The EGALITY study

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The EGALITY study: A confirmatory, randomised, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, versus the originator product in patients with moderate to severe chronic plaque-type psoriasis

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N Hattebuhr, J Poetzl, H Woehling, G Wuerth and M Afonso are employees of Hexal AG.

What is known about this topic?

- Etanercept is a tumour necrosis factor inhibitor successfully used in clinical practice for the treatment of various immune-mediated inflammatory diseases.
- A biosimilar is a biologic medicinal product designed to be essentially the same as the reference biologic (authorised biological medicine - the originator).
- Biosimilarity is established on the basis of the totality-of-the-evidence based on the data from analytical, non-clinical, pharmacokinetic and clinical comparisons with the originator product.

What does this study add?

- GP2015 is a proposed etanercept biosimilar.
- EGALITY, the first etanercept biosimilar study in patients with moderate to severe chronic plaque-type psoriasis was conducted with the purpose of gathering confirmatory clinical evidence of biosimilarity between GP2015 and the etanercept originator in a sensitive indication.
- GP2015 was shown to possess equivalent efficacy and comparable safety and immunogenicity to the etanercept originator, with no new or unexpected safety issues.

Abstract:

Background: GP2015 is a proposed etanercept biosimilar.

Objective: To demonstrate equivalent efficacy, and comparable safety and immunogenicity of GP2015 and etanercept originator (ETN, Enbrel®) in patients with moderate to severe chronic plaque-type psoriasis.

Methods: 531 eligible patients were randomised 1:1 to self-administer GP2015 or ETN twice-weekly subcutaneously. Patients with a 50% improvement in psoriasis area and severity index (PASI 50) at week 12 were re-randomised to continue the same treatment on a once-weekly dosing schedule or to undergo a sequence of 3 treatment switches between GP2015 and ETN until week 30. Thereafter, patients continued treatment with the product they had been assigned to last, up to week 52.

Results: The difference in PASI 75 (75% improvement from baseline PASI score) response rates at week 12 between GP2015 and ETN (primary endpoint) was −2.3%. The 95% confidence interval (−9.85, 5.30) was well contained within the pre-specified margin range of (−18, 18). Incidence of treatment-emergent adverse events up to week 52 was comparable between continued GP2015 (59.8%) and ETN (57.3%); switching treatments revealed comparable safety profiles. Anti-drug antibodies, all non-neutralising, were limited to 5 patients on ETN during treatment period 1, and 1 patient in the switched ETN group, who had been treated with GP2015 for 12 weeks at time of the finding.

Conclusion: The EGALITY study demonstrated equivalent efficacy and comparable safety and immunogenicity of GP2015 and ETN. The study results provided the final clinical confirmation of biosimilarity and contributed to the totality-of-the-evidence proposing that GP2015 is an etanercept biosimilar.

The study is registered at Clinicaltrials.gov (NCT01891864).

Key words: Bioequivalence, biosimilar, efficacy, etanercept, GP2015, immunogenicity, psoriasis, safety

Introduction

Etanercept is a recombinant human tumour necrosis factor alpha (TNFα)receptor–p75Fc fusion protein that, with high affinity and specificity binds TNFα, a naturally occurring cytokine implicated in a range of immune-mediated inflammatory diseases (IMIDs) rendering it biologically inactive.[1-4] Etanercept has been used successfully in clinical practice for more than 15 years and is approved for the treatment of multiple IMIDs, including plaque psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis.

Biological products such as etanercept are derived from unique bioengineered cells or organisms.[5,6] Biosimilars are follow-on versions of authorised biological products.[7] Regulatory authority guidelines require to evaluate and confirm biosimilarity between the active substance of a proposed biosimilar and the approved originator based on the totality of the evidence derived from a complete data package, comprising physicochemical, biological, nonclinical and clinical data.[8,9]

GP2015 is a proposed etanercept biosimilar. The bioequivalence of GP2015 with etanercept originator product (ETN), has been demonstrated in non-clinical[10] and pharmacokinetic studies.[Manuscript submitted] The EGALITY study in psoriasis with GP2015 was conducted to contribute key confirmatory clinical data as part of the totality of biosimilarity evidence. The objective of this study was to demonstrate equivalence in efficacy and to compare safety and immunogenicity of GP2015 and ETN in patients with moderate to severe chronic plaque-type psoriasis. The effects of repeated treatment switching between GP2015 and ETN on efficacy, overall safety, and immunogenicity were also evaluated.

Methods

EGALITY was a multicentre, randomised, double-blind, confirmatory efficacy and safety study conducted from 24 June, 2013, to 30 March, 2015, across 74 centres in 11 European countries and South Africa (NCT01891864).

Study population

Eligible patients included men or women ≥18 years of age, with active but clinically stable chronic plaque-type psoriasis diagnosed ≥6 months before baseline, who had previously received phototherapy or systemic psoriasis therapy at least once or who were candidates for such therapies in the opinion of the investigator. Moderate to severe psoriasis at baseline was defined as a psoriasis area and severity index scores (PASI) score of ≥10, an Investigator's Global Assessment modified 2011 (IGA mod 2011) score of ≥3 (based on a scale of 0-4) and ≥10% of body surface area affected by plaque-type psoriasis.

Key exclusion criteria were any previous exposure to etanercept; exposure to TNF antagonists or other biologic immunomodulating agents in the 6 months prior to randomization; ongoing use of prohibited psoriasis treatments such as topical corticosteroids or ultraviolet-therapy, or prohibited non-psoriasis treatments (all other prior non-psoriasis concomitant treatments had to be on a stable dose for ≥4 weeks before baseline); presence of active systemic infections in the two weeks prior to baseline; or latent tuberculosis detected by imaging or positive QuantiFERON®-TB Gold test (Please see Appendix S1 for detailed exclusion criteria).

Study design

The study consisted of 4 periods (Fig. 1): screening; treatment period 1 (week 0–12); treatment period 2 (week 13–30) and; an extension phase (week 31–52). In treatment period 1, patients were randomised 1:1 to self-administer 50 mg GP2015 or 50 mg ETN (Enbrel® [Amgen Inc., Thousand Oaks, CA 91320] European Union-authorised) twice weekly, subcutaneously. In treatment period 2, patients who had achieved at least a 50% improvement in PASI (PASI 50) from baseline at week 12 were re-randomised to either continue the same treatment on a once-weekly dosing schedule (named 'continued GP2015' and 'continued ETN' groups, respectively), or to undergo a sequence of 3 treatment switches between GP2015 and ETN at 6-weekly intervals until week 30 (named 'switched GP2015' and 'switched ETN' groups, respectively). During the extension phase, patients continued to receive the same treatment received during the final 6 weeks of treatment period 2 (Please see Appendix S1 for randomisation and other study details).

This study was conducted in accordance with the ethical principles derived from the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practices and in compliance with local regulatory requirements, and was reviewed and approved by the Independent Ethics Committee or Institutional Review Board for each centre. All patients provided written informed consent before entering the study.

Efficacy assessments

The primary endpoint was the PASI 75 response rate (proportion of patients showing at least a 75% improvement in PASI score from baseline visit) after the first 12 weeks of treatment. The main secondary endpoint was the percentage change from baseline in PASI score up to week 12. Other efficacy variables assessed at all time points up to week 52 included: (i) PASI 50, 75 and 90 (proportion of patients showing at least a 50%/75%/90% improvement in PASI score from baseline visit) response rates; (ii) observed PASI score; (iii) percentage change from baseline in PASI score; (iv) IGA mod 2011 score assessed using a 5-point rating scale[11] (Supplementary Table 1).

Pharmacokinetic assessments

Trough serum concentrations of etanercept were assessed at baseline and at weeks 2, 4, 8 and 12 in a subset of 147 patients. The etanercept serum concentrations were quantified using a validated enzyme-linked immunosorbent assay (ELISA). (Please see Appendix S1 for detailed assay methodology).

Safety assessments

Adverse event monitoring and injection site reactions (ISRs) were assessed at all visits. Adverse events of special interest (AESIs) were defined by preferred terms encompassing all of the special warnings and precautions given on the label for ETN.[6]

Immunogenicity assessments

The anti-drug antibody (ADA) assessment and analysis followed a tiered approach, and included a screening assay followed by a confirmatory specificity assay and a competitive ligand binding assay to assess neutralizing capacity of ADAs. (Please see Appendix S1 for detailed assay methodology).

Statistical analysis

A sample size of approximately 546 patients to maintain 464 evaluable patients with an assumed drop-out and major protocol deviation rate of 15% was planned to provide a power of 90% to show therapeutic equivalence between GP2015 and ETN.

Based on statistical hypothesis, therapeutic equivalence in terms of PASI 75 was to be established if the 95% confidence interval (CI) for the difference in the PASI 75 response rates was contained within the pre-specified margin range (−18%, 18%). Based on an observed effect size of 45-46% in former placebo-controlled ETN (Enbrel®) studies,[3,12] an equivalence margin of 18% was chosen, so that at least 60% of the treatment effect had to be maintained. Primary analysis was performed using a logistic regression model that included treatment groups (GP2015 or ETN), body weight categories and prior systemic therapy as stratification factors in the model. The stratification-factor adjusted treatment difference between GP2015 and ETN as well as the corresponding 95% CI were derived from the regression model. The primary efficacy analysis was based on the per-protocol set (PPS) that consisted of all patients who completed the study until week 12 without major protocol deviations. Dropouts due to unsatisfactory therapeutic effect were included in the PPS as non-responders provided they received at least 4 weeks of treatment. The analysis was repeated on the full analysis set (FAS) following the intent-to-treat principle as a sensitivity analysis. The main secondary efficacy variable was analysed using a powered mixed-model repeated measures (MMRM) approach[13] and an averaged treatment effect (ATE) approach using an analysis of covariance model. No imputation for missing PASI scores and components of PASI score was performed. Both approaches had a pre-specified margin range (–15%, 15%) to claim therapeutic equivalence and were performed on the PPS and repeated on the FAS. A smaller equivalence margin than for the primary analysis was chosen

because of a lower effect size for the more sensitive variable percentage change from baseline in PASI score. (Please see Appendix S1 for additional details on efficacy analyses and for definitions of data sets).

Results

Of the 531 randomised patients, the drop-out rate was low (GP2015: n=8, 3%; ETN: n=12, 4.5%) during the initial 12 weeks of treatment. The patient disposition is shown in Figure 2. The baseline demographics and disease characteristics of patients were similar across the two treatment groups (Table 1).

Efficacy

Primary endpoint

The treatment difference between GP2015 and ETN (GP2015–ETN) for adjusted PASI 75 response rates in the PPS (n=480) at week 12 was –2.3 (73.4% vs 75.7%; 95% CI [−9.85, 5.30]; Fig.3). As the 95% CI was contained within the pre-specified interval (–18%, 18%), this result demonstrated therapeutic equivalence between GP2015 and ETN. The primary endpoint analysis was further supported by the analysis on the FAS (Fig.3).

Main secondary endpoint

The mean percent change from baseline to week 12 in PASI score was similar between GP2015 and ETN (Fig. 4a). The 95% CIs for the least-squares mean difference in percent change from baseline in PASI score (GP2015-ETN) up to week 12 for both, the MMRM (–0.64 [–3.47, 2.20]) and the ATE (–0.88 [–3.61, 1.85]) approaches were contained within the pre-specified interval of (−15%, 15%, Fig. 4b). These findings on the PPS were supported by similar analyses on the FAS (Supplementary Figure 1).

Other endpoints

From baseline to week 52, the mean scores and percent changes from baseline in PASI score at all time-points were comparable between the continued GP2015 and ETN groups in the PPS, and between the pooled continued and pooled switched treatment groups (Supplementary Figures 2 and 3). In all treatment groups, the adjusted PASI 75 and PASI 90

response rates gradually increased over time until week 30 and thereafter remained stable until week 52 (Fig. 5, Supplementary Figure 4). The adjusted PASI 50 response rate increased until week 12, at which time PASI 50 non-responders were discontinued from the study (Fig. 5). The PASI 50 response rate remained stable from week 18 until week 52 in all treatment groups (Fig. 5, Supplementary Figure 4). At baseline, the majority of patients in the GP2015 (72.0% [n=172/239]) and ETN (68.9% [n=166/241]) groups had an IGA mod 2011 score of 3. At week 12, the proportion of IGA mod 2011 responders (score of '0' or '1') was numerically higher in the GP2015 group than in the ETN group (Fig. 6).

Pharmacokinetic results

Trough concentrations indicated that drug concentrations reached steady-state systemic levels from week 2 onwards in both treatment arms, consistent with reported half-life of 3–4 days for etanercept,[6] and was maintained throughout the 12-week period of evaluation in both treatment groups (Fig.4c). Mean etanercept trough levels at weeks 2, 4, 8, and 12, as well as the variability of etanercept trough levels were similar within and across both treatment groups, indicating sustained exposure to etanercept and comparable clearance of GP2015 and ETN.

Safety results

The median duration of exposure until 12 weeks was similar between the GP2015 and ETN groups (81 days); and until 52 weeks was similar between the continued GP2015 and ETN groups (358 days).

The number of patients with at least 1 treatment-emergent adverse event (TEAE) up to week 52 was similar between the continued GP2015 (n=98 [59.8%]) and the continued ETN groups (n=98 [57.3%]); and between the switched GP2015 (n=61[61.0%]) and switched ETN groups (n=57 [59.4%], Table 2). The incidence of serious adverse events, study discontinuation due to TEAEs, and treatment-related TEAEs was similar between the 2 continued treatment groups and between the 2 switched treatment groups (Table 2, Supplementary Table 2)

The incidence of AESIs was higher for continued GP2015 vs continued ETN (11.0% vs 4.7%); and for switched GP2015 (11 [11.0%]) vs switched ETN (5 [5.2%]; Supplementary Table 3) groups. Malignant melanoma *in situ* was reported in 1 patient in the continued GP2015 group. One patient died during the study, due to cardiopulmonary failure (in the ETN group in treatment period 1). The death was suspected to be due to concomitant conditions such as Type 2 diabetes mellitus and not suspected to be treatment related.

ISRs were reported in 13 (4.9%) patients in the GP2015 group and in 38 (14.2%) patients in the ETN group until week 12. Most ISRs were mild in both treatment groups (11 [4.2%] and 32 [12.0%] patients, respectively). In the continued GP2015 and continued ETN groups, ISRs were reported in 14 (8.5%) and 27 (15.8%) patients respectively, until week 52; most were mild (13 [7.9%] vs 23 [13.5%], respectively).

Immunogenicity

Five patients (1.9%) in the ETN group (n=267) had a confirmed positive low titer non-neutralizing ADA result during treatment period 1. These responses were detected within the first 4 weeks of treatment and the respective patients had ADA negative results at all subsequent visits. One patient (1.1%) in the switched ETN group (n=90) showed a confirmed positive low titer non-neutralizing ADA result at week 36 (patient was receiving GP2015 for 12 weeks at the time of the finding), with no other confirmed ADA results in previous or subsequent visits. No further patients in the study had confirmed positive ADA samples.

Discussion

The results of this study confirm biosimilarity that was established with all previous analytical comparisons to the reference product in that equivalent efficacy was demonstrated as well as similar safety and immunogenicity of GP2015 with ETN in a highly sensitive, generally immune-competent population. In patients with moderate to severe chronic plaque-type psoriasis, GP2015 was shown to be equivalent to ETN regarding the PASI 75 response rate after 12 weeks of treatment. This primary endpoint result was corroborated by the main secondary efficacy outcome. Other efficacy outcomes up to week 52 established both equivalence of efficacy and lack of difference between long-term

treatment with GP2015 and ETN. Switching these 2 treatments did not have any negative effect on efficacy.

A PASI 75 response rate was chosen to demonstrate equivalence between GP2015 and ETN as it is established as a clinically meaningful endpoint in clinical trials, and is considered by clinicians to be indicative of success with treatment in patients with psoriasis.[14] The PASI 75 response rates observed at week 12 in this study were highly comparable between the treatment groups (GP2015: 73.4%; ETN: 75.7%) even though they were above the upper range of those reported at week 12 in previous studies with ETN in this indication (47%-62%).[3,12,15-17] Several possible factors could have contributed to this difference. The biosimilar study design involves use of two active treatment arms lacking a placebo comparator, and it has been previously reported that using only active treatment arms shows an increased effect size compared with placebo-controlled studies.[18-21] The PASI 75 analysis was based on the PPS excluding protocol violators and drop-outs, as it is considered the more sensitive population in equivalence or noninferiority trials,[22,23] unlike the FAS based on the intent-to-treat principle and the last-observation-carried-forward approach used in pivotal trials. Also, patients in the EGALITY study had a lower body weight/body mass index compared to published data[24] (which may have an impact given the fixed dose regimen), higher baseline PASI score and higher affected BSA compared with patients in the ETN pivotal studies.[3,12] Of particular note, long-term response rates (at 24-30 weeks) observed in this study (Fig. 5) were similar to those observed in previous ETN studies.[16,17] Other biosimilar studies have reported higher response rates for the primary efficacy parameter compared with the pivotal studies for the originator product as well.[20,25-27] Moreover, the EGALITY study was designed to establish similarity between GP2015 and ETN in terms of PASI 75 response, and was not aimed at assessing changes in PASI 75 response with treatment over time.

The EGALITY trial, establishing biosimilarity of GP2015 versus ETN, contained specific study design attributes, as recommended by health authorities[9] and further discussed in literature.[28,29] These include use of an equivalence design with pre-specified comparability margins justified on both statistical and clinical grounds by using the data of the originator product, selection of an indication considered most sensitive for the comparison, and

inclusion of applicable stratification factors in the statistical model.[9,28,29] Psoriasis patients constitute a suitable population to demonstrate biosimilarity for TNFα inhibitors, because of the enhanced sensitivity for detecting potential differences in clinical efficacy and immunogenicity in this indication compared with other approved disease conditions.[29] Also, in psoriasis, the selected dosing regimen of 50 mg twice weekly falls into the linear phase of the dose-response curve, in which differences in dose can translate into a difference in efficacy.[3] In addition, there is generally no concomitant immunosuppressive therapy in psoriasis treatment with etanercept, resulting in an unbiased and sensitive detection of any potential difference in immunogenicity.

In a preceding pharmacokinetic study in healthy volunteers, GP2015 pharmacokinetics were shown to be bioequivalent to ETN (Manuscript submitted). In this study, trough serum concentration levels of GP2015 or ETN measured after multiple subcutaneous doses were similar within and across both treatment groups, providing further evidence of similar pharmacokinetics of GP2015 and ETN.

The incidence of TEAEs up to week 52 was generally comparable between the treatment groups and no new or unexpected safety issues were reported. Overall, the safety profile of both GP2015 and ETN were in line with previous large-scale ETN studies.[3,12] The incidence of ISRs up to 12 weeks was lower with GP2015 (4.9%) than ETN (14.2%) while the incidence in the ETN group was consistent with that reported in previous ETN studies (13%[3] and 18%[12]). Although the reasons for the lower incidence of ISRs cannot be fully elucidated, a possible reason could be the difference in formulation between the two products, as has been reported in other biosimilar studies.[20] The higher incidence of TEAEs of special interest reported with GP2015 during the study were not caused by an increased number of events in any specific system organ class, but were due to events spread across several system organ classes, with most occurring in just 1 patient each in the continued GP2015 group vs none in the continued ETN group. Safety was not affected by switching treatments.

Etanercept is known to have a lower incidence of immunogenicity in comparison to other TNFα inhibitors.[30,31] The incidence of ADAs during the study was low and consistent with that reported in other large-scale ETN trials in psoriasis;[3,12,15] 6 patients were ADA-positive and all lacked neutralising antibodies. Switching from ETN to GP2015 or vice versa did not lead to increased ADA formation.

Conclusions

The efficacy of GP2015 was equivalent to ETN in patients with moderate to severe chronic plaque-type psoriasis. There were no clinically meaningful differences in efficacy, safety or immunogenicity between GP2015 and ETN up to 52 weeks of treatment. No new or unexpected safety issues were reported, and the safety profiles of GP2015 and ETN were similar to those observed in previous ETN studies. Switching treatments did not impact efficacy, safety or immunogenicity. The study results provide clinical confirmation of biosimilarity and contribute to the totality-of-the-evidence proposing GP2015 as an etanercept biosimilar.

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References

1 Bradley JR. TNF-mediated inflammatory disease. *J Pathol* 2008; **214**: 149-60.

2 Sedger LM, McDermott MF. TNF and TNF-receptors: From mediators of cell death and inflammation to therapeutic giants - past, present and future. *Cytokine Growth Factor Rev* 2014; **25**: 453-72.

3 Leonardi CL, Powers JL, Matheson RT *et al.* Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349**: 2014-22.

4 Tan JK, Aphale A, Malaviya R *et al.* Mechanisms of action of etanercept in psoriasis. *J Investig Dermatol Symp Proc* 2007; **12**: 38-45.

5 Blauvelt A, Cohen AD, Puig L *et al.* Biosimilars for psoriasis: preclinical analytical assessment to determine similarity. *Br J Dermatol* 2016; **174**: 282-6.

6 European Medicines Agency. Enbrel summary of product characterisitcs. Available at: www.ema.europa.eu/docs/en_GB/document.../WC500027361.pdf. 2010 (1 March 2016).

7 European Medicines Agency. Guideline on similar biological medicinal products. Available at: www.ema.europa.eu/docs/en_GB/...guideline/.../WC500176768.pdf. 2014 (Last accessed 1 March 2016).

8 Weise M, Bielsky MC, De Smet K *et al.* Biosimilars-why terminology matters. *Nat Biotechnol* 2011; **29**: 690-3.

9 European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf. 2014 (Last accessed 3 March 2016).

10 Hofmann HP, Kronthaler U, Fritsch C *et al.* Characterization and non-clinical assessment of the proposed etanercept biosimilar GP2015 with originator etanercept (Enbrel®). *Expert Opin Biol Ther* 2016; **16**: 1185-95.

11 Langley RG, Feldman SR, Nyirady J *et al.* The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatolog Treat* 2015; **26**: 23-31.

12 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.

13 Brown H, Prescott R. *Applied mixed models in medicine*, Second edn. England: John Wiley & Sons, Ltd. 2006.

14 Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. *Ann Rheum Dis* 2005; **64**: ii65-8; discussion ii69-73.

15 Tyring S, Gottlieb A, Papp K *et al.* Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 2006; **367**: 29-35.

16 Sterry W, Ortonne JP, Kirkham B *et al.* Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. *BMJ* 2010; **340**: c147.

17 Strohal R, Puig L, Chouela E *et al.* The efficacy and safety of etanercept when used with as-needed adjunctive topical therapy in a randomised, double-blind study in subjects with moderate-to-severe psoriasis (the PRISTINE trial). *J Dermatolog Treat* 2013; **24**: 169-78.

18 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.

19 Thaci D, Blauvelt A, Reich K *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol* 2015; **73**: 400-9.

20 Emery P, Vencovsky J, Sylwestrzak A *et al.* A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2015: DOI:10.1136/annrheumdis-2015-207588.

21 Mrowietz U, Leonardi CL, Girolomoni G *et al.* Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE). *J Am Acad Dermatol* 2015; **73**: 27-36 e1.

22 US Food and Drug Administration. Guidance for industry. Non-inferiority clinical trials. Available at:

http://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf. 2010 (Last accessed 4 March 2016).

23 Dranitsaris G, Dorward K, Hatzimichael E *et al.* Clinical trial design in biosimilar drug development. *Invest New Drugs* 2013; **31**: 479-87.

24 Tyring S, Gordon KB, Poulin Y *et al.* Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol* 2007; **143**: 719-26.

25 Yoo DH, Oh C, Hong S *et al.* Analysis of clinical trials of biosimilar infliximab (CT-P13) and comparison against historical clinical studies with the infliximab reference medicinal product. *Expert Rev Clin Immunol* 2015; **11 Suppl 1**: S15-24.

26 Yoo DH, Hrycaj P, Miranda P *et al.* A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013; **72**: 1613-20.

27 Choe JY, Prodanovic N, Niebrzydowski J *et al.* A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2015: doi:10.1136/annrheumdis-2015-207764.

28 Zhang A, Tzeng JY, Chow SC. Statistical considerations in biosimilar assessment using biosimilarity index. *J Bioequiv Availab* 2013; **5**: 209-14.

29 Lai Z, La Noce A. Key design considerations on comparative clinical efficacy studies for biosimilars: adalimumab as an example. *RMD Open* 2016; **2**: e000154.

30 Vincent FB, Morand EF, Murphy K *et al.* Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. *Ann Rheum Dis* 2013; **72**: 165-78.

31 de Vries MK, van der Horst-Bruinsma IE, Nurmohamed MT *et al.* Immunogenicity does not influence treatment with etanercept in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; **68**: 531-5.

Figure Legends

Figure 1. EGALITY study design

ETN=etanercept originator product

Figure 2. Patient disposition from baseline to week 52 (FAS)

Of the 14 patients who did not enter treatment period 2, 5 patients did not achieve PASI 50 at week 12 (3 others who also did not achieve PASI 50 continued erroneously in treatment period 2); 7 patients discontinued immediately after week 12 (3 patients were not re-randomized; 4 patients were re-randomized but did not take any study drug in treatment period 2); 2 patients achieved PASI 50 at week 12, but had no data beyond week 12. Of the 5 patients who did not enter the extension phase, 2 patients discontinued at their own decision; 1 patient discontinued due to a treatment-emergent adverse event; 1 patient discontinued due to lack of efficacy; and 1 patient was lost to follow-up.

Switched GP2015 treatment group includes patients who switched to treatment sequence ETN>GP2015>ETN at 6 week intervals during treatment period 2 and Switched ETN treatment group includes patients who switched to treatment sequence GP2015>ETN>GP2015 at 6 week intervals during treatment period 2. During the extension phase, patients continued receiving the last treatment received during treatment period 2.

ETN=etanercept originator product; FAS=full analysis set; PASI=psoriasis area and severity index

Figure 3. Adjusted PASI 75 response rates at week 12

[a]Adjusted response rate difference (%) between GP2015-ETN and associated 95% confidence interval

PPS: GP2015 (n=239), ETN (n=241); FAS: GP2015 (n=264), ETN (n=267)

ETN=etanercept originator product; FAS=full analysis set; PASI=psoriasis area and severity index; PPS=per protocol set

Figure 4. Percent change from baseline in PASI score and GP2015 and ETN plasma concentrations until week 12

The least-squares mean difference in percent change from baseline in PASI score was analysed by employing a MMRM and an ATE approach

One patient from the ETN group was dosed with study drug prior to collection of the blood sample for PK analysis at baseline and was excluded from the analysis.

ATE=averaged treatment effect; CI=confidence interval; ETN=etanercept originator product; MMRM=mixed-model repeated measures; PASI=psoriasis area and severity index; PK=pharmacokinetics; PPS=per protocol set; SD=standard deviation

Figure 5. Adjusted PASI 50, 75 and 90 response rates for continued treatment groups from baseline to week 52 (overall PPS)

ETN=etanercept originator product; PPS= per-protocol set; PASI=psoriasis area and severity index.

Figure 6. Proportion of IGA responders at week 12 (PPS)

An IGA responder was defined as a patient who achieved a score of 0 (“clear”) or 1 (“almost clear”) and improved by at least 2 points of the IGA scale compared with baseline.

ETN=etanercept originator product; IGA=Investigator’s Global Assessment; PPS=per protocol set

Table 1. Baseline demographics and disease characteristics (FAS)

	GP2015 **N=264**	**ETN** **N=267**
Age (years), mean (SD)	42.1 (12.29)	42.7 (12.86)
Sex, n (%)		
- Male	157 (59.5)	172 (64.4)
Race, n (%)[a]		
- Caucasian	263 (99.6)	264 (98.9)
- Black	1 (0.4)	0
- Asian	0	1 (0.4)
Body weight (kg), mean (SD)	86.3 (21.1)	85.9 (18.7)
Body weight category, n (%)		
- <90 kg	160 (60.6)	161 (60.3)
- ≥90 kg	104 (39.4)	106 (39.7)
BMI (kg/m^2), mean (SD)	28.6 (6.1)	28.5 (5.5)
Duration since initial diagnosis of plaque-type psoriasis (years), mean (SD)	17.6 (11.3)	17.8 (11.9)
IGA mod 2011, n (%)		
2=Mild	0	1 (0.4)
3=Moderate	191 (72.3)	186 (69.7)
4=Severe	73 (27.7)	80 (30.0)
PASI score, mean (SD)	22.5 (8.9)	22.5 (9.5)
Presence of psoriatic arthritis, n (%)	54 (20.5)	53 (19.9)
Prior systemic therapy, n (%)		
No	182 (68.9)	184 (68.9)
Any	79 (29.9)	81 (30.3)
TNF antagonist	3 (1.1)	2 (0.7)
BSA affected (%), mean (SD)	30.5 (13.8)	30.9 (14.8)

[a]In the ETN group, 1 (0.4%) patient belonged to the "unknown" category, and another 1 (0.4%) patient to the "other" category

BMI=body mass index; BSA=body surface area; ETN=etanercept originator product; IGA=investigator's global assessment; FAS= full analysis set; PASI=psoriasis area and severity index; SD=standard deviation; TNF=tumour necrosis factor

Table 2. Summary of TEAEs up to week 52 for continued and switched treatment groups (OA safety set)

Preferred term	Continued GP2015 N=164 n (%)	Continued ETN N=171 n (%)	Switched GP2015 N=100 n (%)	Switched ETN N=96 n (%)
Any TEAE	98 (59.8)	98 (57.3)	61 (61.0)	57 (59.4)
Any SAE	7 (4.3)	7 (4.1)	6 (6.0)	6 (6.3)
Any treatment-related TEAE	34 (20.7)	33 (19.3)	22 (22.0)	20 (20.8)
Discontinuations due to TEAE	11 (6.7)	8 (4.7)	2 (2.0)	5 (5.2)
Deaths	0	1 (0.6)	0	0
TEAEs with a ≥ 2% incidence in any of the treatment groups				
Nasopharyngitis	20 (12.2)	17 (9.9)	14 (14.0)	10 (10.4)
Pharyngitis	7 (4.3)	10 (5.8)	5 (5.0)	3 (3.1)
Back pain	7 (4.3)	3 (1.8)	2 (2.0)	4 (4.2)
Alanine aminotransferase increased	6 (3.7)	2 (1.2)	1 (1.0)	2 (2.1)
Gamma-glutamyltransferase increased	6 (3.7)	0	3 (3.0)	0
Tonsillitis	5 (3.0)	1 (0.6)	1 (1.0)	2 (2.1)
Viral upper respiratory tract infection	5 (3.0)	6 (3.5)	4 (4.0)	8 (8.3)
Aspartate aminotransferase increased	5 (3.0)	1 (0.6)	1 (1.0)	2 (2.1)
Arthralgia	5 (3.0)	7 (4.1)	3 (3.0)	5 (5.2)
Hypertension	5 (3.0)	7 (4.1)	3 (3.0)	2 (2.1)
Upper respiratory tract infection	4 (2.4)	5 (2.9)	1 (1.0)	3 (3.1)
Bronchitis	4 (2.4)	3 (1.8)	0	1 (1.0)
Respiratory tract infection viral	4 (2.4)	2 (1.2)	4 (4.0)	1 (1.0)
Diarrhoea	4 (2.4)	2 (1.2)	1 (1.0)	3 (3.1)

Preferred term	Continued GP2015 N=164 n (%)	Continued ETN N=171 n (%)	Switched GP2015 N=100 n (%)	Switched ETN N=96 n (%)
Lymphadenopathy	4 (2.4)	0	1 (1.0)	1 (1.0)
Headache	3 (1.8)	8 (4.7)	4 (4.0)	3 (3.1)
Cough	3 (1.8)	2 (1.2)	3 (3.0)	0
Oropharyngeal pain	3 (1.8)	2 (1.2)	3 (3.0)	1 (1.0)
Herpes simplex	2 (1.2)	1 (0.6)	2 (2.0)	0
Urinary tract infection	2 (1.2)	3 (1.8)	2 (2.0)	1 (1.0)
Rhinitis	2 (1.2)	4 (2.3)	1 (1.0)	3 (3.1)
Weight increased	2 (1.2)	4 (2.3)	3 (3.0)	0
Blood pressure increased	2 (1.2)	2 (1.2)	4 (4.0)	0
Pruritus	2 (1.2)	4 (2.3)	0	1 (1.0)
Toothache	2 (1.2)	1 (0.6)	0	3 (3.1)
Acute tonsillitis	1 (0.6)	1 (0.6)	0	3 (3.1)
Folliculitis	1 (0.6)	2 (1.2)	2 (2.0)	0
Nausea	1 (0.6)	2 (1.2)	1 (1.0)	2 (2.1)
Sciatica	1 (0.6)	0	0	2 (2.1)
Somnolence	1 (0.6)	0	2 (2.0)	0
Fatigue	1 (0.6)	3 (1.8)	2 (2.0)	0
Pain in extremity	0	3 (1.8)	2 (2.0)	1 (1.0)
Psoriasis	0	5 (2.9)	3 (3.0)	1 (1.0)
Gastritis	0	4 (2.3)	2 (2.0)	2 (2.1)
Oral herpes	0	1 (0.6)	2 (2.0)	1 (1.0)
Dental caries	0	1 (0.6)	0	2 (2.1)
Hyperuricaemia	0	1 (0.6)	2 (2.0)	0
Pyrexia	0	1 (0.6)	2 (2.0)	2 (2.1)
Diabetes mellitus	0	0	1 (1.0)	2 (2.1)
Pyelonephritis	0	0	2 (2.0)	0
Hepatitis alcoholic	0	0	0	2 (2.1)

Preferred term	Continued GP2015 N=164 n (%)	Continued ETN N=171 n (%)	Switched GP2015 N=100 n (%)	Switched ETN N=96 n (%)

Patients experiencing multiple events were counted only once within each treatment group.
PTs with events occurring with an incidence ≥ 2% in any of the treatment groups in the OA safety set are presented and sorted by descending order of frequency within the continued GP2015 column.
AE terms are coded using MedDRA version 17.0.

Switched GP2015: Switched to treatment sequence ETN>GP2015>ETN in period 2 and continued with ETN in extension period

Switched ETN: Switched to treatment sequence GP2015>ETN>GP2015 in period 2 and continued with GP2015 in extension period

AE=adverse event; ETN=etanercept originator product; MedDRA=medical dictionary for regulatory activities; OA=overall analysis; PT=preferred term; SAE=serious adverse event; SOC=system organ class; TEAE=treatment-emergent adverse event.