 scores were calculated over 52 weeks;  $\leq 3$ ,  $\leq 1$  and 0 values were assessed at weeks 16 and 52. Modified non-responder imputation was applied for analysis of PASI 75 and 90 outcomes. Analyses of PASI  $\leq 3$ ,  $\leq 1$  and 0 values were performed on observed data.

### Statistical Analysis

Patients from the full analysis sets of the CLEAR and CLARITY studies were included. Categorical variables were expressed as counts and percentages. Continuous variables were presented as mean  $\pm$  standard deviation. As the current analyses were exploratory, no tests for statistical significance were performed. The 95% confidence interval values are presented for all efficacy assessments.

### Ethics Compliance

The CLEAR (NCT02074982) and CLARITY (NCT02826603) studies were conducted in accordance with the ethical principles of the Declaration of Helsinki at all the sites worldwide. Informed consent was obtained from all individual participants included in both studies. The protocols of both CLEAR (NCT02074982) and CLARITY (NCT02826603) studies were approved by the independent ethics committee/institutional review board of each center [11, 12].

## RESULTS

Overall, 886 and 891 patients received secukinumab and ustekinumab, respectively; among whom 269 (30.4%) and 265 (29.7%) patients had a history of nail involvement in the secukinumab and ustekinumab arms, respectively. Of those with a history of nail involvement, nine and four patients in the secukinumab and ustekinumab arms, respectively, did not have ongoing nail psoriasis at study entry; for the subsequent analyses, these patients were included in the group with nail involvement. The baseline demographic and disease characteristics are shown in Table 1.

At baseline, patients with nail involvement had a longer disease duration (secukinumab 20.5 years; ustekinumab 17.3 years) than those without nail involvement (16.6 years in both arms). A higher proportion of patients with nail involvement had PsA (secukinumab 29.0%; ustekinumab 24.2%) than those without

(secukinumab 16.5%; ustekinumab 16.1%) (Table 1).

Regardless of nail involvement, a higher percentage of secukinumab-treated patients versus those treated with ustekinumab attained PASI 75 and 90 responses over 52 weeks (Fig. 1). No significant impact of nail involvement was observed on the efficacy of secukinumab as a similar percentage of patients with and without nail involvement reached PASI 75 and 90 responses (Fig. 1). However, a higher proportion of ustekinumab-treated patients without nail involvement achieved PASI 75 and 90 scores than patients with nail involvement over 52 weeks (Fig. 1).

At weeks 16 and 52, secukinumab-treated patients showed higher PASI  $\leq 3$  responses

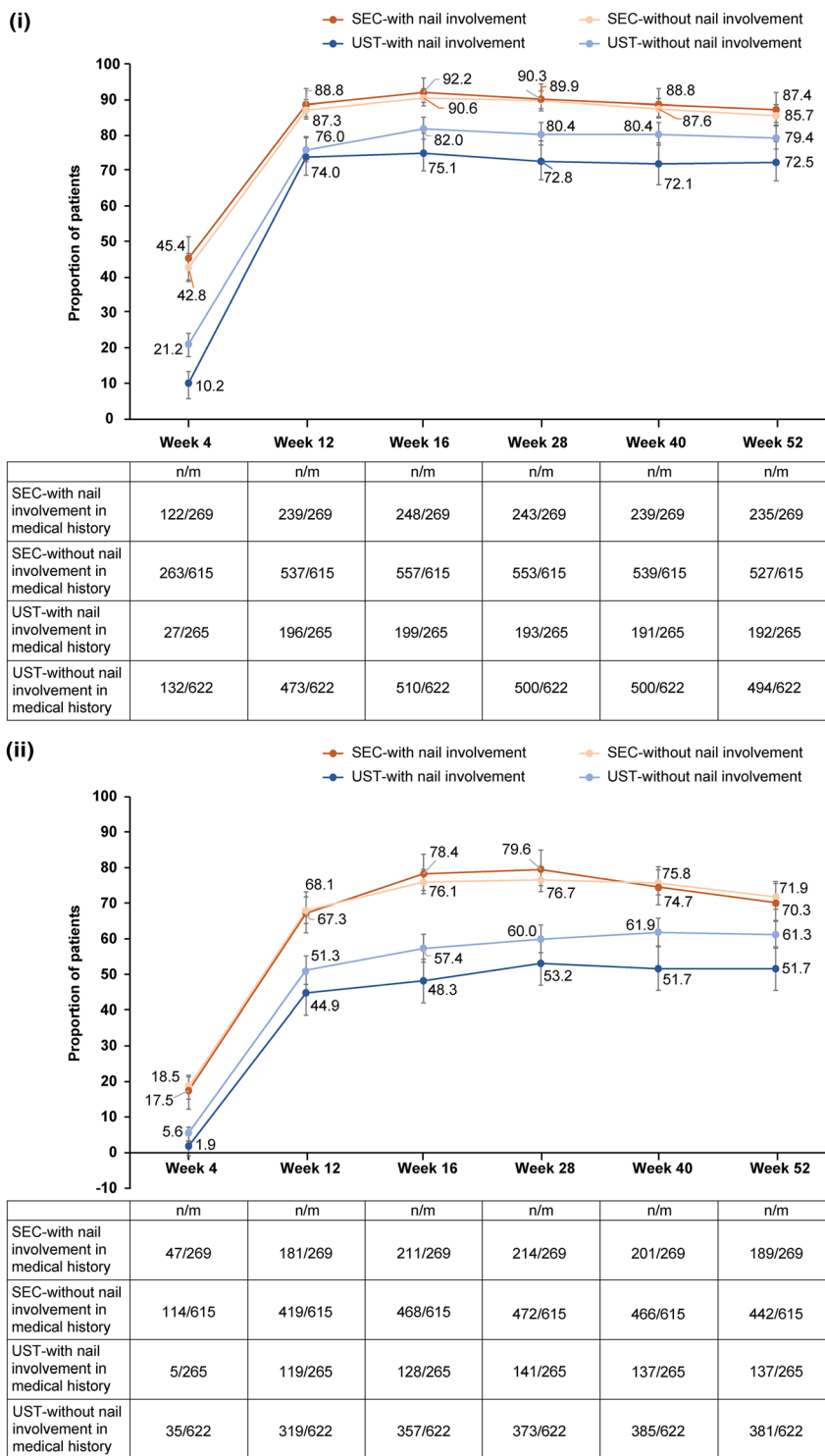
compared with ustekinumab-treated patients, regardless of nail involvement (Fig. 2). Within the secukinumab arm, PASI  $\leq 3$  responses were comparable in patients with (week 16: 87.2%; week 52: 83.4%) and without (week 16: 87.0%; week 52: 86.0%) nail involvement (Fig. 2). In the ustekinumab arm, higher PASI  $\leq 3$  responses were observed in patients without nail involvement (week 16: 71.3%; week 52: 75.8%) than patients with nail involvement (week 16: 64.6%; week 52: 68.7%) (Fig. 2). At weeks 16 and 52, differential efficacy was observed in PASI  $\leq 1$  response; however, the difference between the groups with and without nail involvement was less pronounced in the secukinumab arm (Fig. 2). PASI 0 responses at weeks 16 and 52 are presented in Fig. 2.

**Table 1** Baseline patient demographics and disease characteristics

Demographic/disease characteristics	SEC nails Y ( <i>n</i> = 269) <sup>a</sup>	SEC nails N ( <i>n</i> = 617)	SEC all ( <i>N</i> = 886)	UST nails Y ( <i>n</i> = 265) <sup>a</sup>	UST nails N ( <i>n</i> = 626)	UST all ( <i>N</i> = 891)
Age (years), mean $\pm$ SD	45.4 $\pm$ 13.3	45.2 $\pm$ 14.4	45.3 $\pm$ 14.0	44.8 $\pm$ 12.7	45.1 $\pm$ 14.5	45.0 $\pm$ 14.0
Gender male, <i>n</i> (%)	188 (69.9)	396 (64.2)	584 (65.9)	204 (77.0)	424 (67.7)	628 (70.5)
Race, <i>n</i> (%)						
Caucasian	222 (82.5)	494 (80.1)	716 (80.8)	201 (75.8)	497 (79.4)	698 (78.3)
Black	2 (0.7)	23 (3.7)	25 (2.8)	5 (1.9)	20 (3.2)	25 (2.8)
Asian	32 (11.9)	51 (8.3)	83 (9.4)	45 (17.0)	51 (8.1)	96 (10.8)
Other	13 (4.9)	49 (7.9)	62 (7.0)	14 (5.3)	58 (9.3)	72 (8.1)
Weight (kg), mean $\pm$ SD	90.2 $\pm$ 23.5	89.3 $\pm$ 23.0	89.6 $\pm$ 23.2	90.3 $\pm$ 24.2	90.9 $\pm$ 23.9	90.7 $\pm$ 23.9
Baseline PASI, mean $\pm$ SD	21.9 $\pm$ 8.7	20.8 $\pm$ 8.8	21.1 $\pm$ 8.9	21.7 $\pm$ 8.5	21.2 $\pm$ 8.9	21.4 $\pm$ 8.8
Time since first PsO diagnosis (years), mean $\pm$ SD	20.5 $\pm$ 12.9	16.6 $\pm$ 11.9	17.8 $\pm$ 12.3	17.3 $\pm$ 11.9	16.6 $\pm$ 12.8	16.8 $\pm$ 12.5
Diagnosis of PsA, <i>n</i> (%)	78 (29.0)	102 (16.5)	180 (20.3)	64 (24.2)	101 (16.1)	165 (18.5)
Previous exposure to biologic therapy, <i>n</i> (%)	48 (17.8)	109 (17.7)	157 (17.7)	55 (20.8)	120 (19.2)	175 (19.6)

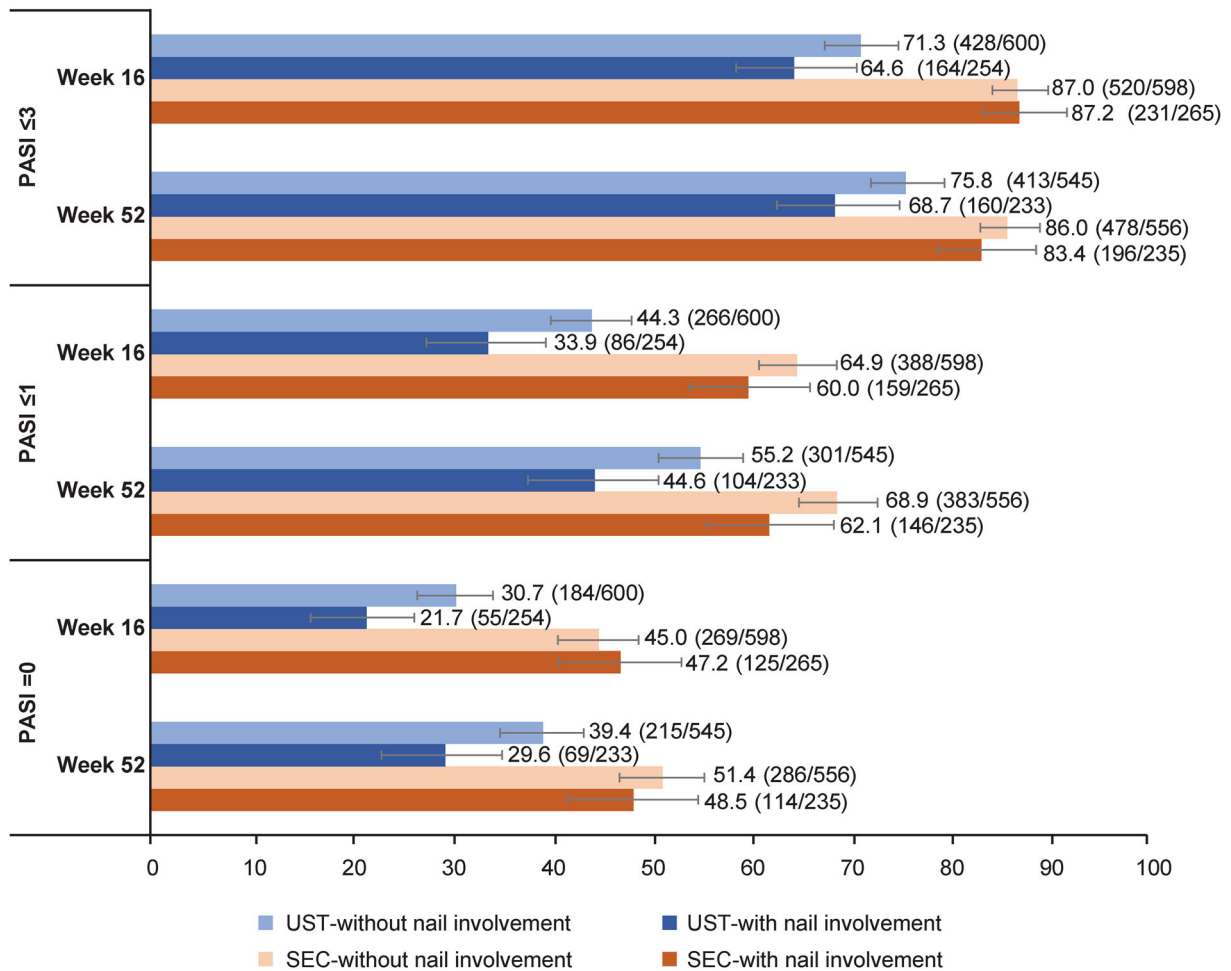
*nails Y* Patients with nail involvement in medical history, *nails N* patients without nail involvement in medical history, *N* total number of evaluable patients, *n* number of evaluable patients, *PASI* Psoriasis Area Severity Index, *PsA* psoriatic arthritis, *PsO* psoriasis, *SD* standard deviation, *SEC* secukinumab, *UST* ustekinumab

<sup>a</sup>In the secukinumab group, 269 patients reported nail psoriasis in their medical history; for 9 patients it was not ongoing at study entry. In the ustekinumab group, 265 patients reported nail psoriasis in their medical history; for 4 patients it was not ongoing at study entry



**Fig. 1** Proportion of patients (95% confidence interval) by treatment group and nail involvement status with PASI 75 (i) and PASI 90 (ii) response by visit (based on modified non-responder imputation). *m* Total number of patients in

the treatment arm, *n* number of patients with response, *PASI* 75/90  $\geq$  75% and  $\geq$  90% reduction from baseline in Psoriasis Area and Severity Index score, *SEC* secukinumab, *UST* ustekinumab



**Fig. 2** Proportion of patients (95% confidence interval) by treatment group and nail involvement status with absolute (total score) PASI  $\leq 3$ ,  $\leq 1$  and 0 response by visit (based

on observed data). *PASI* Psoriasis Area and Severity Index, *SEC* secukinumab, *UST* ustekinumab

## DISCUSSION

In this study, we show that secukinumab demonstrated overall higher efficacy than ustekinumab in psoriasis and provided similar response rates in patients with and without nail involvement. However, among ustekinumab-treated patients, nail involvement was associated with reduced PASI responses, suggesting that nail psoriasis acts a predictor of inferior skin response to ustekinumab. Thus, when nail involvement was considered, secukinumab provided a disproportionately better clinical outcome than ustekinumab. These findings suggest that secukinumab should be favoured

for the treatment of skin psoriasis in patients with nail involvement.

HLA-C\*0602 has previously been identified as a pharmacogenetic marker predicting superior response to ustekinumab in HLA-C\*0602-positive patients [6]. Nail psoriasis, however, is more frequent in HLA-C\*0602-negative patients [2, 8]. Accordingly, the finding that patients with nail involvement have a disproportionately inferior predicted outcome with ustekinumab compared to secukinumab might also be linked to the HLA-C\*0602-status. This hypothesis is further supported by the fact that the HLA-C\*0602-status, just like nail involvement, does not have an influence on the efficacy of secukinumab.

The results of this study also suggest that the predominant pathogenic inflammatory pathways differ in psoriasis patients with and without nail involvement. One intriguing possibility is that early-onset psoriasis, which is associated with the HLA-C\*0602 allele, is triggered by autoantigens that are presented to T cells in the context of the MHC-I HLA-C\*0602. Indeed, two autoantigens, LL37 and ADAMTS-like protein 5 (ADAMTSL5), have recently been shown to activate autoreactive CD8 + T cells in a HLA-C\*0602-dependent manner [13, 14]. Moreover, intraepidermal CD8 + T cells producing interleukin (IL)-17, which have been identified as a key effector cells in psoriasis, are highly dependent on IL-23 [15, 16]. Hence, the inhibition of the pathogenic T cell response via IL-23 blockade could explain why ustekinumab shows an increased efficacy in HLA-C\*0602-positive patients and, in turn, in psoriasis patients without nail involvement. A recent study showed that activated T cells within the entheses are able to secrete IL-17 without the need for additional IL-23 stimulation [17]. Considering similar pathogenic mechanisms in the skin, such as in the entheses, this could explain the lower response rates of ustekinumab in patients with nail psoriasis.

The nail apparatus indeed represents a link between the skin disease and the joint involvement in psoriasis as it is an integral part of both the skin and the entheses organ [18]. The association of nail psoriasis with PsA is well established and predicts future development of PsA [8–10]. IL-17 blockers represent the current gold standard in patients with both relevant skin and joint disease, as they have shown the same efficacy as anti-tumor necrosis factors (TNFs) in the treatment of PsA but were superior in achieving combined skin and joint improvements [19]. Based on indirect comparisons, ustekinumab is associated with lower response rates in PsA than TNF- and IL-17 blockers [20]. Therefore, nail involvement as a predictor for PsA could support the use of anti-IL-17s based on their more robust efficacy in PsA. Moreover, we show here that nail psoriasis serves as an observable prognostic factor for treatment efficacy in skin psoriasis, suggesting

that secukinumab should be preferred over ustekinumab in patients with nail involvement.

The current study is limited by its post hoc nature and the limitations intrinsic to any retrospective analysis. An additional limitation of the current analysis was that the assessment of severity and type of nail involvement and Nail Psoriasis Severity Index measurement was not performed in the study. Furthermore, the results with respect to the HLA-C\*0602 allele should be interpreted with caution as HLA-C\*0602 status of patients was not assessed.

## CONCLUSION

The results from the large dataset reported that nail involvement in psoriasis patients could act as an accessible and readily observable indicator to predict treatment responses. This information has clinically relevant implications and could facilitate clinical stratification and guide the treatment choice between secukinumab and ustekinumab.

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**Compliance with Ethics Guidelines.** The CLEAR (NCT02074982) and CLARITY (NCT02826603) studies were conducted in accordance with the ethical principles of the Declaration of Helsinki at all the sites worldwide. Informed consent was obtained from all individual participants included in both studies. The protocols of both CLEAR (NCT02074982) and CLARITY (NCT02826603) studies were approved by the independent ethics committee/institutional review board of each center [11, 12]

**Data Availability.** The datasets generated and/or analysed during the current study are not publicly available. Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The data may be requested from the corresponding author of the manuscript.

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