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Claus ZACHARIAE[1]
Ulrich MROWIETZ[2]
Jens STRODL ANDERSEN[3]
Lluís PUIG[4]

[1] Department of Dermatology and Allergy, Copenhagen University Hospital–Gentofte, Gentofte Hospitalsvej 15, 2900 Hellerup, Copenhagen, Denmark & Department of Clinical Medicine, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen N, Denmark
[2] Department of Dermatology, University Medical Center Schleswig-Holstein, Arnold-Heller-Straße 3, 24105 Kiel, Germany
[3] LEO Pharma, Industriparken 55, 2750 Ballerup, Denmark
[4] Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Carrer de Sant Quintí, 89, 08041 Barcelona, Spain

Reprints: Claus Zachariae <Claus.Zachariae@regionh.dk>

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Multistate modelling of probability of on-treatment clinical response and time remaining in response in patients with moderate-to-severe psoriasis treated with brodalumab or ustekinumab in the AMAGINE-2 and -3 studies

Background: Relative changes in Psoriasis Area and Severity Index (PASI) are used as outcomes in psoriasis clinical trials but are limited when analysing long-term data and in routine practice. Absolute PASI may be more clinically useful. *Objectives:* To develop and implement a methodology for assessing the probability of achieving and maintaining a "response" in patients with psoriasis, defined using absolute PASI. *Materials & Methods:* This analysis included pooled data from the Phase III AMAGINE-2 and -3 trials. Absolute PASI was described using all available data. Multistate modelling was used to compare the probabilities of achieving (absolute PASI = 0) and maintaining (absolute PASI $\leq$2) a response, and the time in the response state, in patients receiving brodalumab *vs* ustekinumab. *Results:* Higher proportions of patients achieved lower absolute PASI over 52 weeks with brodalumab *vs* ustekinumab. The probability of achieving the response state was greater with brodalumab *vs* ustekinumab over 52 weeks (hazard ratio: 1.96; 95% confidence interval [CI]: 1.66–2.31, $p < 0.001$). At Week 52, there was a higher probability of being in response with brodalumab vs ustekinumab (81% [95% CI: 74-89%] vs 60% [95% CI: 54-67%], respectively). Mean time in response was longer with brodalumab (215 days; 95% CI: 197–233) *vs* ustekinumab (145 days; 95% CI: 130–160); a difference of 70 days (95% CI: 46–94; $p < 0.001$). *Conclusion:* Using a novel multistate modelling approach based on absolute PASI, we found that patients had a greater probability of achieving and maintaining a response with brodalumab *vs* ustekinumab.

Key words: absolute PASI, brodalumab, interleukin-17, psoriasis, response, ustekinumab

Psoriasis is a chronic, disfiguring, systemic inflammatory disease of the skin, affecting 2-3% of the Western population [1]. Approximately 20% of patients with psoriasis have moderate-to-severe disease, defined by the extent of body surface area (BSA) affected and the involvement of specific body regions (*e.g.* hands, feet, face, genitals), which may significantly impact health-related quality of life (QoL) [2, 3]. Disease severity can be influenced by seasonal variation (*e.g.* there is a greater likelihood of flares during winter than summer) [4] and psychological triggers (*e.g.* stress, anxiety, and depression) [5]. In recent years, substantial advances have been made in the treatment of plaque psoriasis, with the introduction of biologic therapies, including inhibitors of tumour necrosis factor-α, interleukin (IL)-12/23, IL-17 and IL-23 [6, 7].

Brodalumab is a fully human monoclonal antibody that targets the IL-17 receptor A subunit, and thereby inhibits downstream signalling of multiple IL-17 family cytokines involved in the pathogenesis of psoriasis, including IL-17A, IL-17A/F, IL-17C, IL-17E and IL-17F [8-10]. Phase III trials have shown that brodalumab treatment achieves high levels of skin clearance for up to 52 weeks in patients with moderate-to-severe psoriasis [11, 12]. Brodalumab is approved in the US and EU for the treatment of adults with moderate-to-severe plaque psoriasis [13, 14].

The Psoriasis Area and Severity Index (PASI) is a widely used tool for measuring the severity and extent of psoriasis, which accounts for the intensity of erythema, desquamation, and induration present as well as the percentage of BSA involved on the head, trunk, and upper and lower limbs [15, 16]. A high clinical response can be defined as achieving 75, 90, or 100% improvement in PASI relative to baseline (PASI 75, 90, or 100, respectively). However, there are limitations associated with the use of relative PASI measures. Relative PASI requires the baseline disease status to be known - something that may be unknown in routine

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clinical practice [17]. Likewise, patients undergoing clinical care often switch between psoriasis treatments without undergoing a washout period (*e.g.* when switching due to reasons associated with efficacy) [18]. Some patients, especially those with moderate-to-severe psoriasis, may achieve PASI 75 or 90 but still have disease activity that has a significant impact on their health-related QoL [19]. The PASI lacks sensitivity in patients with mild psoriasis [20]. In addition, due to the chronic nature of psoriasis, a patient's original baseline PASI becomes less relevant when assessing response to therapy over time.

As a treatment target, absolute PASI has the advantage over relative PASI of being indicative of the individual patient's disease severity at the time of analysis, independent of baseline PASI [19]. Therefore, absolute PASI is more appropriate for the long-term evaluation of treatment efficacy, as it allows for more accurate assessment of fluctuations in disease severity over time. Absolute PASI scores have been proposed and evaluated for their utility in determining the effectiveness of new treatments, but currently no consensus on the optimal target absolute PASI has been reached [17, 19]. However, studies have shown that a higher QoL is achieved more often in patients with low absolute PASI, and absolute PASI ≤2 has been recognized by some guidelines as a possible treatment goal that is indicative of minimal disease activity [21].

Although multistate modelling has been applied to a broad range of medical conditions, including the progression of psoriasis [22-25], it has not yet been utilized to describe response to biologic treatment in psoriasis. In this post hoc analysis of the AMAGINE-2 and AMAGINE-3 trials, we describe absolute PASI outcomes and treatment differences with brodalumab *versus* ustekinumab over 52 weeks in patients with moderate-to-severe psoriasis using a multistate modelling methodology developed to assess the probability of achieving and maintaining a state of on-treatment response, defined using a novel responder definition based on absolute PASI.

Materials and methods

Data were pooled from two Phase III randomized, double-blind, placebo- and ustekinumab-controlled, 52-week trials of brodalumab (AMAGINE-2 [NCT01708603] and AMAGINE -3 [NCT01708629]) [11]. Detailed descriptions of the AMAGINE trial designs have been previously published [11] and are illustrated in *supplementary figure 1*. In brief, both trials enrolled patients ≥18 years of age with moderate-to-severe plaque psoriasis, defined as PASI ≥12, static Physician's Global Assessment (sPGA) ≥3 and ≥10% BSA involvement, with a minimum of six months' duration. Patients were randomized 2:2:1:1 to initially receive subcutaneous brodalumab 210 mg, brodalumab 140 mg or placebo on Day 1 and Weeks 1, 2, 4, 6, 8 and 10; or ustekinumab 45 or 90 mg (dependent on body weight ≤100 or >100 kg) on Day 1, Week 4 and every 12 weeks (Q12W) thereafter. At Week 12, brodalumab patients were re-randomized at 2:2:2:1 to receive a brodalumab maintenance dose of 210 mg every two weeks (Q2W) or 140 mg Q2W, every four weeks or every eight weeks, while ustekinumab patients continued to receive ustekinumab Q12W and placebo patients were switched to brodalumab 210 mg Q2W. This post hoc analysis used data from patients who had consistently received either brodalumab 210 mg (on Day 1, Week 1, 2, then Q2W) or ustekinumab 45 or 90 mg (on Day 1, Week 4, then Q12W) for the entire 52-week treatment period.

Patients were eligible for rescue treatment if they had an inadequate response (defined as sPGA ≥3 or persistent values of 2 over a ≥4-week period at or after Week 16). At Week 16, all patients who had not responded received a rescue treatment with brodalumab 210 mg. After Week 16 and through to Week 52, patients on brodalumab were rescued with brodalumab 210 mg Q2W, while those on ustekinumab remained on ustekinumab. Rescue treatment was blinded. After receiving rescue treatment for ≥12 weeks,

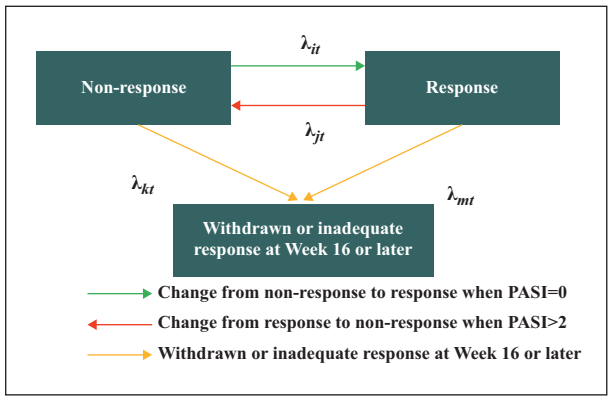

Figure 1. Multistate model framework to calculate the probability of being in response (entry criteria: absolute PASI = 0, exit criteria PASI >2).
λ = transition probabilities; i = ith transition from non-response to response; j = jth transition from response to non-response; k = the transition from non-response to withdrawn; m = the transition from non-response to withdrawn; t = time. PASI: Psoriasis Area and Severity Index.

Table 1. Demographic and baseline characteristics.

Baseline characteristic	Brodalumab (*n* = 339)	Ustekinumab (*n* = 590)
Male, *n* (%)	230 (67.8)	404 (68.5)
Caucasian, *n* (%)	308 (90.9)	532 (90.2)
Age, years	44.5 (±13.4)	45.1 (±13.0)
Weight, kg	90.4 (±24.2)	91.0 (±22.9)
Duration of disease, years	17.3 (±11.7)	18.6 (±12.2)
BSA, % involvement	27.9 (±16.2)	27.6 (±18.6)
PASI	20.4 (±7.9)	20.0 (±8.4)
DLQI	14.8 (±7.3)	14.9 (±7.3)
NAPSI	9.3 (±3.6)	9.9 (±3.6)
PSI	19.1 (±7.0)	18.7 (±6.9)
PsA, *n* (%)	79 (23.3)	110 (18.6)
Prior biologic use, *n* (%)	96 (28.3)	156 (26.4)
Prior biologic failure, *n* (%)	46 (13.6)	61 (10.3)

BSA: body surface area; DLQI: Dermatology Life Quality Index; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; PSI: Psoriasis Symptom Inventory; SD: standard deviation. Values are presented as mean ± SD unless otherwise stated.

patients were assessed for non-response and were discontinued if they were non-responders.

PASI assessment

PASI assessments were performed at least once every 2–4 weeks. Absolute PASI (range: 0–72) was calculated as a combined score for head, arms, trunk and legs. Each section was graded (0–6) by percentage area of skin, and severity (0–4) for each area was estimated by erythema, induration and desquamation. The sum of all three severity parameters was multiplied by the respective area score, and weighted by respective section (0.1 for head, 0.2 for arms, 0.3 for trunk and 0.4 for legs) [15].

Statistical analyses

Baseline demographics and disease characteristics were summarized for each treatment group. A visual descriptive summary was generated of proportion of patients with absolute PASI of: 0, >0 and ≤1, >1 and ≤2, >2 and ≤3, >3 and ≤4, >4 and ≤5, and >5, as well as rescue (equivalent to inadequate response) and missing data over 52 weeks in brodalumab and ustekinumab groups. The proportions of patients with specific absolute PASI scores in the brodalumab and ustekinumab groups over 52 weeks were determined using observed data.

The probability of achieving on-treatment response over time was estimated using multistate modelling, a technique that estimates the transition probabilities (λ) of a group of patients moving between discrete states, which can vary over time and between treatments. Transitions are possible between non-response and response. The rescue or withdrawal state is an absorbing state. All subjects start in the non-response state 1 (S[t = 0] = 1). Possible transitions are illustrated in *figure 1*. The model used was a time-homogeneous continuous-time Markov model. In this model, exact transition times are assumed, meaning that the state at the previous observation is retained until the current observation. The observation scheme is a combination of fixed and patient self-selection; namely, patients are observed at fixed visits specified in advance, but patients may decide to visit their doctor on occasions when they are in a poor condition. Modelling was performed using RStudio Version 1.1.463 64-bit R-3.5.2, mstate package Version 0.2.11 software.

Results

A total of 929 patients (brodalumab 210 mg, $n = 339$; ustekinumab, $n = 590$) were included in this analysis. Demographics and baseline characteristics were generally balanced between treatment groups (*table 1*). The mean age of patients was approximately 45 years and the baseline PASI was 20. Approximately two-thirds of patients were male, and one-quarter had received prior treatment with biologics.

Analysis of observed data showed that the proportions of patients achieving absolute PASI of: 0, between >0 and ≤1, between >1 and ≤2, between >2 and ≤3, between >3 and ≤4, and between >4 and ≤5 were higher in the brodalumab group compared with ustekinumab over the 52 weeks and were sustained through the 52 weeks (*figure 2*). The odds of patients having absolute PASI 0 or >0 to ≤1 were significantly in favour of brodalumab from Week 4 ($p < 0.001$) and sustained up to Week 52 (*figure 3*). In contrast, the ustekinumab group exhibited significantly higher odds of an inadequate response *versus* brodalumab from Week 16 ($p < 0.001$). The proportion of patients on rescue treatment was lower in the brodalumab group over time compared with ustekinumab.

Using multistate modelling, the probability of entering the response state was significantly greater with brodalumab compared with ustekinumab (hazard ratio [HR] = 1.96; 95%

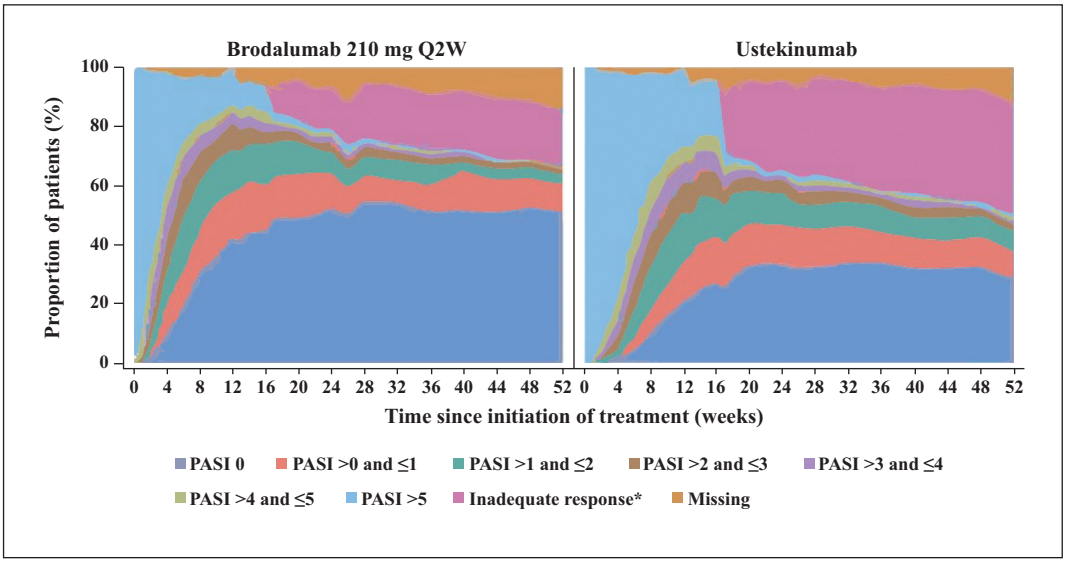

Figure 2. Proportion of patients achieving specific absolute PASI scores over 52 weeks in the brodalumab and ustekinumab treatment groups.

*PASI: Psoriasis Area and Severity Index; Q2W, every 2 weeks. *Defined as static Physician's Global Assessment (range 0–5) ≥3 or persistent values of 2 over at least a four-week period at or after Week 16.*

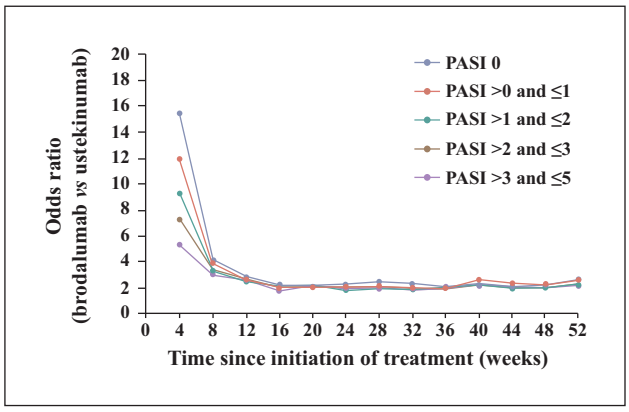

Figure 3. Odds ratios for achieving specific absolute PASI scores over 52 weeks for brodalumab *versus* ustekinumab.
PASI: Psoriasis Area and Severity Index.

confidence interval [CI]: 1.66–2.31, $p < 0.001$). The probability of being in the response state over 52 weeks was higher with brodalumab *versus* ustekinumab; at Week 52, the probability was 81% (95% CI: 74–89%) *versus* 60% (95% CI: 54–67%) (*figure 4A*). At Week 52, the estimated absolute difference in the probability of being in the response state reached 21 percentage points (95% CI: 11–30) in favour of brodalumab (*figure 4B*), which was sustained from Day 120. The estimated mean time spent in the response state was longer with brodalumab (215 days; 95% CI: 197–233) compared with ustekinumab (145 days; 95% CI: 130–160). The estimated difference in length of stay in the response state between groups was 70 days (95% CI: 46–94; $p < 0.001$) in favour of brodalumab.

Discussion

In this *post hoc* analysis of data from the AMAGINE-2 and -3 trials, lower absolute PASI was achieved with brodalumab compared with ustekinumab and was maintained over time. We assessed drug efficacy in terms of absolute PASI and our findings further support the primary results of the AMAGINE-2 and -3 trials and a recent meta-analysis that demonstrated a treatment benefit for brodalumab compared with ustekinumab [11, 12]. Despite the widespread use of relative PASI measures in clinical trials, they possess several limitations that impact their translation into clinical practice [19]. The benefits of using absolute PASI, as per this analysis, include the ability to indicate a patient's current disease severity, independent of baseline PASI. Absolute PASI has also been found to correlate with health-related QoL to a similar degree as relative PASI measures [26]. Consequently, absolute PASI represents a new potential therapeutic target that provides more clinically relevant information about disease severity [19, 27].
This is the first analysis of response to biologic treatment in psoriasis using multistate modelling. The definition of response used in this analysis has the advantage of accounting for the fluctuating course of psoriasis and potential variations in disease assessment over time while staying within proposed goals for absolute PASI indicated by cur-

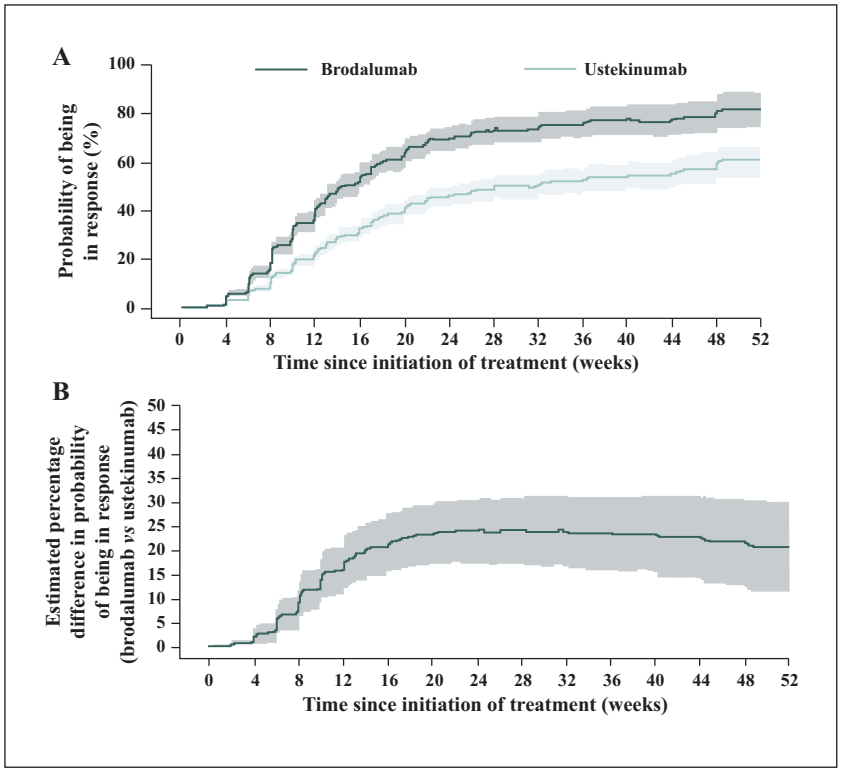

Figure 4. Probability of being in response (achieving absolute PASI of 0 and remaining ≤2) (**A**) and difference in probability of being in response over time between the brodalumab *versus* ustekinumab group (**B**).
PASI: Psoriasis Area and Severity Index. Shaded area represents the 95% confidence interval.

rent guidelines [28]. Using our model, we have shown that treatment with brodalumab was associated with a significantly higher probability of achieving and maintaining complete response and a significantly longer total time spent in a response state *versus* ustekinumab. Using multistate modelling to estimate the probability of achieving and maintaining on-treatment response represents a potential highly clinically relevant measure for evaluating treatment response for psoriasis, both during clinical trials and in routine practice.

This analysis has certain limitations, many arising from its *post hoc* nature. The AMAGINE trials were not designed to investigate these endpoints, and the constraint to use data only from patients who received a constant treatment regimen over 52 weeks reduced the pool of available data. In addition, the strictness of the model's defined entry criteria (absolute PASI = 0) may have excluded individuals who showed significant improvements overall. For example, individuals who achieved a low absolute PASI (*e.g.* between >0 and ≤ 2), but not an absolute PASI = 0, would never be defined as achieving complete response despite likely responding to treatment. Lastly, the clinical trial population used for this analysis may limit the generalisability of our conclusions to the broader patient population encountered in routine practice.

In conclusion, these results demonstrate that consistently lower absolute PASI was achieved and maintained with brodalumab *versus* ustekinumab in the AMAGINE-2 and -3 trials. Furthermore, we demonstrate that brodalumab was associated with a higher probability of achieving response and maintaining a response over time, as well as a longer time spent in response *versus* ustekinumab over 52 weeks of treatment, in patients with moderate-to-severe psoriasis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1684/ejd.2022.4304.
Supplementary figure 1 Study designs for the Phase III randomized controlled AMAGINE-2 and AMAGINE-3 trials of brodalumab in patients with moderate-to-severe psoriasis.
Q2W: every two weeks; Q4W: every four weeks; Q8W: every eight weeks; R: randomization.

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