**Supplementary Appendix S1**

**Efficacy, safety, and immunogenicity of GP2015, an etanercept biosimilar, compared to the reference etanercept in patients with moderate-to-severe rheumatoid arthritis: 24-week results from the comparative Phase III, randomised, double-blind, EQUIRA study**

Marco Matucci-Cerinic,1 Yannick Allanore,2 Arthur Kavanaugh,3 Maya H. Buch,4 Hendrik Schulze-Koops,5 Eugeniusz J. Kucharz,6 Heike Woehling,7 Goran Babic,7 Johann Poetzl,7 Adanna Davis8,Arnd Schwebig7

1Department of Experimental and Clinical Medicine, Division of Rheumatology AOUC; University of Florence, Florence, Italy;

2Cochin Hospital, Rheumatology A department, Paris Descartes University, Paris, France;

3UC San Diego School of Medicine, La Jolla, California, USA;

4University of Leeds & NIHR Leeds Biomedical Research Centre, Leeds, United Kingdom;

5Division of Rheumatology and Clinical Immunology, Department of Internal Medicine IV, Ludwig-Maximilians-University, Munich, Germany;

6Medical University of Silesia, Katowice, Poland;

7Hexal AG, a Sandoz company, Holzkirchen, Germany

8 Sandoz Inc, Princeton NJ, USA

**Corresponding author:**

Marco Matucci Cerinic MD, PhD,

Department of Experimental & Clinical Medicine, Division of Rheumatology AOUC,

University of Florence,

Villa Monna Tessa,

Viale Pieraccini 18 50139 Firenze,

Florence, Italy

**Phone:** 0039055794

**Email:** marco.matuccicerinic@unifi.it

**Randomisation schedule**

All eligible patients were randomised via the Interactive Response Technology (IRT) system to one of the treatment arms at Visit 2. The IRT system assigned a unique patient identification number with the treatment arm to which the patient had been assigned and a unique medication number that allowed the assignment of medication packs to the patient. Randomisation was stratified at baseline by region, body weight (the body weight assessed at baseline), and prior therapy to ensure balance allocation of patients to treatment groups within the strata. The strata for body weight were “body weight < 90 kg” or “body weight ≥90 kg”. The strata for region were “US+ Mexico” and “Europe”. The strata for prior therapy followed a hierarchy and were “prior treatment with methotrexate (MTX) only”, “prior treatment with MTX and one disease modifying anti-rheumatic drug (DMARD)”, “prior treatment with a tumour necrosis factor (TNF) antagonist”, or “prior treatment with other biologics”.

Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment during Treatment Period 1 (TP1) for the duration of the study. Once all patients completed Week 24, designated sponsor team members were unblinded, whereas the patients, investigator staff, and persons performing the assessments remained blinded until final database lock. The study treatments were provided as prefilled syringes for single use.

*Exclusion criteria*

1. Previous exposure to etanercept in the past
2. Treatment with any other biologic therapy for rheumatoid arthritis, including TNFα inhibitors, anti-CD20, immune-modulator drug(s), other investigational drug(s) and /or device(s) within 3 months or 5 half-lives at the time of enrollment whichever is longer
3. Previous use of >2 biologics
4. Primary and secondary biologic therapy failures in the opinion of the investigator (e.g. patients with biologic treatment stopped because of safety and/or efficacy issues)
5. Subjects taking high potency opioid analgesics, or any intramuscular corticosteroid injection, or any therapy by intra-articular injection required for treatment of acute rheumatoid arthritis flare within 4 weeks before baseline
6. History of known hypersensitivity to any ingredients of the investigational medicinal product, to any recombinant human protein or any of the excipients used in GP2015 or ETN
7. Patients who are allergic to rubber or latex (the needle cover on the prefilled syringes for both GP2015 and ETN contains dry natural rubber)
8. Patients with functional status class IV according to the ACR 1991 revised criteria
9. Systemic manifestation of rheumatoid arthritis, with the exception of Sjögren’s syndrome
10. Active ongoing inflammatory diseases other than rheumatoid arthritis that might confound the evaluation of the efficacy
11. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
12. Women of child-bearing potential not willing to use highly effective contraception throughout the study and for at least 3 months after study drug discontinuation
13. Pre-existing or recent-onset central or peripheral nervous system demyelinating disorders according to investigator's discretion, and taking into account neurological assessment; patients who are considered to have an increased risk of developing a demyelinating disease
14. Any serious illness or uncontrolled medical condition, including but not limited to significant hepatic or renal disease, uncontrolled hypertension (defined as ≥ 160/95), congestive heart failure (NYHA class III or IV), or other severe, uncontrolled cardiac disease
15. Patients who have body mass index (BMI) ≥29.9
16. History of active tuberculosis (TB) and presence of latent (inactive) TB detected by imaging (Chest X-ray [PA or PA and lateral according to local practice]), Computerized Tomography (CT) scan or magnetic resonance imaging (MRI) and/or by the QuantiFERON®-TB Gold test at screening. Chronic infectious disease or history of recurrent infectious disease or active systemic infection within 2 weeks prior to selection or during the screening period (except for common cold) and patients with a history or evidence of opportunistic infections (e.g. histoplasmosis, listeriosis, legionellosis)
17. Known immunodeficiency, history of positive serology to human immunodeficiency virus (HIV), or is immunocompromised
18. Positive serology to hepatitis B (HBsAg or anti-HBc) or hepatitis C (HCV-Ab) at screening or baseline
19. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system (except for basal cell carcinoma or actinic keratosis that have been treated with no evidence of recurrence in the past 3 months, except for carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed with no evidence of recurrence), treated or untreated, within the past 5 years
20. Any medical or psychiatric condition which, in the Investigator’s opinion, would preclude the participant from adhering to the protocol or completing the study per protocol
21. History or evidence of ongoing alcohol or drug abuse, within the last six months before baseline
22. Plans for administration of live vaccines during the study period or vaccination within 6 weeks prior to baseline
23. Patient is under judicial protection (France only)

**EULAR response criteria**

A moderate response was defined according to the EULAR response criteria as a disease activity score 28-joint count (DAS28) at Week 24 of >3.2 and ≤5.1, and an improvement from baseline >0.6 or a DAS28 at Week 24 >5.1, and an improvement from baseline >1.2.

**Figure S1. Study design**

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Patients were randomised to self-administer 50 mg GP2015 or ETN subcutaneously, once weekly.

All patients continued to receive concomitant methotrexate at a stable dose (10–25 mg/week), and folic acid (≥ 5 mg/week) until end of study.

A moderate response was defined according to the EULAR response criteria as a disease activity score 28-joint count (DAS28) >3.2 and ≤5.1 at Week 24 and an improvement from baseline >0.6, or DAS28>5.1 at Week 24 and an improvement from baseline >1.2.

ETN, reference etanercept

**Figure S2. Change from baseline in HAQ-DI scores over 24 weeks (TP1 per-protocol set)**

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The Per-protocol set consists of all patients completing the study until Week 24 without major protocol deviations. Error bar represents the standard error.

Per protocol set: GP2015 (n=168), ETN (n=155).

ETN, reference etanercept; HAQ-DI, Health assessment questionnaire disability index; TP1, Treatment Period 1.

**Figure S3. Change from baseline in FACIT-fatigue scores over 24 weeks (TP1 per-protocol set)**

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The per-protocol set consists of all patients completing the study until Week 24 without major protocol deviations. Error bar represents the standard error. High score indicates less fatigue.

Per protocol set: GP2015 (n=168), ETN (n=155).

ETN, reference etanercept; FACIT, Functional Assessment of Chronic Illness Therapy; TP1, Treatment Period 1.

**Figure S4. Incidence of anti-drug antibodies over 24 weeks (TP1, safety set)**

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The safety set includes all patients who received at least one dose of study treatment during the treatment period

ADA, anti-drug antibodies; ETN, reference etanercept; TP1, Treatment Period 1

Table S1. DAS28-CRP change from baseline at Week 24 by subgroups (TP1 per-protocol set)

|  |  |  |
| --- | --- | --- |
| **Subgroups by prior treatment** | **GP2015 (N=168)** | **ETN (N=155)** |
| **LS mean (SE)** | |
| Prior use MTX+any anti-TNF | −3.06 (0.24) | −2.77 (0.27) |
| Prior use MTX+any biologic | −3.12 (0.35) | −2.98 (0.34) |
| Prior use MTX+any DMARDs | −2.67 (0.18) | −2.63 (0.19) |
| Prior use MTX only | −2.89 (0.24) | −2.87 (0.23) |

A mixed-model repeated measures analysis performed for DAS28-CRP change from baseline including treatment, body weight strata, prior systemic therapy, region, time (visits), the interaction between time (visits) and treatment all as categorical variables, and baseline DAS28-CRP value as a continuous variable. The per-protocol set consists of all patients completing the study until Week 24 without major protocol deviations

DMARDs, disease modifying anti-rheumatic drugs; ETN, reference etanercept; LS, least squares; MTX, methotrexate; SE, standard error; TNF, tumour necrosis factor; TP1, treatment period 1

Table S2. Treatment-related adverse events up to 24 weeks (TP1 safety set)

| **Preferred term** | **GP2015** | **ETN** |
| --- | --- | --- |
|  | **N=186** | **N=190** |
|  | **n (%)** | **n (%)** |
| **Any treatment-related TEAE** | 39 (21.0) | 46 (24.2) |
| Treatment-related TEAEs with a ≥1% incidence in any group | | |
| Injection site reaction | 12 (6.5) | 35 (18.4) |
| Alanine aminotransferase increased | 5 (2.7) | 1 (0.5) |
| Nasopharyngitis | 4 (2.2) | 0 |
| Urinary tract infection | 3 (1.6) | 0 |
| Anaemia | 2 (1.1) | 0 |
| Dyspepsia | 2 (1.1) | 0 |
| Hepatitis toxic | 2 (1.1) | 0 |
| Respiratory tract infection | 2 (1.1) | 0 |
| Upper respiratory tract infection | 1 (0.5) | 3 (1.6) |
| Preferred terms with events occurring in any of the treatment groups in the safety set are presented and sorted by descending order of frequency in the GP2015 column. A patient with multiple occurrences of event within the same system organ class or preferred term under one treatment is counted only once.  Treatment emergent adverse events are events started after the first dose of study treatment and before study discontinuation or 30 days after last dose, whichever occurs later.  Adverse event terms are coded using MedDRA version 19.1.  ETN, reference etanercept; MedDRA, medical dictionary for regulatory activities; TP1, Treatment Period 1. | | |

Table S3. TEAEs of special interest up to 24 weeks (TP1 safety set)

| **Preferred term** | **GP2015** | **ETN** |
| --- | --- | --- |
|  | **N=186** | **N=190** |
|  | **n (%)** | **n (%)** |
| **Patients with at least one event** | 12 (6.5) | 9 (4.7) |
| Alanine aminotransferase increased | 8 (4.3) | 4 (2.1) |
| Hepatitis toxic | 2 (1.1) | 0 |
| Interstitial lung disease | 1 (0.5) | 0 |
| Oedema peripheral | 1 (0.5) | 1 (0.5) |
| Psoriasis | 1 (0.5) | 0 |
| Pustular psoriasis | 1 (0.5) | 0 |
| Aspartate aminotransferase increased | 0 | 1 (0.5) |
| Hepatic enzyme increased | 0 | 1 (0.5) |
| Hepatic steatosis | 0 | 1 (0.5) |
| Peripheral swelling | 0 | 1 (0.5) |
| Urticaria | 0 | 1 (0.5) |
| Preferred terms are presented and sorted by descending order of frequency in the GP2015 column. A patient with multiple occurrences of event within the same system organ class or preferred term under one treatment is counted only once.  Treatment emergent adverse events are events started after the first dose of study treatment and before study discontinuation or 30 days after last dose, whichever occurs later.  Adverse event terms are coded using MedDRA version 19.1.  ETN, reference etanercept; MedDRA, medical dictionary for regulatory activities; TEAEs, treatment emergent adverse events, TP1, Treatment Period 1 | | |