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ADIS BIOSIMILAR BRIEF

GP2015: An Etanercept Biosimilar

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Abstract GP2015 is the second biosimilar of the reference p75 TNF receptor-Fc fusion protein etanercept. It is approved for use in all indications for which reference etanercept is approved, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis and paediatric plaque psoriasis. GP2015 has similar physiochemical and pharmacodynamic properties to those of reference etanercept, and the pharmacokinetic biosimilarity of the agents has been shown in healthy volunteers. GP2015 demonstrated clinical efficacy equivalent to that of reference etanercept in patients with moderate-to-severe plaque psoriasis; the tolerability, safety and immunogenicity profiles of the two agents were also generally similar. Switching between GP2015 and reference etanercept had no impact on clinical efficacy, tolerability or immunogenicity. The role of reference etanercept in the management of inflammatory autoimmune conditions is well established and GP2015 provides an effective biosimilar alternative for patients requiring etanercept therapy.

GP2015: Key Points
Biosimilar to reference etanercept
Equivalent efficacy and generally similar tolerability to reference etanercept in patients with moderate-to-severe plaque psoriasis
Switching between GP2015 and reference etanercept did not appear to impact efficacy or tolerability
Approved for all indications for which reference etanercept is approved

1 Introduction

GP2015 is the second biosimilar of the reference p75 TNF receptor-Fc fusion protein etanercept, and is approved in the EU [1] for the same indications as the reference drug (Table 1). GP2015 has similar physicochemical characteristics [2] and pharmacodynamic properties [3] to those of reference etanercept, and pharmacokinetic biosimilarity of the agents has also been demonstrated [4]. This article summarizes, from an EU perspective, the key features of GP2015 and its clinical use in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis and paediatric plaque psoriasis.

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Table 1 GP2015 (Erelzi™) prescribing summary in the EU [1][a]

Approved indications	
Rheumatoid arthritis	In combination with MTX for the treatment of moderate to severe active rheumatoid arthritis in adults who have inadequately responded to DMARDs (including MTX); can be used as monotherapy in cases of MTX intolerance or when continuing MTX is inappropriate
	Adults with severe, active and progressive rheumatoid arthritis not previously treated with MTX
Juvenile idiopathic arthritis	Polyarthritis (rheumatoid factor +/−) and extended oligoarthritis in children and adolescents aged ≥ 2 years who have inadequately responded to, or proved intolerant of, MTX
	Psoriatic arthritis in adolescents aged ≥ 12 years who have inadequately responded to, or proved intolerant of, MTX
	Enthesitis-related arthritis in adolescents aged ≥ 12 years who have inadequately responded to, or proven intolerant of, conventional therapy
Psoriatic arthritis	Active and progressive psoriatic arthritis in adults who have inadequately responded to DMARD therapy
Ankylosing spondylitis	Adults with severe active ankylosing spondylitis who have inadequately responded to conventional therapy
Non-radiographic axial spondyloarthritis	Adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have inadequately responded to NSAIDs
Plaque psoriasis	Adults with moderate to severe plaque psoriasis who failed to respond to, have a contraindication to, or are intolerant of other systemic therapy (including ciclosporin, MTX or psoralen plus UVA)
Paediatric plaque psoriasis	Chronic severe plaque psoriasis in children and adolescents aged ≥ 6 years who are inadequately controlled by, or are intolerant of, other systemic therapies or phototherapies
Dosage regimens	
Juvenile idiopathic arthritis	0.4 mg/kg (≤ 25 mg per dose) twice weekly (3–4 day interval) or 0.8 mg/kg (≤ 50 mg per dose) once weekly
Paediatric plaque psoriasis	0.8 mg/kg (≤ 50 mg per dose) once weekly for up to 24 weeks
For all other indications	25 mg twice weekly or 50 mg once weekly; an alternative for plaque psoriasis is 50 mg twice weekly for ≤ 12 weeks, followed by a dose of 25 mg twice weekly or 50 mg once weekly
Administration	
GP2015 is a 50 mg/mL solution available in a pre-filled syringe (25 or 50 mg) or pre-filled pen (50 mg) for subcutaneous injection	

CRP C-reactive protein, *DMARDs* disease-modifying anti-rheumatic drugs, *MRI* magnetic resonance imaging, *MTX* methotrexate, *NSAIDs* nonsteroidal anti-inflammatory drugs

[a]Consult local prescribing information for details including pre- and post-medications, contraindications, warnings and precautions

2 Clinical Efficacy

Clinical efficacy data for GP2015 are available from a randomized, double-blind, multicentre, phase 3 trial (EGALITY) in adults with moderate-to-severe plaque psoriasis [5]. A phase 3 confirmatory study of GP2015 in patients with moderate-to-severe rheumatoid arthritis has also been completed (NCT02638259; EQUIRA), although data are not yet available; thus EGALITY is the focus of this section.

In EGALITY, eligible patients had a Psoriasis Area and Severity Index (PASI) score ≥ 10, an Investigator's Global Assessment (IGA) score ≥ 3 and ≥ 10% body surface area affected by the condition [5]. Patients were also required to have had stable active disease for ≥ 6 months and to have received, or be eligible to receive, phototherapy or systemic psoriasis therapy; however, patients treated with biological immunomodulating agents in the last 6 months were among those excluded.

EGALITY comprised three treatment periods. In the first, eligible patients were randomized to GP2015 50 mg or reference etanercept 50 mg (EU authorized), each self-administered subcutaneously twice weekly for 12 weeks [5]. Patients who achieved ≥ 50% improvement in PASI score (i.e. a PASI50 response) at 12 weeks were re-randomized at the start of period 2 to either continue their treatment (at a reduced frequency of once weekly) or to switch three times between GP2015 and reference etanercept (those in the original GP2015 group received etanercept → GP2015 → etanercept and those in the original etanercept group received GP2015 → etanercept → GP2015; each drug taken for 6 weeks) until week 30. Patients could then enter period 3, a 22-week extension during which they continued the regimen they were receiving during the last 6 weeks of period 2 [5].

The primary efficacy analysis used the per-protocol set (PPS) [239 GP2015 and 241 reference etanercept recipients], with findings then corroborated in the full-analysis set (FAS) [264 and 267 recipients]; discussion here focuses on the PPS unless otherwise specified [5]. At baseline, patients had a mean age of ≈ 42 years and had first been diagnosed with plaque psoriasis a mean of ≈ 18 years

previously; most patients (69%) had received prior systemic therapy [5].

GP2015 demonstrated equivalent efficacy to that of reference etanercept in reducing the severity and extent of moderate-to-severe plaque psoriasis over 12 weeks [5], as the between-group difference in the proportion of patients who achieved a PASI75 response (primary endpoint) had a 95% confidence interval (CI) within the prespecified equivalence margin of ± 18 both in the PPS and the FAS (Fig. 1). The two agents also demonstrated equivalent efficacy with regard to the mean change from baseline in PASI score (key secondary endpoint), with the 95% CI for the least-squares mean between-group difference being within the prespecified margin of ± 15, regardless of whether the assessment used a mixed-model repeated-measures approach (− 0.64; 95% CI −3.47 to 2.20) or an average treatment effect approach with ANCOVA (− 0.88; 95% CI −3.61 to 1.85). The proportion of patients who were clear/almost clear of psoriatic skin symptoms (i.e. had an IGA score of 0 or 1) at 12 weeks was also similar in the GP2015 and reference etanercept groups (59.4 vs. 55.6%) [5].

Longer term, no marked differences in efficacy were evident between GP2015 and reference etanercept over the remainder of the study (i.e. from week 12 to 52) [5]. For instance, among patients who received continued GP2015 ($n = 122$) or reference etanercept ($n = 118$) during the trial, at week 52, 96 versus 96% had achieved a PASI50 response, 86 versus 81% a PASI75 response and 59 versus 57% a PASI90 response (values estimated from a graph).

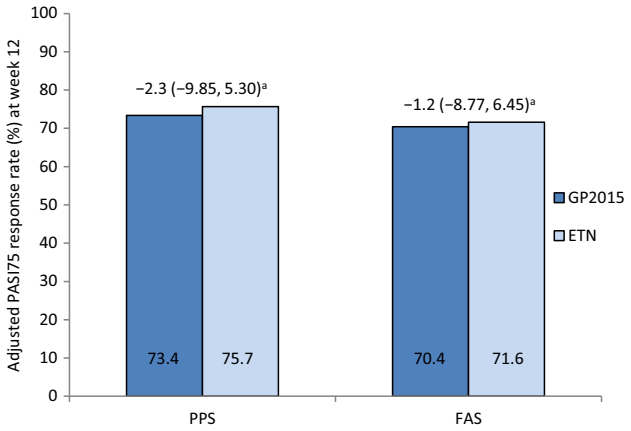

Fig. 1 Adjusted ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) response rates at week 12. **a** Adjusted response rate difference (%) between GP2015 and the etanercept originator product (ETN) and the associated 95% confidence interval. Per protocol set (PPS): GP2015 ($n = 239$), ETN ($n = 241$); full analysis set (FAS): GP2015 ($n = 264$), ETN ($n = 267$). Adapted from Griffiths et al. [5], with permission. © 2016 The Authors. *British Journal of Dermatology* published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists

2.1 Switching Data

Switching between GP2015 and reference etanercept, and vice versa, did not appear to impact clinical efficacy, indicating interchangeability. All reported efficacy outcomes in the switching groups (GP2015 → etanercept → GP2015 and etanercept → GP2015 → etanercept; pooled $n = 168$) were similar to those from the continued therapy groups (pooled $n = 240$) over the course of the trial, including PASI50, PASI75 and PASI90 response rates [5].

3 Tolerability and Safety

GP2015 had a tolerability and safety profile generally similar to that of reference etanercept in patients with moderate-to-severe plaque psoriasis [5]. Over the 52-week EGALITY study, treatment-related adverse events (AEs) occurred with an incidence of 20.7% in the continued GP2015 group ($n = 164$) and 19.3% in the continued reference etanercept group ($n = 171$), with the most common treatment-emergent AE (TEAE) in each of these groups being nasopharyngitis (12.2 vs. 9.9%). Serious TEAEs were uncommon (4% incidence each group) and the one death that occurred (in the etanercept group) was not considered to be treatment related [5]. Therapy was discontinued because of TEAEs in 6.7 and 4.7% of patients in the GP2015 and reference etanercept groups [5].

The overall incidence of special interest TEAEs (which encompassed all special warnings/precautions of the EU prescribing information for reference etanercept) was 2.3-fold greater with continued GP2015 than continued reference etanercept (11.0 vs. 4.7%), although this difference was not due to TEAEs in any particular system organ class; one GP2015 recipient developed malignant melanoma [5]. However, injection-site reactions were numerically less frequent with GP2015 than with reference etanercept at 12 weeks (4.9 vs. 14.2%), as well as at 52 weeks in the continued groups (8.5 vs. 15.8%); most were mild [5].

Switching between GP2015 and reference etanercept, and vice versa, did not appear to impact the tolerability/safety of either agent [5].

4 Immunogenicity

Anti-drug antibodies (ADAs) occurred with low incidence in the EGALITY trial [5]. ADAs (all low-titre and non-neutralizing) were detected in a total of six patients. These included five reference etanercept recipients (1.9%) who tested positive during the first 4 weeks of treatment period 1 (but tested negative for ADAs at subsequent time points). The other patient had been originally randomized to reference etanercept in period 1, was subsequently re-

Table 2 Biosimilarity summary for GP2015

Mechanism of action	Fusion of two human p75 TNFα receptor fragments and a linking IgG1 Fc region, that binds and sequesters TNF, thus preventing it binding to cellular receptors and inducing inflammatory signalling pathways [1, 2]
Physicochemical characterization	Indistinguishable primary and higher order structure, charge, glycosylation and other amino acid modifications to those of ref etanercept; product-related impurities are also below the maximum level of ref etanercept batches [2]
Pharmacodynamic biosimilarity	Similar to ref etanercept in binding affinity to TNFα and functional neutralization of TNFα and TNFβ in vitro [3]
	Similar to ref etanercept in binding affinity to Fc receptors and C1q complement in vitro; higher CDC and lower ADCC than ref etanercept, but differences not considered clinically relevant [3]
	Similar inhibition of arthritis progression as ref etanercept in a murine model of polyarthritis [3]
Pharmacokinetic biosimilarity	Equivalent exposure to ref etanercept in healthy volunteers, with other pharmacokinetic parameters also similar [4]
	Equivalent exposure when administered via autoinjector as via prefilled syringe in healthy volunteers [4]
Immunogenicity	No unexpected immunogenicity issues
Efficacy and tolerability (in ref trial)	Equivalent/similar efficacy and tolerability to ref etanercept in patients with moderate-to-severe plaque psoriasis
	Switching between GP2015 and ref etanercept, and vice versa, had no impact on efficacy or tolerability in patients with moderate-to-severe plaque psoriasis

ADCC antibody-dependent cell mediated cytotoxicity, *CDC* complement-dependent cytotoxicity, *ref* reference

randomized to the GP2015 → etanercept → GP2015 switching group and tested positive for ADAs at week 36 (i.e. while receiving GP2015).

5 Conclusion

GP2015 is an etanercept biosimilar with similar efficacy, tolerability, safety and physicochemical and biological characteristics to the reference product (Table 2). Based on bioequivalence and biosimilarity data, GP2015 has been approved in the EU for all indications for which reference etanercept is approved, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis and paediatric plaque psoriasis. Budget impact analyses suggest that use of etanercept biosimilars in Europe [6] and the UK [7] could be associated with substantial cost savings (e.g. £8.4 million over 1 year in the UK if etanercept biosimilars are discounted by 30%, and 25% of patients with rheumatoid arthritis or chronic plaque psoriasis switch from reference etanercept to an etanercept biosimilar [7]).

Compliance with Ethical Standards

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