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ADIS BIOSIMILAR BRIEF

PF-06438179/GP1111: An Infliximab Biosimilar

Zaina T. Al-Salama[1]

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Abstract
PF-06438179/GP1111 (Zessly®; Ixifi®) [hereafter referred to as GP1111] is a biosimilar of the reference monoclonal anti-TNF-α antibody infliximab, and is approved in the EU and USA for the same indications as the reference drug, including rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis (including paediatric ulcerative colitis in the EU), ankylosing spondylitis, psoriatic arthritis and plaque psoriasis; GP1111 is also approved in Japan. GP1111 has similar physicochemical characteristics and pharmacodynamic properties to those of reference infliximab, and the pharmacokinetic similarity of the agents has been shown in healthy volunteers and patients with moderate-to-severe RA despite methotrexate therapy. GP1111 demonstrated clinical efficacy equivalent to that of reference infliximab in patients with moderate-to-severe RA, despite methotrexate therapy, and was generally well tolerated in this population. The tolerability, immunogenicity and safety profiles of GP1111 were similar to those of reference infliximab, and switching from reference infliximab to GP1111 had no impact on safety, efficacy or immunogenicity. The role of reference infliximab in the management of autoimmune inflammatory conditions is well established and GP1111 provides an effective biosimilar alternative for patients requiring infliximab therapy.

PF-06438179/GP1111: Key Points

Biosimilar to reference infliximab.

Similar efficacy, tolerability and immunogenicity to reference infliximab in patients with moderate-to-severe RA despite treatment with methotrexate.

Switching from reference infliximab to GP1111 appears to have no impact on efficacy, safety or immunogenicity.

Approved for all indications for which reference infliximab is approved.

1 Introduction

PF-06438179/GP1111 (Zessly®; Ixifi®) [hereafter referred to as GP1111] is a biosimilar of the reference monoclonal anti-TNF-α antibody infliximab, and is approved in the EU [1] and USA for the same indications as the reference drug; it is also approved in Japan. GP1111 has similar physicochemical characteristics and pharmacodynamic properties to those of reference infliximab [2] (Table 2). Pharmacokinetic similarity of the agents has also been demonstrated [3]. This article summarizes, from an EU perspective (Table 1), the key features of GP1111 and its clinical use in the treatment of rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis (UC) [including paediatric UC in the EU], ankylosing spondylitis (AS), psoriatic arthritis (PsA) and plaque psoriasis, focusing on moderate-to-severe RA.

2 Clinical Efficacy

Clinical efficacy data for GP1111 are available from a randomized, double-blind, parallel-group phase III trial in adults with moderate-to-severe active RA, with an inadequate response to methotrexate and ≤ 2 doses of one non-depleting, non-infliximab biologic (REFLECTIONS B537-02) [4–6]. Eligible patients had an RA diagnosis for ≥ 4 months, ≥ 6/68 tender and ≥ 6/66 swollen joints at screening and baseline, and a high-sensitivity C-reactive protein (hs-CRP) level of ≥ 10 mg/L [7]. Patients must have used methotrexate for ≥ 12 weeks, with ≥ 4 weeks of stable dosages.

Patients were randomized to receive a 3 mg/kg intravenous infusion of GP1111 or reference infliximab at weeks 0, 2 and 6, and every 8 weeks thereafter, with continued use of methotrexate at doses of 10–25 mg/kg; dose escalation of GP1111 to

The manuscript was reviewed by: ***F. Araujo,*** Rheumatology and Osteoporosis Unit, Hospital Ortopédico de Sant'Ana, SCML, Lisbon, Portugal; ***S. R. Feldman,*** Department of Dermatology, Wake Forest School of Medicine, Winston-Salem, NC, USA

✉ Zaina T. Al-Salama
demail@springer.com

[1] Springer, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

Table 1 GP1111 (Zessly®) prescribing summary in the EU [1][a]

Approved indications	
Rheumatoid arthritis	In combination with MTX to reduce signs and symptoms and improve physical function in adults with active disease who have had an inadequate response to DMARDs (including MTX), or with severe, active and progressive disease not previously treated with MTX or other DMARDs
Crohn's disease	*Moderate-to-severe active disease:* adults who have not responded despite a full and adequate course of therapy with a CS and/or an immunosuppressant, or who are intolerant to, or contraindicated for, such therapy
	Fistulating, active disease: adults who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy)
Paediatric Crohn's disease	Children and adolescents aged 6–17 years with severe, active disease who have not responded to conventional therapy (including a CS, an immunomodulator and primary nutrition therapy), or who are intolerant to, or contraindicated for, such therapies
Ulcerative colitis	Adults with moderate-to-severe active disease who have responded inadequately to conventional therapy (including CSs, 6-MP or AZA), or who are intolerant to, or contraindicated for, such therapies
Paediatric ulcerative colitis	Children and adolescents aged 6–17 years with severe active disease who have responded inadequately to conventional therapy (including CSs, 6-MP or AZA), or who are intolerant to, or contraindicated for, such therapies
Ankylosing spondylitis	Adults with severe, active disease who have had an inadequate response to conventional therapy
Psoriatic arthritis	In combination with MTX in adults with active and progressive disease with an inadequate response to previous DMARD therapy, or as monotherapy in patients who are intolerant to, or are contraindicated for, MTX
Psoriasis	Adults with moderate-to-severe plaque psoriasis who have failed to respond to, have a contraindication for, or are intolerant to, other systemic therapy (including CYS, MTX or PUVA)
Dosage regimens	
Rheumatoid arthritis	3 mg/kg on day 1, then at 2 and 6 wks after the first infusion, then q8w thereafter
Ankylosing spondylitis	5 mg/kg on day 1, then at 2 and 6 wks after the first infusion, then q6–8w thereafter
All other indications	5 mg/kg on day 1, then at 2 and 6 wks after the first infusion, then q8w thereafter
Administration	
GP1111 is a powder for concentrate for solution for infusion; intravenous administration over 2 h; shortened infusions to ≥ 1 h can be considered in carefully selected adults who are receiving maintenance therapy and who have tolerated the induction phase (i.e. ≥ 3 initial 2 h infusions)	

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

6-MP 6-mercaptopurine, *AZA* azathioprine, *CS(s)* corticosteroid(s), *CYS* cyclosporine, *DMARD(s)* disease-modifying antirheumatic drug(s), *MTX* methotrexate, *PUVA* psoralen and ultraviolet A, *qxw* every x weeks, *wks* weeks

5 mg/kg was allowed in patients with an inadequate response starting at week 14 [5]. The trial consisted of three treatment periods; the first ending at week 30 pre-dose assessments, a second period where patients who had been receiving reference infliximab were blindly re-randomized at week 30 to continue receiving it or to switch to GP1111 until week 54 pre-dose assessments, and a third period where all patients received open-label GP1111 from week 54 until week 78 [7]. The primary efficacy endpoint was the proportion of patients achieving ≥ 20% improvement in ACR (ACR20) clinical response at week 14 in the intent-to-treat (ITT) population.

At baseline, the majority of patients were female (80.3%), white (77.5%) and seropositive for rheumatoid factor or anti-citrullinated protein antibodies (79.4%); the mean duration of disease was 6.9 years and the mean Disease Activity Score-28; 4-components based on hs-CRP (DAS28-CRP) was 6.0 [5].

GP1111 demonstrated equivalent efficacy to reference infliximab with regard to ACR20 response rates at week 14, with a two-sided 95% confidence interval (CI) for the difference between groups within the prespecified margin of ±13.5% in the ITT (Fig. 1) and per-protocol [66.7 vs. 67.2%; between-group difference (BGD) −0.58%; 95% CI −8.42 to 7.23%] populations [5]. Additionally, the 90% CI for the BGD with regard to ACR20 response rate in the ITT at week 14 (–8.75 to 4.02%) was within the prespecified asymmetric equivalence margin of −12 to 15% [5]. At week 30, the ACR20 response (secondary endpoint) was achieved in 60.8 and 64.1% of patients in the GP1111 and reference infliximab groups [8]. Regarding other secondary endpoints, the ACR50 and ACR70 response rates were generally similar in the GP1111 and reference infliximab groups at weeks 14 (Fig. 1) and 30 [5]. Through week 30, ACR50 and ACR70 response rates, were generally similar at all study visits; the mean change from baseline in DAS28-CRP at week 30 was −2.1 for both treatment groups [5].

2.1 Switching to GP1111

During the 24-week switching period of the study (weeks 30–54), efficacy was sustained regardless of whether patients continued to receive GP1111, switched from reference infliximab to GP1111 or continued to receive reference infliximab, as indicated by similar ACR20 rates and DAS28-CRP scores at week 54 across the GP1111/GP1111 (n = 280), reference infliximab/GP1111 (n = 143) and reference infliximab/reference infliximab (n = 143) groups [5]. ACR50 and ACR70 response rates were also generally similar across treatment groups [8]. Consistently, results from weeks 54 to 78 showed no clinically meaningful differences in efficacy between treatment groups regardless of a single treatment switch from reference infliximab to GP1111 at week 30 or week 54, as indicated by ACR20

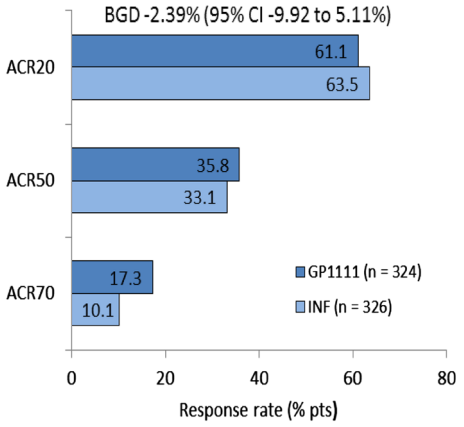

Fig. 1 The proportion of patients meeting ACR criteria for ≥ 20% improvement (ACR20) [primary endpoint], ≥ 50% improvement (ACR50) and ≥ 70% improvement (ACR70) at week 14 with GP1111 and reference infliximab, in the intent-to-treat population [5, 8]. Non-responder imputation was used to perform the primary analyses for ACR20 at week 14. *BGD* between-group difference, *INF* reference infliximab, *pts* patients

response rates being sustained and similar across the GP1111/GP1111/GP1111 (n = 253), reference infliximab/GP1111/GP1111 (n = 126) and reference infliximab/reference infliximab/GP1111 (n = 126) treatment groups; DAS-CRP scores were also sustained and similar across the treatment groups [6].

3 Tolerability and Safety

The safety and tolerability profiles of GP1111 were comparable to those of reference infliximab and there were no significant safety issues with treatment for up to 54 weeks in adults with moderate-to-severe RA, who had an inadequate response to methotrexate therapy [4, 5]. During the 30-week study period, treatment-emergent adverse events (TEAEs) occurred in 57.3% of patients in the GP1111 group and 54.0% of patients in the reference infliximab group, most commonly reported in the 'infections and infestations' system organ class, with adverse events (AEs) leading to permanent treatment discontinuation occurring in 7.1% of GP1111 recipients and 7.4% of reference infliximab recipients [5]. Treatment-related AEs (TRAEs) occurred in 25.1% of GP1111 recipients and 23.0% of reference infliximab recipients, most commonly infusion-related reactions (IRRs) [5.3% (17/323) vs. 6.1% (20/326) of patients in the GP1111 and reference infliximab groups]. Grade ≥ 3 TRAEs were reported in < 5 % of patients across both treatment groups, with IRRs being the only grade ≥ 3 TRAE reported in ≥ 1% of patients in the GP1111 or reference infliximab groups [8]. Serious AEs occurred in 5 and 6.1% of patients in the GP1111 and reference infliximab groups [5], and were considered to be treatment-related in 1.2% of patients in each group [8].

In terms of AEs of special interest, treatment-emergent infectious AEs occurred in 26.9 and 22.4% of patients in the GP1111 and the reference infliximab groups [5], with hospitalization due to infectious AEs required in 5.7 and 13.7%, and discontinuation of treatment occurring in 1.5 and 2.1% of patients in these groups [8]. In each of the GP1111 and reference infliximab groups, there were three cases of pneumonia reported (0.9%) and one case of latent/active tuberculosis (0.3%) [5]. Serious infectious AEs occurred in 1.9% of patients in the GP1111 group and 2.8% of patients in the reference infliximab group. Treatment-emergent IRRs occurred in 5.9% of GP1111 and 6.4% of reference infliximab recipients and led to discontinuation of treatment in 1.9 and 1.8% of patients in these groups [5, 8]; the majority (89.5–95.2%) of IRRs were considered treatment-related, but none were considered serious [8]. Hypersensitivity AEs occurred in 13.6 and 15.6% of patients in the GP1111 and reference infliximab groups [5]; one grade 5 serious hypersensitivity AE was reported in the reference infliximab group and was considered not related to treatment [8]. As regards malignancy and lymphoma-related AEs, one patient in each of the GP1111 and reference infliximab groups reported grade 3 colon cancer that was not considered to be treatment-related [5, 8]; one additional patient in the reference infliximab group was diagnosed with a non-malignant lipoma [8]. Two deaths occurred in each treatment group, none of which considered treatment-related [5, 8].

During the 24-week switching period (weeks 30–54), safety profiles were comparable across the three treatment groups, with incidence rates of TEAEs of 36.8, 37.8 and 33.6% among GP1111/GP1111, reference infliximab/GP1111 and reference infliximab/reference infliximab recipients, respectively [4]. In patients who were switched from reference infliximab to GP1111, the incidence of serious AEs was not higher than in those who continued to receive reference infliximab (2.8 vs. 7.7%), nor was the incidence of IRRs (4.2 vs. 8.4%) [4]. Furthermore, the safety profiles were similar across the three treatment groups during the third treatment period (weeks 54–78), with TEAEs occurring in 28.9–30.2% of patients in these groups [6].

4 Immunogenicity

Anti-drug antibodies (ADAs) occurred at a similar incidence with GP1111 as with reference infliximab regimens. In the phase III RA trial, 48.5% of GP1111 and 51.2% of reference infliximab recipients developed ADAs over 30 weeks and neutralizing antibodies were detected in 79.0 and 85.6% of these patients [9]. The impact of detectable ADAs was similar in the GP1111 and reference infliximab groups, with a trend towards reduced efficacy and increased rates of IRRs in both treatment groups [9]. During the 24-week switch period, there were no clinically meaningful differences in immunogenicity amongst the treatment groups, with ADA

Table 2 Biosimilarity summary of GP1111 (Zessly®)

Mechanism of action	Chimeric human-murine mAb that binds with high affinity to both forms of TNF-α (soluble and transmembrane), thus inhibiting its functional activity [8]
Physicochemical characterization	Similar to reference (EU- and US-sourced) infliximab with respect to primary, secondary and tertiary structures [8]
	Similar product purity, total afucosylation, terminal galactosylation and glycosylation profiles, charge heterogeneity, protein concentration, disulphide bonds and stability (minor differences not considered clinically relevant) [8]
Pharmacodynamic similarity	Similar to EU- and US-sourced reference infliximab with respect to Fab-related properties (blinding to soluble TNF-α and inhibition of its responses; binding kinetics to TNF-α); overall similarity was also demonstrated with respect to Fc-related properties (e.g. ADCC activity, CDC activity) [8]
Pharmacokinetic similarity	Three-way equivalence demonstrated between GP1111, EU- and US-sourced reference infliximab for primary pharmacokinetic parameters in healthy volunteers [3]
	GP1111 serum trough concentrations over time were similar to those of reference infliximab in patients with moderate-to-severe rheumatoid arthritis despite MTX therapy [8]
Immunogenicity	No unexpected immunogenicity issues [4, 5, 9]
	Switching from EU-sourced infliximab to GP1111 had no impact on immunogenicity [4]
Efficacy and tolerability (in reference trial)	Similar efficacy and tolerability to reference infliximab in patients with moderate-to-severe rheumatoid arthritis despite MTX treatment [5]
	Switching from reference infliximab to GP1111 had no significant impact on efficacy or tolerability [4]

ADCC antibody-dependent cell-mediated cytotoxicity, *CDC* complement-dependent cytotoxicity, *mAb* monoclonal antibody, *MTX* methotrexate

rates in the GP1111/GP1111, reference infliximab/GP1111 and reference infliximab/reference infliximab of 52.1, 58.0 and 60.1%, respectively [4]. Moreover, results from the third treatment period indicate that the absence of clinically meaningful differences in immunogenicity amongst treatment groups continued from weeks 54 to 78 [6].

5 Conclusion

GP1111 is an infliximab biosimilar with similar efficacy, tolerability, safety and physicochemical and biological characteristics to the reference product (Table 2). Based on totality of the evidence, GP1111 has been approved in the EU for all indications for which reference infliximab is approved, including RA, Crohn's disease, UC, AS, PsA and plaque psoriasis.

Compliance with Ethical Standards

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