Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials

Kristian Reich, Kim A Papp, Andrew Blauvelt, Stephen K Tyring, Rodney Sinclair, Diamant Thaçi, Kristine Nograles, Anish Mehta, Nicole Cichanowitz, Qing Li, Kenneth Liu, Carmen La Rosa, Stuart Green, Alexa B Kimball

Lancet 2017; 390: 276–88

Published Online June 5, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31279-5

See Comment page 208

This online publication has been corrected. The corrected version first appeared at thelancet.com on July 13, 2017

SCIderm Research Institute and Dermatologikum Hamburg, Hamburg, Germany (Prof K Reich MD); Probity Medical Research, Waterloo, ON, Canada (K A Papp MD); Oregon Medical Research Center, Portland, OR, USA (A Blauvelt MD); Department of Dermatology, University of Texas Health Science Center, Houston, TX, USA (Prof S K Tyring MD); Epworth Hospital Department of Dermatology, University of Melbourne, Melbourne, VIC, Australia (Prof R Sinclair MD); Comprehensive Center for Inflammation Medicine, University Medical School Schleswig-Holstein, University of Lübeck, Lübeck, Germany (Prof D Thaçi MD); Merck & Co, Kenilworth, NJ, USA (K Nograles MD, A Mehta BA, N Cichanowitz MSJ, Q Li PhD, K Liu PhD, C La Rosa MD, S Green MD); and Harvard Medical School, Boston, MA, USA (Prof A B Kimball MD)

Correspondence to: Prof Kristian Reich, Dermatologikum Hamburg, Stephansplatz 5, Hamburg 20354, Germany kreich@dermatologikum.de

Summary

Background Tildrakizumab is a high-affinity, humanised, IgG1 κ antibody targeting interleukin 23 p19 that represents an evolving treatment strategy in chronic plaque psoriasis. Previous research suggested clinical improvement with inhibition of interleukin 23 p19. We did two phase 3 trials to investigate whether tildrakizumab is superior to placebo and etanercept in the treatment of chronic plaque psoriasis.

Methods We did two three-part, parallel group, double-blind, randomised controlled studies, reSURFACE 1 (at 118 sites in Australia, Canada, Japan, the UK, and the USA) and reSURFACE 2 (at 132 sites in Europe, Israel, and the USA). Participants aged 18 years or older with moderate-to-severe chronic plaque psoriasis (body surface area involvement ≥10%, Physician's Global Assessment [PGA] score ≥3, and Psoriasis Area and Severity Index [PASI] score ≥12) were randomised (via interactive voice and web response system) to tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo in reSURFACE 1 (2:2:1), or to tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg (2:2:1:2). Randomisation was done by region and stratified for bodyweight (≤90 kg or >90 kg) and previous exposure to biologics therapy for psoriasis. Investigators, participants, and study personnel were blinded to group allocation and remained blinded until completion of the studies. Assigned medication was identical in appearance and packaging. Tildrakizumab was administered subcutaneously at weeks 0 and 4 during part 1 and at week 16 during part 2 (weeks 12 and 16 for participants re-randomised from placebo to tildrakizumab; etanercept was given twice weekly in part 1 of reSURFACE 2 and once weekly during part 2). The co-primary endpoints were the proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥2 grade score reduction from baseline) at week 12. Safety was assessed in the all-participants-as-treated population, and efficacy in the full-analysis set. These trials are registered with ClinicalTrials.gov, numbers NCT01722331 (reSURFACE 1) and NCT01729754 (reSURFACE 2). These studies are completed, but extension studies are ongoing.

Findings reSURFACE 1 ran from Dec 10, 2012, to Oct 28, 2015. reSURFACE 2 ran from Feb 12, 2013, to Sept 28, 2015. In reSURFACE 1, 772 patients were randomly assigned, 308 to tildrakizumab 200 mg, 309 to tildrakizumab 100 mg, and 155 to placebo. At week 12, 192 patients (62%) in the 200 mg group and 197 patients (64%) in the 100 mg group achieved PASI 75, compared with 9 patients (6%) in the placebo group ($p<0·0001$ for comparisons of both tildrakizumab groups *vs* placebo). 182 patients (59%) in the 200 mg group and 179 patients (58%) in the 100 mg group achieved PGA responses, compared with 11 patients (7%) in the placebo group ($p<0·0001$ for comparisons of both tildrakizumab groups *vs* placebo). In reSURFACE 2, 1090 patients were randomly assigned, 314 to tildrakizumab 200 mg, 307 to tildrakizumab 100 mg, 156 to placebo, and 313 to etanercept. At week 12, 206 patients (66%) in the 200 mg group, and 188 patients (61%) in the 100 mg group achieved PASI 75, compared with 9 patients (6%) in the placebo group and 151 patients (48%) in the etanercept group ($p<0·0001$ for comparisons of both tildrakizumab groups *vs* placebo; $p<0·0001$ for 200 mg *vs* etanercept and $p=0·0010$ for 100 mg *vs* etanercept). 186 patients (59%) in the 200 mg group, and 168 patients (55%) in the 100 mg group achieved a PGA response, compared with 7 patients (4%) in the placebo group and 149 patients (48%) in the etanercept group ($p<0·0001$ for comparisons of both tildrakizumab groups *vs* placebo; $p=0·0031$ for 200 mg *vs* etanercept and $p=0·0663$ for 100 mg *vs* etanercept). Serious adverse events were similar and low in all groups in both trials. One patient died in reSURFACE 2, in the tildrakizumab 100 mg group; the patient had alcoholic cardiomyopathy and steatohepatitis, and adjudication was unable to determine the cause of death.

Interpretation In two phase 3 trials, tildrakizumab 200 mg and 100 mg were efficacious compared with placebo and etanercept and were well tolerated in the treatment of patients with moderate-to-severe chronic plaque psoriasis.

Funding Merck & Co.

Introduction

Chronic plaque psoriasis is an immune-mediated disease with a prevalence of around 2% in Europe and North America.[1] Symptoms include painful, pruritic, well demarcated, scaly, and erythematous plaques, which lead to detrimental physical effects and reduced

Research in context

Evidence before this study

We searched PubMed with the terms "psoriasis", "IL-23p19", "IL-12/23p40", "IL-17", "ustekinumab", "briakinumab", "secukinumab", "ixekizumab", "guselkumab", "tildrakizumab", "risankizumab", "BI 655066", "etanercept", and "adalimumab" for studies published in English on or before Oct 12, 2016, the date of our final search. Antibodies targeting interleukins 12 and 23 p40 were an efficacious treatment for psoriasis in several phase 3 studies. However, subsequent research identified interleukin 23, rather than interleukin 12, as the more important driver of psoriasis pathogenesis, leading to a focus on specifically blocking the interleukin 23–interleukin–17 inflammatory pathway. Phase 1 and 2 studies have shown the potential to treat psoriasis by specifically targeting interleukin 23 with anti-interleukin 23 p19 antibodies, without affecting interleukin 12 signalling.

Added value of this study

We report the results of two phase 3 studies of the anti-interleukin 23 p19 treatment tildrakizumab, reSURFACE 1 and reSURFACE 2. With a combined population of 1862 patients with moderate-to-severe psoriasis, these data provide evidence of efficacy and safety of tildrakizumab in the largest psoriasis population (so far) treated with anti-interleukin 23 p19 antibodies.

Implications of all the available evidence

Our results support the therapeutic potential of anti-interleukin 23 p19 antibodies. No apparent reduction of efficacy was noted with specific targeting of interleukin 23 and sparing of interleukin 12, which is consistent with the hypothesis that interleukin 23–interleukin 17 inflammatory pathway is critical in pathogenesis of psoriasis. Adverse events, including malignancy, cardiovascular events, serious infections, and drug-related hypersensitivity were rare in this large patient sample over 28 weeks. Open-label extension data showing multi-year clinical experience in reSURFACE 1 and 2 are forthcoming. These studies and additional randomised and observational studies will help to further characterise the efficacy profile of tildrakizumab and to further investigate adverse events.

psychological wellbeing.[2,3] Comorbid disorders associated with psoriasis can limit social interactions, impair school or work productivity, and lead to suicidality.[2,4,5] Thus, psoriasis can lead to substantial disability and reduced quality of life.[6]

T-helper 17 (Th17) cells, the major effector cells present in psoriatic lesions, stimulate activation and proliferation of surrounding keratinocytes and endothelial cells via production of interleukin 17A and other pro-inflammatory cytokines.[7] The introduction of biological treatments, initially with anti-tumour necrosis factor α (TNFα) agents, led to improved outcomes in psoriasis when compared with previous treatments.[8–11] Specific targeting of interleukins 12 and 23 p40 with ustekinumab resulted in further improved clinical outcomes.[12,13] Subsequent research showed that interleukin 23 is a key regulatory cytokine in psoriasis that stimulates differentiation, proliferation, and survival of Th17 cells; interleukin 12 is not. Specific targeting of the interleukin 23–interleukin 17 inflammatory pathway has become an effective therapeutic approach.[14,15] Initial phase 1 and 2 clinical studies[16–20] have shown that targeting interleukin 23 alone via antibodies directed against the p19 subunit is at least as effective in the treatment of psoriasis as is inhibition of both interleukins 12 and 23.

Tildrakizumab is a high affinity, humanised IgG1 κ monoclonal antibody that targets the p19 subunit of interleukin 23. We did two large, randomised, controlled, three-part, phase 3 studies, reSURFACE 1 and reSURFACE 2 to assess the efficacy, safety and tolerability of tildrakizumab compared with placebo and etanercept.

Methods

Study design and participants

Both reSURFACE 1 and reSURFACE 2 were three-part, double-blind, randomised, placebo-controlled, parallel-group studies. reSURFACE 1 was done from Dec 10, 2012, to Oct 28, 2015 at 118 sites (including hospital dermatology units, specialty clinics, private practices, and research sites) in Australia, Canada, Japan, the UK, and the USA. reSURFACE 2 was done from Feb 12, 2013, to Sept 28, 2015, at 132 sites in Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Israel, Netherlands, Poland, and the USA. Trial designs are in the appendix.

See Online for appendix

Eligible participants were aged 18 years or older, had moderate-to-severe chronic plaque psoriasis (body surface area involvement ≥10%, Physician's Global Assessment [PGA] score ≥3, and Psoriasis Area and Severity Index [PASI] score ≥12) at baseline, and were candidates for phototherapy or systemic therapy (a full list of inclusion criteria is in the appendix). Women could not be pregnant and those of child-bearing potential had to practise abstinence or use medically accepted contraception methods. Exclusion criteria were active or untreated latent tuberculosis; infection or recurrent infection requiring antibiotic treatment within 2 weeks of the study screening; severe infection requiring hospital admission or intravenous antibiotics within 8 weeks of the study; live viral or bacterial vaccination within 4 weeks of the study; positive test for HIV, hepatitis B virus infection, or hepatitis C virus infection; previous malignancy (except for patients with successfully treated basal cell carcinoma, squamous cell carcinoma of the skin in situ, squamous cell carcinoma with no evidence

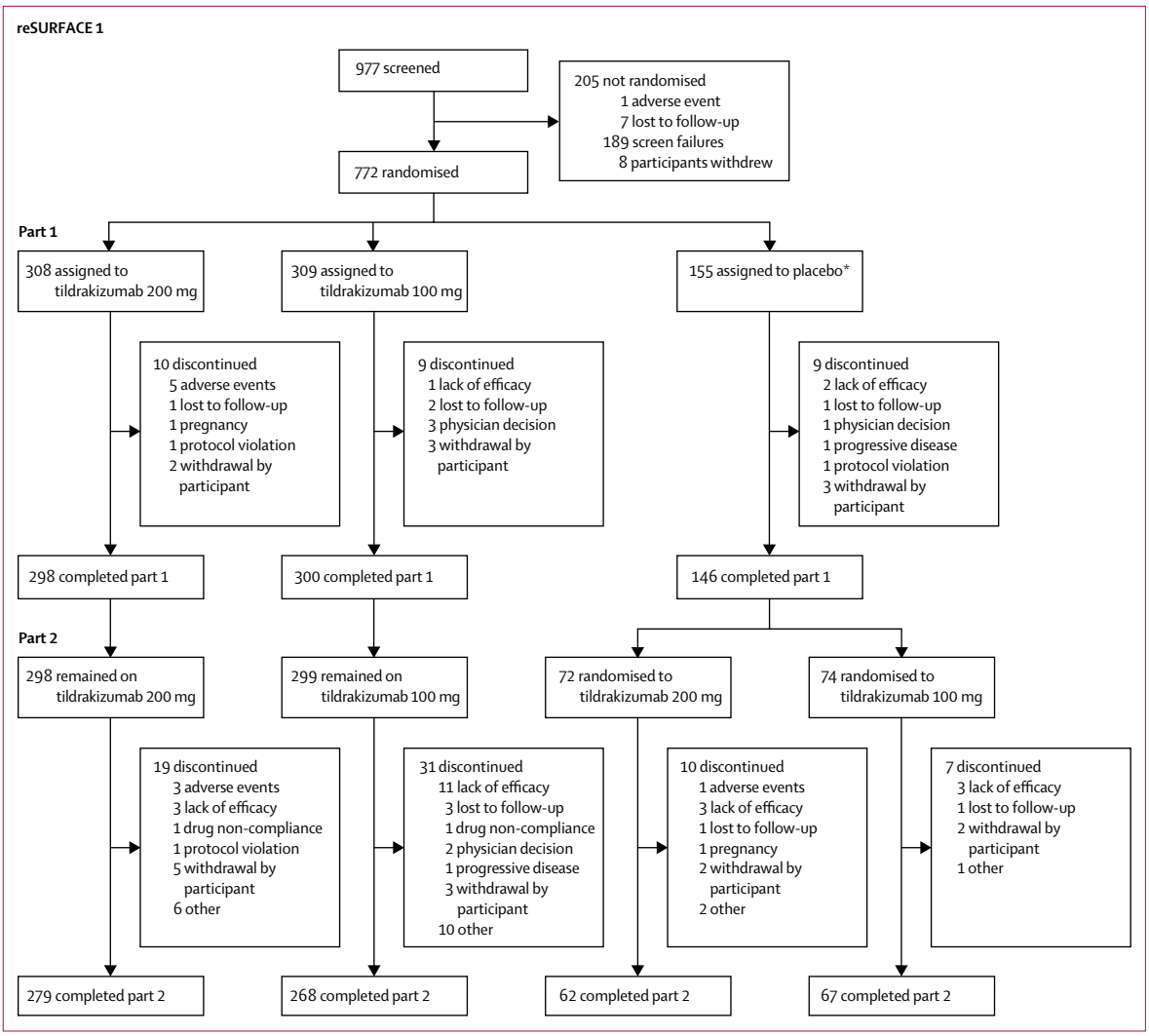

Figure 1: **reSURFACE 1 trial profile**
*One patient did not receive study medication and was excluded from the full analysis set and all-participants-as-treated population.

of recurrence within 5 years, or carcinoma in situ of the cervix that had been adequately treated); hospital admission for an acute cardiovascular event, illness, or surgery within 6 months of the trials; uncontrolled hypertension (systolic blood pressure of ≥160 mm Hg or diastolic blood pressure of ≥100 mm Hg at screening); uncontrolled diabetes; and previous use of tildrakizumab or other interleukin 23 and 17 pathway inhibitors (p40, p19, and interleukin 17 antagonists) or etanercept (in reSURFACE 2). A full list of inclusion criteria is in the appendix. Local institutional review boards or ethics panels reviewed and approved the protocols. All participants provided written informed consent.

Randomisation and masking

In reSURFACE 1, participants were randomly assigned (2:2:1) to tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo, then in part 2, those in the placebo group were re-randomised (1:1) to either tildrakizumab 200 or 100 mg. In reSURFACE 2, participants were randomly assigned (2:2:1:2) to tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg. In part 2, the placebo group was re-randomised (1:1) to tildrakizumab 200 mg or 100 mg. In part 3 of both studies, responders (PASI ≥75) and partial responders (PASI ≥50 and PASI <75) to tildrakizumab 200 mg and 100 mg were re-randomised at 28 weeks to continue the same treatment, a different dose of tildrakizumab, or placebo (appendix).

Participants were enrolled by study investigators. Randomisation was done on day 1. Parexel International, the contract research organisation, generated computer-generated randomisation sequences, and an interactive voice-response system and interactive web-response system was used by Parexel to allocate participants to groups. Randomised treatment assignments on day 1 were done by region (eg, North America, European Union,

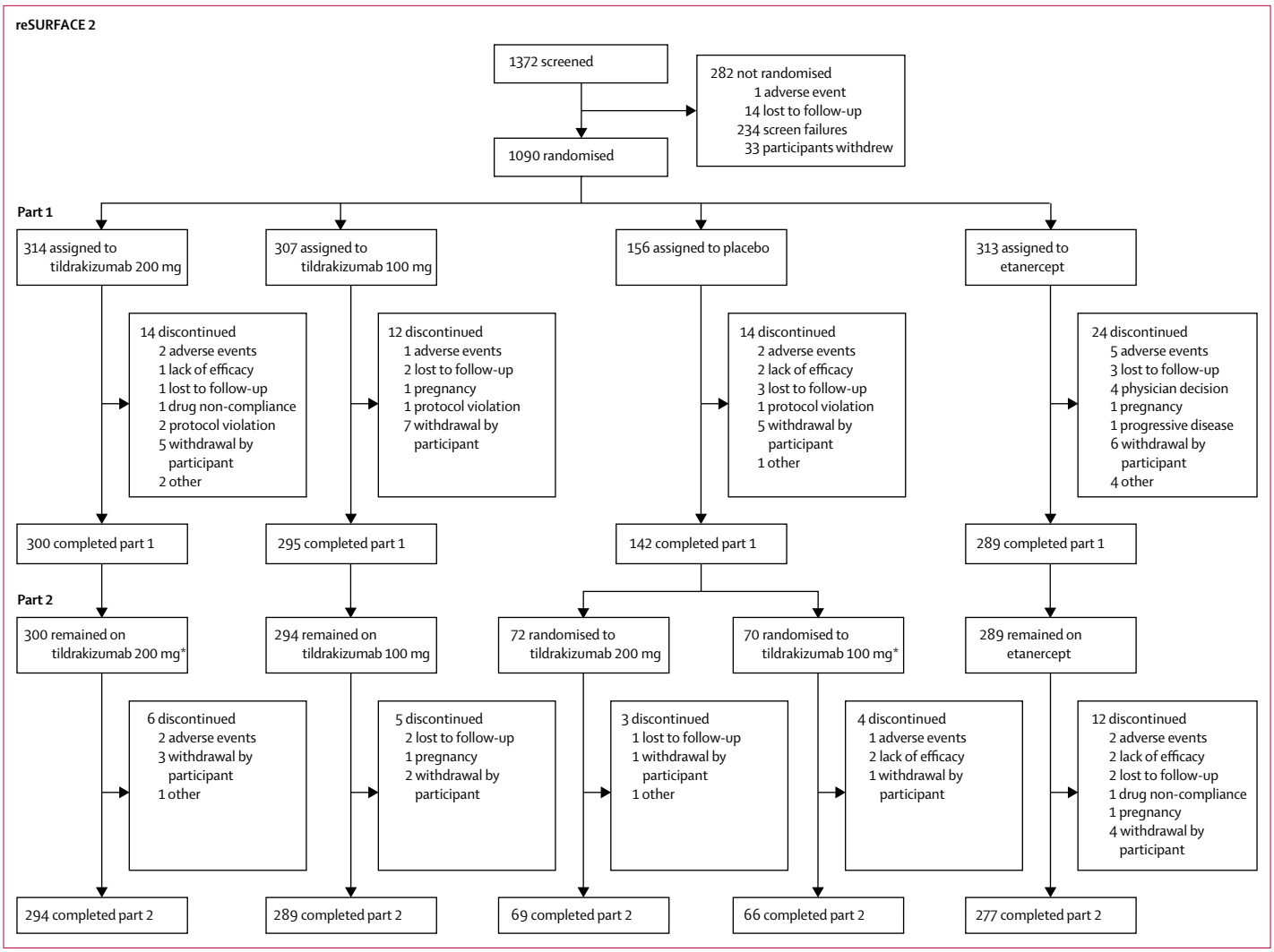

Figure 2: **reSURFACE 2 trial profile**
*In part 2, one patient in each of these groups did not receive study medication and were excluded from the full-analysis set and the all-participants-as-treated population.

and Japan) and stratified for bodyweight (≤90 kg or >90 kg) and previous exposure to biologics therapy for psoriasis. In reSURFACE 1, participants in Japan were also stratified for psoriatic arthritis at baseline. In reSURFACE 2, participants were also stratified for non-response to at least one traditional systemic medication (ie, methotrexate, cyclosporin, or phototherapy). A maximum of 40% of randomised participants were permitted to have had previous exposure to biologics. A maximum of 30% of randomised participants were permitted to have a diagnosis of psoriatic arthritis at baseline. Re-randomisation assignments at weeks 12 and 28 were done by region and stratified by bodyweight (≤90 kg or >90 kg).

Investigators, participants, and study personnel were blinded to group allocation and remained blinded until completion of the studies. A double-masking technique was used, in which tildrakizumab and its matching placebo or etanercept and its matching placebo were were identical in appearance and packaging. Additional placebo doses were administered to maintain masking. The team doing the analysis was blinded until the database was locked.

Procedures

Tildrakizumab 200 mg and 100 mg doses given at baseline and week 4 and subsequently every 12 weeks were identified for phase 3 assessment after a phase 2b study,[17] and an exposure–response model that further analysed data from the phase 2b study. In reSURFACE 1, participants were given tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo subcutaneously at baseline and week 4. In part 2, tildrakizumab patients received another dose at week 16; re-randomised placebo patients received either tildrakizumab 200 or 100 mg at weeks 12 and 16. In reSURFACE 2, participants received tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or

	reSURFACE 1			reSURFACE 2			
	Tildrakizumab 200 mg (n=308)	Tildrakizumab 100 mg (n=309)	Placebo (n=155)	Tildrakizumab 200 mg (n=314)	Tildrakizumab 100 mg (n=307)	Etanercept (n=313)	Placebo (n=156)
Male	226 (73%)	207 (67%)	100 (65%)	225 (72%)	220 (72%)	222 (71%)	112 (72%)
Age (years)	46·9 (13·2)	46·4 (13·1)	47·9 (13·5)	44·6 (13·6)	44·6 (13·6)	45·8 (14·0)	46·4 (12·2)
Age range (years)	18–76	18–82	19–76	19–80	19–80	19–81	20–76
Race							
White	209 (68%)	217 (70%)	101 (65%)	284 (90%)	279 (91%)	289 (92%)	144 (92%)
Asian	83 (27%)	70 (23%)	42 (27%)	14 (4%)	9 (3%)	10 (3%)	3 (2%)
Other	16 (5%)	22 (7%)	12 (8%)	16 (5%)	19 (6%)	14 (4%)	9 (6%)
Weight (kg)	88·87 (24·09)	88·53 (23·87)	87·50 (26·04)	88·35 (21·23)	89·35 (22·12)	87·97 (21·48)	88·74 (22·73)
% body surface area	30·9 (17·79)	29·7 (17·44)	29·6 (17·28)	31·8 (17·16)	34·2 (18·44)	31·6 (16·58)	31·3 (14·75)
Psoriasis Area and Severity Index score	20·7 (8·51)	20·0 (7·85)	19·3 (7·07)	19·8 (7·52)	20·5 (7·63)	20·2 (7·36)	20 (7·57)
Previously treated with biologics	71 (23%)	71 (23%)	35 (23%)	38 (12%)	39 (13%)	37 (12%)	20 (13%)
Dermatology Life Quality Index	13·2 (6·87)	13·9 (6·68)	13·2 (7·25)	13·2 (7·03)	14·8 (7·24)	14·5 (7·20)	13·7 (6·98)
Previous medical conditions							
Hypercholesterolaemia	18 (6%)	19 (6%)	9 (6%)	19 (6%)	19 (6%)	18 (6%)	8 (5%)
Hyperlipidaemia	29 (9%)	18 (6%)	10 (6%)	13 (4%)	17 (6%)	18 (6%)	9 (6%)
Hypertriglyceridaemia	1 (<1%)	4 (1%)	1 (1%)	1 (<1%)	..	1 (<1%)	1 (1%)
Hypertension	97 (31%)	85 (28%)	46 (30%)	76 (24%)	76 (25%)	85 (27%)	41 (26%)
Obesity	25 (8%)	15 (5%)	10 (6%)	20 (6%)	23 (7%)	22 (7%)	16 (10%)
Type 2 diabetes mellitus	26 (8%)	21 (7%)	15 (10%)	9 (3%)	9 (3%)	13 (4%)	8 (5%)

Data are n (%) or mean (SD), unless otherwise specified.

***Table 1*: Baseline Characteristics**

etanercept 50 mg (etanercept 50 mg was given twice a week). In part 2, tildrakizumab patients received their doses at week 16. Etanercept patients received one dose weekly; re-randomised placebo patients received tildrakizumab 200 mg or 100 mg (at weeks 12 and 16). In part 3 of both studies, participants received doses of tildrakizumab or placebo until week 64 (reSURFACE 1) or week 52 (reSURFACE 2). We focus in this Article on efficacy and safety during the first 28 weeks of treatment in patients who continued the same tildrakizumab dose from baseline until the end of part 3—results for all other patients will be reported separately.

Efficacy and safety measurements were done at baseline and weeks, 4, 8, 12, 16, 22, and 28 in parts 1 and 2. In part 3, efficacy was assessed at weeks 32, 36, 40, 46, and 52 in both studies, and efficacy and safety were assessed at week 64 in reSURFACE 1. No interim analyses were done. Safety was monitored by an external data monitoring committee, which made recommendations to the funder as appropriate. Changes to the study protocol are detailed in the appendix.

Outcomes

The main objectives of these studies were to assess the efficacy of tildrakizumab 200 mg and 100 mg versus placebo, and the safety and tolerability of tildrakizumab at week 12 (Part 1). Our co-primary endpoints were the proportion of participants achieving at least 75% improvement in the Psoriasis Area and Severity Index (PASI 75) and the proportion of participants achieving a PGA score of "clear" or "minimal", with at least a two-grade reduction from baseline, at week 12. Protocol-defined key secondary endpoints were PASI 90 and PASI 100 at week 12 in both studies. In reSURFACE 2, PASI 75 and PGA response at week 28 were also key secondary endpoints. Dermatology Quality-of-Life Index at weeks 12 and 28 was a secondary endpoint (ie, proportion of patients with score of 0 or 1) in both trials. PASI 75 in tildrakizumab patients receiving continuous treatment from baseline to the end of week 64 in reSURFACE 1 and week 52 in reSURFACE 2 was also assessed as a secondary outcome.

Safety was assessed in the all-participants-as-treated population, which included all randomised patients who received at least one dose of part 1 or part 2 study medication. Adverse events, laboratory tests, and vital signs measurements were monitored. All deaths and serious cardiovascular events were adjudicated by an external clinical adjudication committee.

Statistical analysis

We specified full-analysis-set, intention-to-treat, and per-protocol patient populations in the study protocols. The intention-to-treat population included all randomised patients on the basis of the treatment assigned. The per-protocol population included patients in the full analysis who met key eligibility and assessment criteria. The data we present here are based on the full analysis set: the other populations were used as supportive analyses (appendix).

For part 1, the full analysis set included all randomised patients who received at least one dose of study

medication. For part 2, it included patients who completed part 1, entered part 2, and received at least one dose of study medication (for placebo patients who were re-randomised, the full analysis set included patients who entered part 2 and received at least one dose of study medication). For part 3, the full analysis included all patients who completed part 2, entered part 3, and received at least one dose of study medication. The primary and key secondary endpoints were analysed in the full analysis set. Patients with missing data were treated as non-responders (non-responder imputation [NRI]). In other secondary analyses we used full-analysis-set observed data (ie, no missing data imputation) for prespecified analyses. We did additional post-hoc analyses with NRI for secondary endpoints in parts 2 and 3.

We analysed the co-primary endpoints with the Cochran-Mantel-Haenszel test, which was stratified by bodyweight (≤90 kg or >90 kg) and previous exposure to biologics for psoriasis. Each tildrakizumab dose was compared with placebo. The study was considered positive if the response rate of tildrakizumab was superior to that of placebo at week 12 on both co-primary endpoints on the basis of the full analysis set. The percent differences in effect sizes reported here are absolute differences.

A step-down multiplicity strategy was used (appendix). For the primary hypothesis, PASI 75 and PGA at week 12 were tested for tildrakizumab 200 mg versus placebo, followed by 100 mg versus placebo. For reSURFACE 1, the primary endpoints were followed by PASI 90 at week 12 (200 mg *vs* placebo), then PASI 90 at week 12 (100 mg *vs* placebo) and PASI 100 at week 12 (200 mg *vs* placebo), then PASI 100 at week 12 (100 mg *vs* placebo). For reSURFACE 2, the primary endpoints were followed by PASI 90 at week 12 (200 mg *vs* placebo), then PASI 90 at week 12 (100 mg *vs* placebo), then PASI 75 and PGA at week 12 (200 mg *vs* etanercept), then PASI 75 and PGA at week 28 (200 mg *vs* etanercept), then PASI 100 at week 12 (200 mg *vs* placebo), then PASI 75 and PGA at week 12 (100 mg *vs* etanercept).

Key secondary endpoints were analysed in the same way as the primary endpoints were, with comparisons to placebo and etanercept. Dermatology Quality-of-Life Index was also analysed with the Cochran-Mantel-Haenszel test, on the basis of recorded data. In reSURFACE 2, for the other secondary efficacy endpoints during part 2, analyses were done in a similar manner as in part 1, in which tildrakizumab 200 mg and tildrakizumab 100 mg were each compared with etanercept. Descriptive summary statistics by treatment are provided for participants who were re-randomised from placebo to tildrakizumab 100 mg or tildrakizumab 200 mg.

The planned sample sizes were driven by assessment of safety: we planned to randomise 750 patients in reSURFACE 1 and 1050 patients in reSURFACE 2. These sample sizes provided (assuming a placebo rate of 10% for both PASI 75 response and PGA response) more than 99% power to detect a 57% difference between tildrakizumab and placebo in PASI 75 response and to detect a 55% difference in PGA "clear" or "minimal" with at least a two-grade reduction from baseline. Additionally, a difference of 17% between a tildrakizumab dose and etanercept for PASI 75 response rate was to be detected with more than 98% power assuming an etanercept rate of approximately 56%, and a difference of 20% between a tildrakizumab dose and etanercept for PGA "clear" or "minimal", with at least a two-grade reduction from baseline, could be detected with more than 99% power assuming an etanercept rate of approximately 49%, with a two-sided test at significance α level of 0·05. Assumed effect sizes are based on the phase 2b study of tildrakizumab.[17] Power calculations were prespecified in the study protocols before the start of the trials; power calculations for PASI 100 for reSURFACE 1 and PASI 90 and PASI 100 for reSURFACE 2 were done during the protocol amendments before the data were unmasked (appendix). These trials are registered with ClinicalTrials.

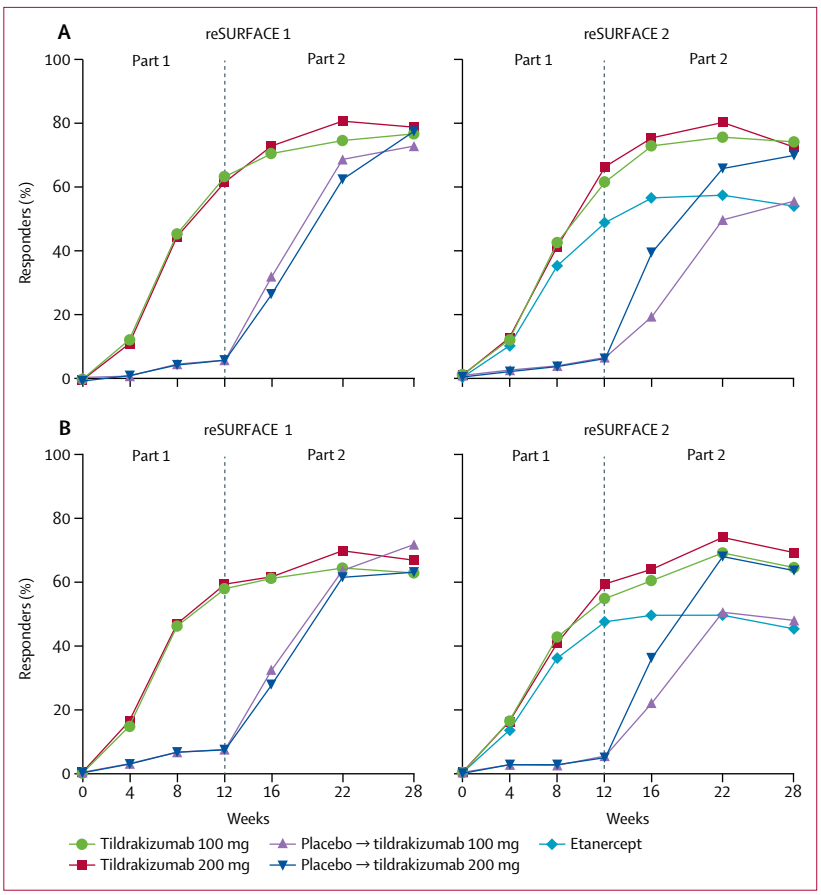

Figure 3: **Proportion of patients achieving PASI 75 (A) and PGA "clear" or "minimal" with at least 2 grade reduction (B) in reSURFACE 1 and reSURFACE 2**

Full analysis set population included all randomised patients who received one or more dose of study medication; in part 2, it included all patients who entered part 2 and received one or more doses of study medication. Data presented are non-responder-imputed data. PGA=Physician's Global Assessment. PASI 75=75% reduction in Psoriasis Area and Severity Index score.

	Tildrakizumab 200 mg (n=308)	Tildrakizumab 100 mg (n=309)	Placebo (n=154)
PASI 75			
n (%)	192 (62%)	197 (64%)	9 (6%)
% difference from placebo (95% CI; p value)	56·6% (49·6–62·8; p<0·0001)	58·0% (51·0–64·1; p<0·0001)	N/A
Clear or minimal PGA			
n (%)	182 (59%)	179 (58%)	11 (7%)
% difference from placebo (95% CI; p value)	52·1% (44·8–58·5; p<0·0001)	50·9% (43·6–57·4; p<0·0001)	N/A
PASI 90			
n (%)	109 (35%)	107 (35%)	4 (3%)
% difference from placebo (95% CI; p value)	32·9% (26·8–38·8; p<0·0001)	32·1% (25·9–38·0; p<0·0001)	N/A
PASI 100			
n (%)	43 (14%)	43 (14%)	2 (1%)
% difference from placebo (95% CI; p value)	12·7% (8·3–17·2; p<0·0001)	12·7% (8·0–17·3; p<0·0001)	N/A
DLQI score 0 or 1			
n (%)	132 (44%)	126 (42%)	8 (5%)
% difference from placebo (95% CI; p value)	38·9% (31·9–45·4; p<0·0001)	36·1% (29·3–42·5; p<0·0001)	N/A

The full-analysis-set population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90 kg *vs* >90 kg) and previous exposure to biologic therapy for psoriasis (yes *vs* no) with sample size weights. p values were calculated with the Cochran-Mantel-Haenszel and stratified by bodyweight and exposure to biologic therapies; p values were not adjusted for multiplicity. Non-responder imputation was pre-specified and is shown for all data, except for DLQI, which were observed data. PASI=Psoriasis Area and Severity Index. N/A=not applicable. PGA=Physician's Global Assessment. DLQI=Dermatology Life Quality Index.

***Table 2*: Primary and secondary efficacy endpoints at 12 weeks in reSURFACE1 part 1 (full analysis set)**

gov, numbers NCT01722331 (reSURFACE 1) and NCT01729754 (reSURFACE 2).

Role of the funding source

The study funder had roles in study design, data analysis, and data interpretation. Safety data were reviewed at regular intervals by an independent data monitoring committee. All authors had full access to all study data and final responsibility for the decision to submit for publication.

Results

In reSURFACE 1, 772 patients were randomly assigned, 308 to tildrakizumab 200 mg, 309 to tildrakizumab 100 mg, and 155 to placebo (figure 1). 744 (96%) completed part 1, all but one of whom continued into part 2. 676 participants (91%) completed part 2 (figure 1). In reSURFACE 2, 1090 patients were randomly assigned, 314 to tildrakizumab 200 mg, 307 to tildrakizumab 100 mg, 156 to placebo, and 313 to etanercept. 1026 participants (94%) completed part 1, all but one of whom continued into part 2. 995 patients (97%) completed part 2 (figure 2). Baseline demographic characteristics were similar in all treatment groups (table 1).

A significantly higher proportion of patients in the tildrakizumab groups than in the placebo groups achieved PASI 75 response at week 12 in both studies (p<0·0001; figure 3; tables 2, 3). Additionally, a significantly higher proportion of patients in the tildrakizumab groups than in the placebo groups achieved a PGA score of "clear" or "minimal," with at least a 2-grade reduction from baseline at week 12 (p<0·0001; figure 3; tables 2, 3). Among patients receiving tildrakizumab from baseline to week 28, PASI 75 and PGA responses peaked at week 22 (figure 3). Among patients who received placebo until week 12 and were then re-randomised to tildrakizumab, PASI and PGA improved until week 28, at which point efficacy was similar to that in patients randomised to tildrakizumab at baseline (table 4).

In reSURFACE 2, a significantly higher proportion of patients in the tildrakizumab 200 mg group than in the etanercept group achieved PASI 75 (p<0·0001) and PGA (p=0·0031) responses at week 12 (table 3). Although a higher proportion of patients in the tildrakizumab 100 mg group than in the etanercept group achieved PASI 75 at week 12 (nominal unadjusted p<0·0001), the proportion of patients achieving PGA responses did not differ significantly between these groups at week 12 (table 3; appendix).

At week 12, the proportions of patients achieving PASI 90 and PASI 100 were significantly higher in the tildrakizumab groups than in the placebo groups in both trials (p<0·0001 for all comparisons [p value for tildrakizumab 100 mg *vs* placebo for PASI 100 at week 12 was not adjusted for multiplicity]; tables 2, 3). In both studies 1, PASI 90 and 100 responses were higher for both tildrakizumab doses at week 28 than at week 12 (tables 2, 4). Multiplicity-adjusted efficacy results are presented in the appendix. The proportion of patients achieving a Dermatology Life Quality Index score of 0 or 1 was also higher in the tildrakizumab groups than in the etanercept groups (tables 3, 5). The appendix shows representative photographic improvement in the appearance of psoriasis plaques over 28 weeks.

In reSURFACE 1, in the tildrakizumab 200 mg group, 107 (94% [90% in NRI analysis]) of 114 responders at week 28 maintained PASI 75, and 15 (40% [37% in NRI analysis]) of 38 partial responders at week 28 achieved PASI 75 in part 3. In the tildrakizumab 100 mg group, 100 (88% [85% in NRI analysis]) of 113 responders at week 28 maintained PASI 75, and 12 (75% [63% in NRI analysis]) of 16 partial responders achieved PASI 75 in part 3. Meanwhile in reSURFACE 2, in the tildrakizumab 200 mg group, 102 (97% [94% in NRI analysis]) of 105 responders at week 28 maintained PASI 75, and 40 (67% [66% in NRI

	Tildrakizumab 200 mg (n=314)	Tildrakizumab 100 mg (n=307)	Placebo (n=156)	Etanercept (n=313)
PASI 75				
n (%)	206 (66%)	188 (61%)	9 (6%)	151 (48%)
% difference from placebo (95% CI; p value)	59·8% (52·9 to 65·9; p<0·0001)	55·5% (48·3 to 61·8; p<0·0001)	N/A	N/A
% difference from etanercept (95% CI; p value)	17·4% (9·7 to 24·9; p<0·0001)	13·1 (5·3 to 20·7; p=0·001)	N/A	N/A
Clear or minimal PGA				
n (%)	186 (59%)	168 (55%)	7 (4%)	149 (48%)
% difference from placebo (95% CI; p value)	54·7 (47·9 to 60·8; p<0·0001)	50·2 (43·2 to 56·5; p<0·0001)	N/A	N/A
% difference from etanercept (95% CI; p value)	11·7 (4·0 to 19·3; p=0·0031)	7·3 (–0·5 to 15·0; p=0·0663)	N/A	N/A
PASI 90				
n (%)	115 (37%)	119 (39%)	2 (1%)	67 (21%)
% difference from placebo (95% CI; p value)	35·3% (29·2 to 41·1; p<0·0001)	37·5% (31·1 to 43·4; p<0·0001)	N/A	N/A
% difference from etanercept (95% CI; p value)	15·2% (8·3 to 22·1; p<0·0001)	17·4% (10·3 to 24·4; p<0·0001)	N/A	N/A
PASI 100				
n (%)	37 (12%)	38 (12%)	0	15 (5%)
% difference from placebo (95% CI; p value)	11·7% (7·8 to 16·0; p<0·0001)	12·4% (8·5 to 16·6; p<0·0001)	N/A	N/A
% difference from etanercept (95% CI; p value)	7·0% (2·8 to 11·6; p=0·0014)	7·6% (3·3 to 12·3; p=0·0006)	N/A	N/A
DLQI				
n (%)	145 (47%)	119 (40%)	12 (8%)	108 (36%)
% difference from placebo (95% CI; p value)	39·3% (31·8 to 46·1; p<0·0001)	32·1% (24·5 to 39·1; p<0·0001)	N/A	N/A
% difference from etanercept (95% CI; p value)	11·9% (4·1 to 19·5; p=0·0029)	4·8% (–2·9 to 12·5; p=0·2206)	N/A	N/A

The full-analysis-set population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90 kg *vs* >90 kg) and previous exposure to biologic therapy for psoriasis (yes *vs* no) with sample size weights. p values were calculated with the Cochran-Mantel-Haenszel (CMH) and stratified by bodyweight and exposure to biologic therapies; p values were not adjusted for multiplicity. Non-responder imputation was pre-specified and is shown for all data, except for DLQI, for which observed data are shown. PASI=Psoriasis Area and Severity Index. N/A=not applicable. PGA=Physician's Global Assessment. DLQI=Dermatology Life Quality Index.

***Table 3*: Primary and secondary efficacy endpoints at 12 weeks in reSURFACE2 part 1 (full analysis set)**

analysis]) of 60 partial responders at week 28 achieved PASI 75 in part 3. In the tildrakizumab 100 mg group, 191 (94% [90% in NRI analysis]) of 204 responders at week 28 maintained PASI 75, and 13 (68% [62% in NRI analysis]) of 19 partial responders at week 28 achieved PASI 75 in part 3 (appendix). Maintenance of response over time in part 3 is detailed in the appendix.

Discontinuations because of adverse events were infrequent (tables 6, 7). The most common adverse event in both studies was nasopharyngitis. One patient (receiving tildrakizumab 100 mg) died in reSURFACE 2 study on day 96: the patient had alcoholic cardiomyopathy and steatohepatitis, although independent adjudication was unable to determine the cause of death. This patient completed part 1 of the study, but no part 2 dose was recorded (the last active dose of study medication was on day 30). The incidence of severe infections, malignancies, and major adverse cardiovascular events were low and similar across treatment groups (tables 6, 7). Malignancies consisted mostly of non-melanoma skin cancer; no patients had melanoma skin cancer.

Discussion

In these two phase 3, randomised, controlled clinical studies, tildrakizumab was associated with significantly higher proportions of patients with moderate-to-severe chronic plaque psoriasis achieving PASI 75 and clear or minimal PGAs than placebo. In reSURFACE 2, tildrakizumab 200 mg was associated with significantly higher proportions of patients achieving PASI 75 and PGA responses at week 12 than was etanercept, an effective anti-TNFα treatment for psoriasis.[10,11,21]

In both studies, results for PASI 75 and PGA for both doses of tildrakizumab continued to improve to week 28. Maximal efficacy for tildrakizumab was reached between week 22 and week 28. Patients initially assigned to placebo who were re-randomised to receive tildrakizumab 200 mg or 100 mg improved from week 12 to week 28. At week 28, these patients achieved similar levels of response as those who received tildrakizumab continuously from baseline. A higher proportion of patients who received either dose of tildrakizumab than of patients who received placebo achieved the more rigorous endpoints of PASI 90 (minimal) and PASI 100 (clear) in reSURFACE 1 and reSURFACE 2 at week 12, although these were secondary and not primary endpoints. These findings were supported by a higher proportion of tildrakizumab patients than of placebo or etanercept patients achieving a Dermatology Life Quality Index score of 0 or 1 (indicating no effect of psoriasis on quality of life). The results for primary and secondary endpoints at week 12 and week 28 were similar for tildrakizumab 200 mg and 100 mg. In nearly all PASI 75 responders at week 28 continuing the same dose in part 3, PASI 75 responses with tildrakizumab

	Tildrakizumab 200 mg (n=298)*	Tildrakizumab 100 mg (n=299)*	Placebo→tildrakizumab 200 mg (n=72)*	Placebo→ tildrakizumab 100 mg (n=74)*
PASI 75				
Observed data	236 (82%)	229 (80%)	56 (86%)	54 (77%)
Non-responder imputation	236 (79%)	229 (77%)	56 (78%)	54 (73%)
Clear or minimal PGA				
Observed data	199 (69%)	188 (66%)	46 (71%)	53 (76%)
Non-responder imputation	199 (67%)	188 (63%)	46 (64%)	53 (72%)
PASI 90				
Observed data	170 (59%)	147 (52%)	34 (52%)	41 (59%)
Non-responder imputation	170 (57%)	147 (49%)	34 (47%)	41 (55%)
PASI 100				
Observed data	91 (32%)	67 (24%)	17 (26%)	22 (31%)
Non-responder imputation	91 (31%)	67 (22%)	17 (24%)	22 (30%)
DLQI score 0 or 1				
Observed data	164 (57%)	152 (52%)	38 (56%)	37 (52%)

Data are n (%). The full-analysis-set population included all patients entering part 2 who received at least one dose of study medication. Non-responder imputation was pre-specified and is shown for key secondary outcomes. Observed data were pre-specified for all other secondary outcomes. Post-hoc analyses for PASI 75, PGA, PASI 90, and PASI 100 at week 28 (reSURFACE 1) were done with non-responder imputation. PASI=Psoriasis Area and Severity Index. PGA=Physician's Global Assessment. DLQI=Dermatology Life Quality Index. *Numbers shown include participants with missing data.

Table 4: **Secondary efficacy endpoints at 28 weeks in reSURFACE1 part 2 (full analysis set)**

were maintained until the end of part 3. Among patients who were only partial responders to tildrakizumab at week 28 and continued on the same dose, the PASI 75 response rate improved until the end of part 3 in both studies.

Previous research suggested that Th17 cells are crucial mediators of autoimmunity, and several biologic treatments targeting the interleukin 23–interleukin 17 inflammatory pathway were subsequently developed or are in development for the treatment of autoimmune disorders, including psoriasis.[22] The anti-interleukin 17A antibodies secukinumab and ixekizumab are approved for clinical use. Phase 3 evidence suggests that interleukin 17A antibodies have impressive efficacy.[23,24] Ustekinumab is an antibody for the interleukin 12 and 23 p40 subunit and was among the first successful treatments targeting the interleukin 23–interleukin 17 pathway. Ustekinumab's clinical effects in psoriasis have been linked to the role of interleukins 12 and 23 in the development or expansion of Th1 and Th17 cells. The relative contribution of interleukin 12 blockade to the therapeutic effect, however, is controversial,[25] and biologic activities of interleukin 23 are emerging that might contribute to psoriasis beyond effects on Th17 cells.[26] The rationale for the use of selective interleukin 23 p19 blockers, such as tildrakizumab, is that interleukin 23 rather than interleukin 12 is a key driver of T-cell and non T-cell pathology in psoriasis and that a more pronounced inhibition of this pathway will lead to an improved risk–benefit profile.

Human disease association data and preclinical studies later suggested that interleukin 23 rather than interleukin 12 is the primary driver of psoriasis, thus leading to the development of interleukin 23 p19 antibodies.[22,27–29] Our phase 3 data support previous evidence from phase 2 studies of tildrakizumab, and suggest no reduction in efficacy when interleukin 23 is selectively blocked and interleukin 12 is spared.[17,19]

Additional interleukin 23 p19 antibodies in development include risankizumab and guselkumab, the latter of which has shown strong efficacy in patients with moderate-to-severe chronic plaque psoriasis in a phase 2 study.[18] PASI 75 was achieved by approximately 80% of patients receiving the two highest doses of guselkumab (100 and 200 mg) at week 16, which is higher than the 66% and 74% reported with tildrakizumab 100 mg and 200 mg, respectively, at week 16 in the phase 2 study of tildrakizumab.[17,18] In the VOYAGE-1 and VOYAGE-2 phase 3 studies of guselkumab 100 mg (administered at weeks 0, 4, and then every 8 weeks) in patients with moderate-to-severe chronic plaque psoriasis, 91% and 86% of patients achieved PASI 75 at week 16, respectively. PASI 75 proportions were not substantially different at week 24 compared with week 16.[30,31] In the reSURFACE studies, PASI 75 was achieved with either dose of tildrakizumab in around 60% of patients at week 12, which improved to roughly 75% at week 28. The safety and tolerability profile of tildrakizumab and guselkumab in the phase 3 studies was generally similar. However, interpretation of the comparison of effect sizes across separate trials with variations in study designs and dosing intervals should be done with caution, because such comparisons lack the scientific rigour and validity of head-to-head trials. Further research will be needed to assess the benefits and risks of each treatment for individual patients.

Although the availability of effective medications for patients with psoriasis has improved since the introduction of biologics, drugs must be assessed on the basis of both benefits and potential risks to individual patients. Novel treatments with combined high efficacy and little to no safety and tolerability risks will be important to achieve therapeutic goals. A previous phase 2 study[17] of tildrakizumab did not show safety concerns in a sample of 355 patients with chronic plaque psoriasis. The reSURFACE 1 and 2 studies provide further support for an encouraging safety profile for tildrakizumab. In both studies, the proportions of patients with serious adverse events or who discontinued because of adverse events were low and similar between treatment groups. The most common adverse event was nasopharyngitis. Injection-site erythema was among the most common adverse events in reSURFACE 2; many of these adverse events were recorded in the etanercept group. No significant differences were noted between treatment groups for adverse events of special interest, such as severe infections, malignancies, confirmed major adverse cardiac events, and drug-related hypersensitivity.

	Tildrakizumab 200 mg (n=299)*	Tildrakizumab 100 mg (n=294)*	Placebo→tildrakizumab 200 mg (n=72)*	Placebo→tildrakizumab 100 mg (n=69)*	Etanercept (n=289)*
PASI 75 (NRI)					
n (%)	217 (73%)	216 (73%)	50 (69%)	38 (55%)	155 (54%)
% difference from etanercept (95% CI; p value)	19·2% (11·5–26·7; p<0·0001)	20·1% (12·4–27·6; p<0·0001)	N/A	N/A	N/A
Clear or minimal PGA (NRI)					
n (%)	207 (69%)	190 (65%)	46 (64%)	33 (48%)	131 (45%)
% difference from etanercept (95% CI; p value)	24·1% (16·2–31·7; p<0·0001)	19·6% (11·7 to 27·3; p<0·0001)	N/A	N/A	N/A
PASI 90 (OD)					
n (%)	169 (58%)	161 (56%)	33 (49%)	26 (39%)	85 (31%)
% difference from Etanercept (95% CI; p value)	27·1% (19·1, 34·7; p<0·0001)	24·9% (17·0–32·6; p<0·0001)	N/A	N/A	N/A
PASI 90 (NRI)					
n (%)	169 (57%)	161 (55%)	33 (46%)	26 (38%)	85 (29%)
% difference from etanercept (95% CI; p value)	27·3% (19·5–34·7; p<0·0001)	25·5% (17·6–33·0; p<0·0001)	N/A	N/A	N/A
PASI 100 (OD)					
n (%)	79 (27%)	66 (23%)	13 (19%)	9 (14%)	31 (11%)
% difference from etanercept (95% CI; p value)	15·7% (9·4–22·1; p<0·0001)	11·7% (5·6–17·9; p=0·0002)	N/A	N/A	N/A
PASI 100 (NRI)					
n (%)	79 (26%)	66 (22%)	13 (18%)	9 (13%)	31 (11%)
% difference from etanercept (95% CI; p value)	15·7% (9·6–22·0; p=0·0001)	11·8% (5·9–17·9; p<0·0001)	N/A	N/A	N/A
DLQI score 0 or 1 (OD)					
n (%)	193 (65%)	157 (54%)	39 (57%)	26 (38%)	111 (39%)
% difference from etanercept (95% CI; p value)	25·7% (17·7–33·4; p<0·0001)	15·0% (6·9–22·9; p=0·0003)	N/A	N/A	N/A

The full-analysis-set population included all patients entering part 2 who received at least one dose of study medication. NRI was pre-specified and is shown for key secondary outcomes. OD were pre-specified for all other secondary outcomes. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90 kg *vs* >90 kg) and previous exposure to biologic therapy for psoriasis (yes *vs* no) with sample size weights. p values were calculated with the Cochran-Mantel-Haenszel and stratified by bodyweight and exposure to biologic therapies; p values were not adjusted for multiplicity. Post-hoc analyses for PASI 90 and PASI 100 at week 28 were done with NRI. PASI=Psoriasis Area and Severity Index. NRI=non-responder imputation. N/A=not applicable. PGA=Physician's Global Assessment. OD=observed data. DLQI=Dermatology Life Quality Index. *Numbers shown include participants with missing data.

***Table 5*: Secondary efficacy endpoints at 28 weeks in reSURFACE2 part 2 (full analysis set)**

The interleukin 23–interleukin 17 inflammatory pathway not only mediates autoimmune pathology, but also is important for resistance to infection, particularly resistance against microbes and fungi such as *Candida*.[32–35] Candida infections have been reported to be more common in patients taking anti-interleukin 17A antibodies than in those taking etanercept or ustekinumab.[36] A pooled analysis[37] of secukinumab studies showed a risk of candida infections of 2·56 cases per 100 patient-years for any dose and 3·55 cases per 100 patient-years for high doses—ie, a dose-related increase. Candida infections in the reSURFACE trials were infrequent, suggesting that interleukin 23 p19 neutralisation with tildrakizumab is not associated with the same risk of fungal infection as anti-interleukin 17 antibodies.

Inflammatory bowel disease is another issue of interest. Previous evidence suggests that targeting of interleukin 23 is therapeutic in inflammatory bowel disease, whereas neutralisation of interleukins 17A or 17RA has either no effect or exacerbates the disease.[24,38–42] No cases of new-onset inflammatory bowel disease or exacerbations of pre-existing disease were reported in the reSURFACE studies, although the number of patients with inflammatory bowel disease in the study was low. Further research is needed to better characterise the effect of selective neutralisation of interleukin 23 on inflammatory bowel disease.

Brodalumab, an anti-interleukin 17RA antibody, has shown efficacy in psoriasis, but suicidal ideation and behaviour have been noted (although a causal relationship has not been confirmed).[43] This adverse event has not been reported with other treatments that target the interleukin 23–interleukin 17 pathway, and was not recorded in our studies of tildrakizumab.[44,45] Major adverse cardiovascular events are of interest because they are associated with the interleukins 12 and 23 p40 antibody briakinumab.[46] Such events were rare in the reSURFACE trials. Although patients in the reSURFACE

	Part 1			Part 2			
	Tildrakizumab 200 mg (n=308)	Tildrakizumab 100 mg (n=309)	Placebo N=154 n (%)	Tildrakizumab 200 mg → tildrakizumab 200 mg (n=298)	Tildrakizumab 100 mg → tildrakizumab 100 mg (n=300)	Placebo → tildrakizumab 200 mg (n=72)	Placebo → tildrakizumab 100 mg (n=74)
≥1 adverse events*	130 (42%)	146 (47%)	74 (48%)	118 (40%)	133 (44%)	29 (40%)	31 (42%)
Serious adverse events	8 (3%)	5 (2%)	1 (1%)	7 (2%)	6 (2%)	1 (1%)	1 (1%)
Deaths	0	0	0	0	0	0	0
Discontinued because of adverse events	5 (2%)	0	1 (1%)	3 (1%)	1 (<1%)	0	0
Most common adverse events							
Nasopharyngitis	20 (6%)	24 (8%)	8 (5%)	12 (4%)	20 (7%)	5 (7%)	4 (5%)
Upper respiratory tract infection	15 (5%)	10 (3%)	9 (6%)	20 (7%)	13 (4%)	0	3 (4%)
Psoriasis	0	3 (1%)	8 (5%)	0	0	0	0
Adverse events of special interest							
Severe infections†	1 (<1%)	1 (<1%)	0	1 (<1%)	2 (1%)	0	0
Malignancies‡	0	0	0	2 (1%)	1 (<1%)	0	1 (1%)
Non-melanoma skin cancer	0	0	0	1 (<1%)	1 (<1%)	0	1 (1%)
Confirmed major adverse cardiovascular events§	0	1 (<1%)	0	0	0	0	0
Drug-related hypersensitivity reactions	1 (<1%)	0	0	0	0	0	0

Data are n (%). *Participants who took at least one dose of part 1 study drug; based on the treatment actually received. †Infection meeting the regulatory definition of a serious adverse event, or any infection requiring intravenous antibiotics, irrespective of whether it was reported as a serious adverse event, as per the regulatory definition. ‡Excluding carcinoma in situ of the cervix. §Includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths that are confirmed as "cardiovascular" or "sudden".

***Table 6*: Summary of adverse events in reSURFACE 1**

	Part 1				Part 2				
	Tildrakizumab 200 mg (n=314)	Tildrakizumab 100 mg (n=307)	Placebo (n=156)	Etanercept (n=313)	Tildrakizumab 200 mg→ tildrakizumab 200 mg (n=299)	Tildrakizumab 100 mg→ tildrakizumab 100 mg (n=294)	Etanercept→ etanercept (n=289)	Placebo→ tildrakizumab 200 mg (n=72)	Placebo→ tildrakizumab 100 mg (n=69)
≥1 adverse events*	155 (49%)	136 (44%)	86 (55%)	169 (54%)	135 (45%)	135 (46%)	164 (57%)	31 (43%)	37 (54%)
Serious adverse events	6 (2%)	4 (1%)	4 (3%)	7 (2%)	6 (2%)	9 (3%)	14 (5%)	2 (3%)	1 (1%)
Deaths†	0	1 (<1%)	0	0	0	0	0	0	0
Discontinued because of adverse events	3 (1%)	3 (1%)	2 (1%)	6 (2%)	1 (<1%)	1 (<1%)	3 (1%)	0	1 (1%)
Most common adverse events									
Injection site erythema	2 (1%)	2 (1%)	1 (1%)	27 (9%)	1 (<1%)	3 (1%)	3 (1%)	0	0
Nasopharyngitis	35 (11%)	41 (13%)	12 (8%)	36 (12%)	43 (14%)	23 (8%)	34 (12%)	3 (4%)	8 (12%)
Upper respiratory tract infection	0	0	0	0	6 (2%)	5 (2%)	7 (2%)	0	0
Adverse events of special interest									
Severe infections‡	1 (<1%)	0	1 (1%)	0	2 (1%)	1 (<1%)	3 (1%)	0	0
Malignancies§	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0	3 (1%)	1 (1%)	1 (1%)
Non-melanoma skin cancer	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	1 (1%)	1 (1%)
Confirmed major adverse cardiovascular events¶	0	0	0	0	0	0	0	0	0
Drug-related hypersensitivity reactions	0	1 (<1%)	1 (1%)	0	0	0	0	0	2 (3%)

Data are n (%). *Participants who took at least one dose of part 1 study drug; based on the treatment actually received. †A patient on tildrakizumab 100 mg died; the patient had alcoholic cardiomyopathy and steatohepatitis, although adjudication was unable to determine the cause of death. ‡Infection meeting the regulatory definition of a serious adverse event, or any infection requiring intravenous antibiotics, irrespective of whether it was reported as a serious adverse event, as per the regulatory definition. §Excluding carcinoma in situ of the cervix. ¶Includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths that are confirmed as "cardiovascular" or "sudden".

***Table 7*: Summary of adverse events in reSURFACE 2**

trials had fewer cardiovascular risk factors (eg, obesity, diabetes mellitus, and hypercholesterolaemia) than those in the briakinumab trial, the cardiovascular risk factors in our trials were generally similar (with the exception of a lower proportion of patients with obesity) to those in patients with severe psoriasis who were included in a large population-based study.[47] This similarity suggests that our population is generally reflective of patients with moderate-to-severe psoriasis, although a more rigorous assessment in patients with greater cardiovascular risk factors would provide more definitive evidence of the cardiovascular safety of tildrakizumab.

Our trials had several limitations. Etanercept was a commonly used active comparator in psoriasis trials at the time these studies were initiated,[23,24] but comparisons with newer, more effective anti-TNFα therapies or ustekinumab might have been more informative for assessment of the therapeutic benefits of tildrakizumab. Additionally, by design, non-responders in the tildrakizumab groups discontinued treatment before part 3: therefore, dropout in these treatment arms was low because patients had already demonstrated response to tildrakizumab within 28 weeks of treatment. Finally, in view of improvements in PASI 75 PGA response in patients who continued treatment until week 28, the 12 week timepoint that was chosen for the primary efficacy endpoints might have been too early to assess adequately the efficacy potential of tildrakizumab. Specifically, tildrakizumab 100 mg was not significantly more effective than etanercept at week 12 (several weeks before peak efficacy with tildrakizumab) for PGA response. Therefore, between-treatment statistical testing for superiority of tildrakizumab 100 mg was not done for several endpoints, including PASI 75 and PGA response at week 28.

Even in this revolutionary era of highly effective psoriasis therapies, patients with moderate-to-severe disease usually need to be treated for decades. These patients are still in need of long-term persistent efficacy and drugs with robust long-term safety. The refinement of therapies that increasingly narrow the range of biological effects to only those desired, including antibodies specifically antagonising interleukin 23 such as tildrakizumab, continues to provide momentum towards these long-term goals.

Contributors

KAP was coordinating investigator for reSURFACE 1, and KR was coordinating investigator for reSURFACE 2; both contributed equally to the conduct of the studies. KR, KAP, and ABK contributed to study design and collected data. AB, SKT, RS, and DT collected data. KN and NC contributed to study design. AM wrote sections of the initial draft of the article. QL and KL did or supervised data analyses. CLR and SG Contributed to study design and supervised analyses. All authors interpreted the results, provided substantive suggestions and critically reviewed each iteration of the manuscript, and gave final approval for the Article.

Declaration of interests

KR has served as a consultant or paid speaker for, or participated in clinical trials sponsored by, Abbvie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo, Lilly, Medac, Merck & Co, Novartis, Pfizer, Vertex, and Takeda. KAP has served as a consultant or paid speaker for, or participated in clinical trials sponsored by, Amgen, Anacor, AbbVie, Active Biotech, Allergan, Astellas, AstraZeneca, Basilea, Bayer, Biogen-Idec, BMS, Boehringer-Ingelheim, CanFite, Celgene, Dermira, Eli-Lilly, Forward Pharma, Genentech, GlaxoSmithKline, Janssen, Kyowa Hako Kirin, Kythera, Leo Pharma, Merck & Co, Merck-Serono, Novartis, Pfizer, Regeneron, Rigel, Roche, Sanofi-Genzyme, Takeda, UCB, Valeant, Xenon, and Xoma. AB has served as a scientific adviser and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Genentech, GSK, Janssen, Lilly, Merck & Co, Novartis, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun, UCB, and Valeant, and as a paid speaker for Lilly. SKT has participated in trials supported by grants from Merck & Co. RS has served as a consultant or paid speaker for, or participated in clinical trials sponsored by, Leo Pharma, Amgen, Novartix, Merck & Co, Celgene, Coherus Biosciences, Janssen, Regeneron, MedImmune, GlaxoSmithKline, Cutanea, Samson Clinical, Boehringer Ingelheim, Pfiizer, MSD, Oncobiologics, Roche, Eli Lilly, and Bayer. DT has served as a consultant, advisory board member, or an investigator for Abbott (AbbVie), Almiral, Amgen, Astellas, Biogen-Idec, Boehringer Ingelheim, Celgene, Dignity, Forward-Pharma, Galderma, GlaxoSmithKline, Isotechnika, Janssen-Cilag, Leo Pharma, Lilly, Maruho, Medac, Medimmune, Merck & Co, Merck-Serono, Novartis, Pfizer, Regeneron, Sandoz, Sanofi-Aventis, and Takeda. KN is a former employee of Merck & Co; AM, NC, QL, KL, CLR, and SG are current Merck & Coemployees. ABK is a consultant and investigator for Merck & Co, Amgen, AbbVie, Janssen, Novartis, Dermira, and Pfizer, a consultant for Sun Pharmaceuticals, Bristol-Myers Squibb, Lilly, and VBL, and has received fellowship funding from Janssen.

Acknowledgments

We thank Jonathan Barker (King's College, London, England), for input on study design, the patients and investigators who participated in our trials, and Jennifer Pawlowski (Merck & Co) for editorial and administrative assistance with the Article.

References

1 Christophers E. Psoriasis—epidemiology and clinical spectrum. *Clin Exp Dermatol* 2001; **26:** 314–20.
2 Boehncke WH, Schön MP. Psoriasis. *Lancet* 2015; **386:** 983–94.
3 Zhao Y, Fishelevich R, Petrali JP, et al. Activation of keratinocyte protein kinase C zeta in psoriasis plaques. *J Invest Dermatol* 2008; **128:** 2190–97.
4 Kimball AB, Jacobson C, Weiss S, Vreeland MG, Wu Y. The psychosocial burden of psoriasis. *Am J Clin Dermatol* 2005; **6:** 383–92.
5 Lewis-Beck C, Abouzaid S, Xie L, Baser O, Kim E. Analysis of the relationship between psoriasis symptom severity and quality of life, work productivity, and activity impairment among patients with moderate-to-severe psoriasis using structural equation modeling. *Patient Prefer Adherence* 2013; **7:** 199–205.
6 Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 1999; **41:** 401–07.
7 Lowes MA, Russell CB, Martin DA, Towne JE, Krueger JG. The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. *Trends Immunol* 2013; **34:** 174–81.
8 Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008; **58:** 106–15.
9 Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous *vs* intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2007; **56:** e1–15.
10 Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349:** 2014–22.
11 Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; **152:** 1304–12.
12 Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; **371:** 1665–74.

13 Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371:** 1675–84.

14 Duvallet E, Semerano L, Assier E, Falgarone G, Boissier MC. Interleukin-23: a key cytokine in inflammatory diseases. *Ann Med* 2011; **43:** 503–11.

15 Tonel G, Conrad C, Laggner U, et al. Cutting edge: a critical functional role for IL-23 in psoriasis. *J Immunol* 2010; **185:** 5688–91.

16 Kopp T, Riedl E, Bangert C, et al. Clinical improvement in psoriasis with specific targeting of interleukin-23. *Nature* 2015; **521:** 222–26.

17 Papp K, Thaci D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol* 2015; **173:** 930–39.

18 Gordon KB, Duffin KC, Bissonnette R, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *N Engl J Med* 2015; **373:** 136–44.

19 Sofen H, Smith S, Matheson RT, et al. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. *J Allergy Clin Immunol* 2014; **133:** 1032–40.

20 Krueger JG, Ferris LK, Menter A, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2015; **136:** 116–24.

21 Luger T, Schopf RE, Schwanke A, Langhammer S, Meng T, Loschmann PA. An observational study to evaluate the long-term outcomes of treatment with etanercept in patients with plaque-type psoriasis. *J Eur Acad Dermatol Venereol* 2016; **30:** 1730–41.

22 Langrish CL, Chen Y, Blumenschein WM, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med* 2005; **201:** 233–40.

23 Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med* 2014; **371:** 326–38.

24 Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med* 2016; **375:** 345–56.

25 Lee E, Trepicchio WL, Oestreicher JL, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgarism. *J Exp Med* 2004; **199:** 125–30.

26 Taylor PR, Roy S, Leal SM Jr, et al. Activation of neutrophils by autocrine IL-17A-IL-17RC interactions during fungal infection is regulated by IL-6, IL-23, RORγt and dectin-2. *Nat Immunol* 2014; **15:** 143–51.

27 Chan JR, Blumenschein W, Murphy E, et al. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *J Exp Med* 2006; **203:** 2577–87.

28 Cua DJ, Sherlock J, Chen Y, et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* 2003; **421:** 744–48.

29 Lee E, Trepicchio WL, Oestreicher JL, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med* 2004; **199:** 125–30.

30 Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator–controlled VOYAGE 1 trial. *J Am Acad Dermatol* 2017; **76:** 405–17.

31 Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol* 2017; **76:** 418–31.

32 Boisson B, Wang C, Pedergnana V, et al. An *ACT1* mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. *Immunity* 2013; **39:** 676–86.

33 Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat Rev Immunol* 2014; **14:** 585–600.

34 Hernandez-Santos N, Gaffen SL. Th17 cells in immunity to *Candida albicans*. *Cell Host Microbe* 2012; **11:** 425–35.

35 Puel A, Cypowyj S, Bustamante J, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science* 2011; **332:** 65–68.

36 Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in psoriasis and psoriatic arthritis patients treated with IL-17 inhibitors and their practical management. *Br J Dermatol* 2016; published online Aug 31. DOI:10.1111/bjd.15015.

37 Van de Kerkhof PC, Griffiths CE, Reich K, et al. Secukinumab long-term safety experience: a pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. *J Am Acad Dermatol* 2016; **75:** 83–98.

38 Blauvelt A. Safety of secukinumab in the treatment of psoriasis. *Expert Opin Drug Saf* 2016; **15:** 1413–20.

39 Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut* 2012; **61:** 1693–700.

40 Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012; **367:** 1519–28.

41 Reich K, Leonardi C, Langley RG, et al. Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: a presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials. *J Am Acad Dermatol* 2017; **76:** 441–48.

42 Targan SR, Feagan B, Vermeire S, et al. A randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn's disease. *Am J Gastroenterol* 2016; **111:** 1599–607.

43 Schmidt C. Suicidal thoughts end Amgen's blockbuster aspirations for psoriasis drug. *Nat Biotechnol* 2015; **33:** 894–95.

44 Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol* 2016; **175:** 273–86.

45 Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med* 2015; **373:** 1318–28.

46 Gordon KB, Langley RG, Gottlieb AB, et al. A phase III, randomized, controlled trial of the fully human IL-12/23 mAb briakinumab in moderate-to-severe psoriasis. *J Invest Dermatol* 2012; **132:** 304–14.

47 Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006; **55:** 829–35.