Pharmacokinetics and Safety of GP2015, a Proposed Etanercept Biosimilar, and Etanercept Originator Product in Healthy Male Subjects: A Randomised Two-way Cross-over Study

Poster Number
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INTRODUCTION

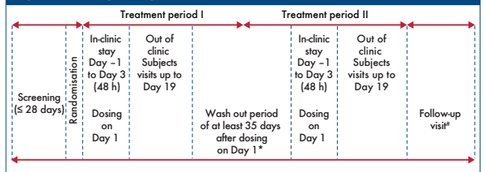
- A biosimilar is a biologic product that is 'comparable' (EMA) or 'highly similar' (US FDA) to an approved biological drug, i.e. the originator
- GP2015 is a proposed etanercept biosimilar
- Here, we present results from a study conducted in healthy male subjects to compare the pharmacokinetics (PK) and safety of GP2015 with etanercept originator (Enbrel® EU-authorised)

METHODS

Study design

- This was a Phase I, single-centre, randomised, double-blind, two-way cross-over study with two treatment periods (**Figure 1**)
- In treatment period I, subjects were randomised to receive a single 50 mg subcutaneous (sc) injection of GP2015 or etanercept originator on Day 1. Following a wash-out period of at least 35 days after dosing, in treatment period II, subjects underwent cross-over and received a single s.c. injection of GP2015 or etanercept originator on Day 1

Figure 1. Study design



*Wash-out period of at least 35 days between two IMP administrations; #follow-up visit at 'Day 29' (28 days after IMP administration in treatment period II)
IMP, investigational medicinal product

Subjects

- Healthy subjects aged 18–49 years, with body weight of 50–99.9 kg and body mass index (BMI) of 19.0 to 29.9 kg/m² were included
- Subjects were not eligible to participate if they had previously received a recombinant human anti-TNFα inhibitor or if they had active infections within 4 weeks before treatment administration

Objectives

- Primary: To determine the bioequivalence of GP2015 and etanercept originator in terms of the following PK parameters:
  - maximum observed serum concentration (C_{max})
  - area under the serum concentration-time curve measured from the time of dosing to the last measurable concentration ($AUC_{0-tlast}$)
  - AUC measured from the time of dosing and extrapolated to infinity (AUC_{0-inf})
- Secondary: To compare GP2015 and etanercept originator with respect to the following criteria:
  - time to the maximum observed serum concentration (t_{max})
  - elimination rate constant (k_{el})
  - the apparent terminal half-life of elimination phase ($t_{½}$)
  - immunogenicity, safety and tolerability

Assessments

- PK: Blood samples were drawn at 0, 6, 12, 24, 36, 48, 60, 72, 84, 96, 120, 168, 216, 264, 336 and 432 hours after dosing in each treatment period. Etanercept concentrations in the serum were quantified using a validated enzyme-linked immunosorbent assay (Range: 6.7–800 ng/mL; intra-assay accuracy: 82–113%; inter-assay accuracy: 97–109%)
- Safety: Assessments included collecting all treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), with their severity and relationship to study drug
- Immunogenicity: Blood samples were collected at −0.5 h pre-dose on Day 1 of each treatment period and at the follow-up visit on Day 29 of treatment period 2. Anti-drug antibody (ADA) development was evaluated using a validated electrochemiluminescence assay and neutralising capacity was evaluated using a competitive ligand binding neutralising assay

Statistical analysis

- The planned and actual sample size was 54 subjects
- Bioequivalence between GP2015/etanercept originator for primary PK parameters was considered to be demonstrated if the 90% confidence intervals (CIs) for the ratio of geometric means were completely contained within the predefined bioequivalence limits of 0.80–1.25
- Secondary PK parameters were analysed descriptively
- The PK analysis set comprised all subjects who completed the study without major protocol deviations. The safety set comprised subjects who received study drug at least once and had at least one post-baseline safety assessment

RESULTS

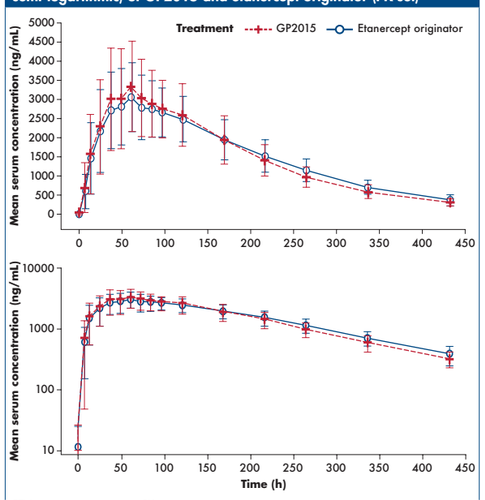
- 54 subjects were randomised, 27 each to the treatment sequences GP2015/etanercept originator and etanercept originator/GP2015 and all completed the study without major protocol deviations. All 54 subjects were included in the safety and PK analysis sets. The demographic and baseline characteristics of the subjects are shown in **Table 1**
- The mean serum concentration time profiles were comparable between GP2015 and etanercept originator (**Figure 2**)
- The 90% CI of GP2015/etanercept originator for the primary PK parameters were within the pre-defined bioequivalence range of 0.80–1.25, indicating comparable bioavailability and PK between GP2015 and etanercept originator (**Table 2**)
- The mean $t_{½}$ for GP2015 and etanercept originator was 104.7 h and 110.7 h, respectively. The mean k_{el} for GP2015 and etanercept originator was 0.0067/h and 0.0066/h, respectively

Table 1. Demographic and baseline characteristics (safety set)

Demographic variables	GP2015/ etanercept originator N=27	Etanercept originator/GP2015 N=27	Total N=54
Age, years, mean (SD)	35.2 (8.45)	30.6 (7.55)	32.9 (8.27)
Race, n (%)			
White	15 (55.6)	14 (51.9)	29 (53.7)
Asian	7 (25.9)	6 (22.2)	13 (24.1)
Black/African American	3 (11.1)	5 (18.5)	8 (14.8)
Other	2 (7.4)	2 (7.4)	4 (7.4)
Weight, kg, (mean SD)	75.51 (10.08)	76.71 (9.48)	76.11 (9.71)
BMI, kg/m², (mean, range)	24.58 (19.0–29.4)	25.11 (20.5–29.4)	24.85 (19.0–29.4)

GP2015/etanercept originator, subjects received GP2015 during treatment period 1 and etanercept originator in treatment period 2; Etanercept originator/GP2015, subjects received etanercept originator during treatment period 1 and GP2015 in treatment period 2
BMI, body mass index; SD, standard deviation

Figure 2. Mean serum concentration-time profiles (linear and semi-logarithmic) of GP2015 and etanercept originator (PK set)



ETN, etanercept originator; PK, pharmacokinetic

Table 2. Mean ratio and 90% CI for primary PK parameters based on nominal dose

PK parameters	Geometric Means		Mean Ratio (%)	90% CI of Ratio	Intraindividual CV (%)
	GP2015	Etanercept originator			
C_{max} (µg/mL)	3.4	3.1	1.11	1.05–1.17	16.4
$AUC_{0-tlast}$ (h*µg/mL)	630	642	0.98	0.94–1.02	12.1
AUC_{0-inf} (h*µg/mL)	679	705	0.96	0.93–1.00	12.3

AUC_{0-inf}, area under the serum concentration-time curve measured from the time of dosing and extrapolated to infinity; $AUC_{0-tlast}$, measured from the time of dosing to the last measurable concentration; C_{max}, maximum observed serum concentration; CI, confidence interval; CV, coefficient of variation; PK, pharmacokinetic

- The median t_{max} was 58.3 h for GP2015 and 59.8 h for etanercept originator

Safety

- At least one TEAE was reported in 23 (42.6%) subjects in the GP2015 group and 20 (37%) subjects in the etanercept originator group. The most common TEAEs overall, regardless of relationship to study drug are presented in **Table 3**

Table 3. Most common TEAEs regardless of relationship to study drug by preferred term

Preferred term	GP2015 N=54 n (%)	Etanercept originator N=54 n (%)	Overall N=54 n (%)
Neutropenia	7 (13)	8 (14.8)	10 (18.5)
Headache	5 (9.3)	5 (9.3)	9 (16.7)
Nasopharyngitis	4 (7.4)	4 (7.4)	8 (14.8)
Oropharyngeal pain	3 (5.6)	4 (7.4)	7 (13.0)
Cough	3 (5.6)	0	3 (5.6)
Feeling hot	0	3 (5.6)	3 (5.6)
Back pain	2 (3.7)	0	2 (3.7)
Musculoskeletal chest pain	1 (1.9)	1 (1.9)	2 (3.7)
Fatigue	1 (1.9)	1 (1.9)	2 (3.7)

TEAEs that occurred in at least 2 subjects overall are presented. All TEAEs are presented in descending order in the overall group
TEAE, treatment-emergent adverse event; N, the number of subjects dosed with each treatment, or the number of subjects in the safety population for the total summary; n, the number of subjects in the specific category

- TEAEs considered related to the study drug were reported in 10 (18.5%) and 13 (24.1%) subjects for GP2015 and etanercept originator, respectively. All TEAEs were of mild or moderate intensity. No SAEs or deaths occurred during the study

Immunogenicity

- 3 subjects (treatment sequence GP2015/etanercept originator) showed a positive ADA response (non-neutralising) at the follow-up visit. The ADA titres in all 3 subjects were very low, i.e. near the detection limit of the highly sensitive binding ADA assay and were considered to be not clinically meaningful
- All samples from the pre-dose (Day 1) of each period were ADA negative. No direct association between the occurrence of ADA in the 3 ADA positive subjects and exposure to one of the two drugs administered in this treatment sequence having caused this effect could be made

CONCLUSIONS

- This PK study (EudraCT number 2013–004902–25) demonstrated that GP2015, a proposed etanercept biosimilar is bioequivalent to the etanercept originator
- There were no clinically relevant differences in safety, tolerability and immunogenicity between GP2015 and etanercept originator in this study

Acknowledgment

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Pharmacokinetics and Safety of GP2015, a Proposed Etanercept Biosimilar, Administered Subcutaneously by Autoinjector or Prefilled Syringe in Healthy Male Subjects

Poster Number
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INTRODUCTION

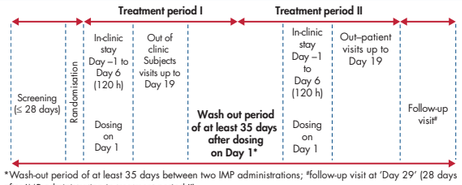
- Joint-destructive diseases, such as rheumatoid arthritis, are often associated with impaired dexterity
- The use of an autoinjector (AI) for drug delivery has been shown to increase patient adherence, acceptability and convenience, in comparison to conventional or pre-filled syringes (PFS)[1,2]
- GP2015, a proposed etanercept biosimilar, is planned to be presented in a ready to use, fixed dose, disposable AI, identical to the secukinumab autoinjector, allowing one-hand injection without requiring fine finger manipulations
- Here, we present the pharmacokinetics (PK) and safety results from a study in healthy subjects comparing the administration of GP2015 by AI or PFS

METHODS

Study design

- This was a single center, open-label, randomised, two-way cross-over study with two treatment periods (**Figure 1**)
- In treatment period I, subjects were randomised to receive a single 50 mg subcutaneous (sc) injection of GP2015 administered via AI or PFS on Day 1. Following a wash-out period of at least 35 days after dosing, in treatment period II, subjects underwent cross-over and received a single s.c. injection of GP2015 administered via AI or PFS on Day 1

Figure 1. Study design



*Wash-out period of at least 35 days between two IMP administrations; #follow-up visit at 'Day 29' (28 days after IMP administration in treatment period II)
IMP, investigational medicinal product

Subjects

- Healthy subjects (aged 18–55 years) with a body weight of 50–140 kg and BMI of 18.5–49.9 kg/m² were included. Randomisation was stratified into 3 body weight categories (i.e. 50.0–79.9, 80.0–99.9 and 100.0–140.0 kg)
- Subjects were not eligible to participate if they had previously received a recombinant human anti-TNFα inhibitor or if they had active infections within 4 weeks before treatment

Objectives

- Primary: To determine the bioequivalence of GP2015 administered by an AI or PFS in terms of the following PK parameters:
  - maximum observed serum concentration (C_{max})
  - area under the serum concentration-time curve measured from the time of dosing to the last measurable concentration (AUC_{0-last})
  - AUC measured from the time of dosing and extrapolated to infinity (AUC_{0-inf})
- Secondary objectives were:
  - To compare PK parameters of GP2015 administered by an AI or PFS by body weight category [low (50.0–79.9 kg); medium (80.0–99.9 kg) and high (100.0–140.0 kg)]
  - Comparison of other PK parameters, t_{max} [time to the maximum observed serum concentration], k_{el} [elimination rate constant] and $t_{½}$ [the apparent terminal half-life of elimination phase] in the total population as well as by body weight categories
  - To compare the overall safety, tolerability and local tolerance

Assessments

- PK: Blood samples were drawn at 0, 6, 12, 24, 36, 48, 60, 72, 84, 96, 120, 168, 216, 264, 336 and 432 hours after dosing in each treatment period. Etanercept concentrations in the serum were quantified using a validated enzyme-linked immunosorbent assay (Range: 6.7–800 ng/mL; intra-assay accuracy: 82–113%; inter-assay accuracy: 97–109%)
- Safety assessments: Treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), with their severity and relationship to study drug were analysed
- Immunogenicity: Blood samples were collected at −0.5 h pre-dose on Day 1 of each period and at the follow-up visit on Day 29 of treatment period 2. Anti-drug antibody (ADA) development was evaluated using a validated electrochemiluminescence assay

Statistical analysis

- Planned sample size was 51 assuming a 15% drop-out rate
- The bioequivalence of primary PK parameters was considered to have been demonstrated if the 90% confidence intervals (CIs) for the geometric mean ratios were completely contained within the predefined bioequivalence limits of 0.80–1.25. Secondary PK parameters were analysed descriptively
- The PK analysis set comprised all subjects who completed the study without major protocol deviations. The safety set comprised of subjects who received study drug at least once and had at least one post-baseline safety assessment

RESULTS

- 51 subjects (AI/PFS, N=25; PFS/AI, N=26) were randomized and 49 completed the study without major protocol deviations
- All 51 subjects were included in the safety analysis set. 48 subjects were included in the PK analysis set (2 subjects discontinued during the study and received only one out of the two treatment administrations). The demographics and baseline characteristics of the subjects are presented in **Table 1**

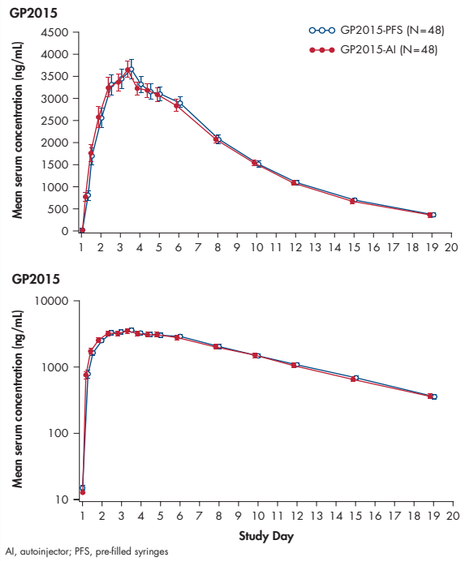
Table 1. Demographic and baseline characteristics (safety set)

Demographic variables	AI/PFS N=25	PFS/AI N=26	Total N=51
Age, years (mean, SD)	33.8 (10.02)	34.3 (10.29)	34.1 (10.06)
Race, n (%)			
White	22 (88)	18 (69)	40 (78)
Black	3 (12)	6 (23)	9 (18)
American Indian/Alaska native	0	1 (4)	1 (2)
Other	0 (0)	1 (4)	1 (2)
Body weight group, n (%)			
50–79.9 kg	9 (36)	8 (31)	17 (33)
80–99.9 kg	8 (32)	9 (35)	17 (33)
100–140 kg	8 (32)	9 (35)	17 (33)
BMI, kg/m², (mean, range)	27.20 (19.3–39.0)	28.22 (20.1–37.0)	27.72 (19.3–39.0)

AI/PFS, subjects received AI in treatment period 1 followed by PFS in treatment period 2; PFS/AI, subjects received PFS in treatment period 1 followed by AI in treatment period 2
AI, autoinjector; BMI, body mass index; PFS, pre-filled syringe; SD, standard deviation N, indicates the safety analysis set

- Mean serum concentration-time profiles of GP2015 were comparable when administered by an AI or a PFS (**Figure 2**)

Figure 2. Mean serum concentration-time profiles (linear and semi-logarithmic) of GP2015 AI and PFS



AI, autoinjector; PFS, pre-filled syringes

- The 90% CIs for the ratio of the geometric means for the primary PK parameters were within the pre-defined bioequivalence range of 0.80–1.25 (**Table 2**)

Table 2. Geometric means and 90% confidence intervals for PK parameters

PK Parameter	Geometric Means		Mean Ratio (%)	90% CI of Ratio
	AI	PFS		
C_{max} (µg/mL)	3.7	3.6	1.01	0.94–1.08
AUC_{0-last} (h*µg/mL)	684.1	678.4	1.01	0.95–1.07
AUC_{0-inf} (h*µg/mL)	745.2	737.4	1.01	0.96–1.07

AUC_{0-inf}, area under the serum concentration-time curve measured from the time of dosing and extrapolated to infinity; AUC_{0-last}, measured from the time of dosing to the last measurable concentration; AI autoinjector; C_{max}, maximum observed serum concentration; CI, confidence interval; PK, pharmacokinetic; PFS, pre-filled syringe

- The median t_{max} was 60 h following both AI and PFS administrations of GP2015, providing additional evidence for a similar delivery of GP2015 via the two devices
- The mean $t_{½}$ of GP2015 was identical (109 h) for both AI and PFS treatment administrations and was expected from using an identical PFS batch in both devices. The mean k_{el} was also similar (0.006/h) for both AI and PFS treatment administrations
- Within each body weight category, the mean serum concentration profiles of GP2015 were comparable for both treatment administrations (**Table 3**)

Table 3. Primary PK parameters within each body weight category

Weight categories	PK Parameter	Mean (SD)	
		AI	PFS
Low (50.0–79.9 kg) N=17	C_{max} (µg/mL)	5.21 (1.4)	5.55 (1.3)
	t_{max} (h)	50.83 (15.0)	57.18 (13.8)
	AUC_{0-last} (h*µg/mL)	941 (199)	975 (199)
	AUC_{0-inf} (h*µg/mL)	1006 (213)	1049 (224)
	$t_{1/2}$ (h)	101 (13.5)	104 (13.3)
Medium (80.0–99.9 kg) N=14	C_{max} (µg/mL)	3.52 (1.1)	3.48 (0.9)
	t_{max} (h)	64.3 (13.0)	60.0 (24.9)
	AUC_{0-last} (h*µg/mL)	629 (174)	647 (119)
	AUC_{0-inf} (h*µg/mL)	686 (180)	695 (122)
	$t_{1/2}$ (h)	109 (18.2)	104 (16.1)
High (100.0–140.0 kg) N=17	C_{max} (µg/mL)	2.97 (0.8)	2.84 (1.1)
	t_{max} (h)	72.7 (21.9)	72.8 (33.4)
	AUC_{0-last} (h*µg/mL)	571 (97.5)	539 (171)
	AUC_{0-inf} (h*µg/mL)	629 (92.7)	592 (173)
	$t_{1/2}$ (h)	117 (31.6)	118 (33.8)

AI autoinjector; AUC_{0-inf}, area under the serum concentration-time curve measured from the time of dosing and extrapolated to infinity; AUC_{0-last}, measured from the time of dosing to the last measurable concentration; C_{max}, maximum observed serum concentration; PK, pharmacokinetic; SD, standard deviation; t_{max}, time to the maximum observed serum concentration, $t_{½}$, the apparent terminal half-life of elimination phase, PFS, pre-filled syringe

- GP2015 PK data confirms earlier findings on the influence of body weight on the exposure to etanercept that were derived from population PK analysis with etanercept originator in healthy volunteers and ankylosing spondylitis patients[3]

Safety

- The incidence of TEAEs was similar (25 subjects each) in the AI and PFS groups. The most common TEAEs regardless of relationship to the study drug are presented in **Table 4**. TEAEs considered related to the study drug were reported in 11 (22%) and 9 (18%) subjects for AI and PFS group, respectively. All treatment-related AEs were of mild intensity and resolved during the study
- None of the cases of reduction of absolute neutrophil count, reported as neutropenia, were considered clinically significant. No SAEs or deaths occurred during the study

Immunogenicity

- None of the subjects developed ADAs upon treatment with GP2015 administered by AI or PFS

Table 4. Incidence of most frequent TEAEs* by preferred term

Preferred term	GP2015 AI N=50 n (%)	GP2015 PFS N=50 n (%)	Overall N=51 n (%)
Headache	8 (16)	5 (10)	10 (20)
Neutropenia	5 (10)	5 (10)	6 (12)
Hematoma	1 (2)	3 (6)	4 (8)
Rhinitis	1 (2)	3 (6)	4 (8)
Nausea	3 (6)	1 (2)	4 (8)
Pollakiuria	2 (4)	3 (6)	3 (6)
Back pain	1 (2)	2 (4)	3 (6)
Neck pain	1 (2)	2 (4)	3 (6)
Pain in extremity	2 (4)	1 (2)	3 (6)
Vessel puncture site pain	1 (2)	2 (4)	3 (6)
Cough	2 (4)	1 (2)	2 (4)
Flatulence	2 (4)	1 (2)	2 (4)
Myalgia	0	2 (4)	2 (4)
Erythema	0	2 (4)	2 (4)
Gamma-glutamyltransferase increased	1 (2)	1 (2)	2 (4)
Vomiting	1 (2)	1 (2)	2 (4)

*includes TEAEs that occurred in at least 2 subjects in the overall group. All TEAEs are presented in descending order in the overall group
AI, autoinjector; PFS, pre-filled syringe; TEAE, treatment-emergent adverse event; N, number of subjects studied; n (%), number of subjects (percentage) with at least one TEAE

CONCLUSIONS

- This study (EudraCT number 2013–004901–24) demonstrated PK bioequivalence of GP2015 administered by AI or PFS. The AI provided dosing and tolerability equivalent to the PFS across subjects with a large range of body weights
- A single dose of 50 mg GP2015 administered by AI or PFS was well tolerated, with no unexpected adverse events
- These results suggest that the AI is an effective mode of administration of GP2015 with a safety profile similar to the PFS

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3. Zhou H, et al. *Int J Clin Pharmacol.* 2004; 42: 267–76.

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