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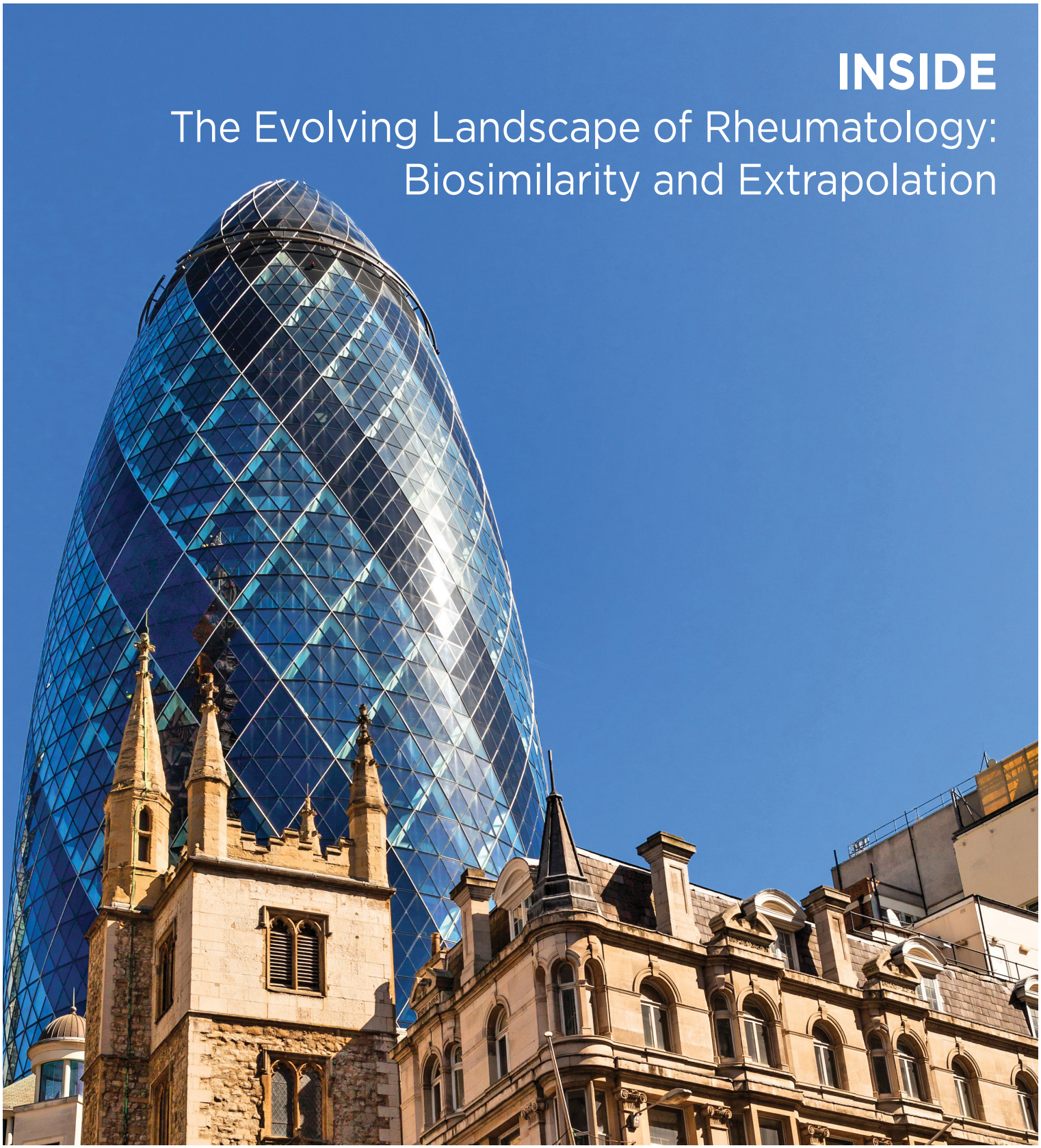

INSIDE

The Evolving Landscape of Rheumatology: Biosimilarity and Extrapolation

THE EVOLVING LANDSCAPE OF RHEUMATOLOGY: BIOSIMILARITY AND EXTRAPOLATION

This symposium took place on 9th June 2016, as part of the European League Against Rheumatism (EULAR) Congress 2016 in London, UK

Chairperson

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Speakers

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MEETING SUMMARY

Targeted biological therapies have revolutionised the treatment of inflammatory diseases in rheumatology and new agents continue to be developed. The growing demand, coupled with limited competition, is a challenge for healthcare budgets and limits patients' access to these therapies. Biosimilars, which are biologicals with comparable safety, quality, and efficacy to a reference product, have the potential to address these challenges. Despite biosimilars having been available since 2006, initially in other indications than rheumatoid arthritis (RA), confidence in their use is still an issue for rheumatologists. This symposium discussed the rigorous scientific and regulatory processes by which biosimilarity is determined, the rationale for extrapolation to different indications, and the evidence needed to support incorporating biosimilars into clinical practice in rheumatology.

Dr Emily Shacter explained the US Food and Drug Administration (FDA) biosimilar regulatory process, focussing on the importance of structural and functional analyses to characterise protein products and demonstrate molecular similarity. Prof Craig Leonardi, a dermatologist, discussed the rationales for the choice of an adequate patient population and disease setting in studies confirming biosimilarity. The issues around extrapolation to other indications not studied in clinical trials with the biosimilar were discussed; extrapolation being based on the same mechanism of action; the totality of the evidence of all analytical, non-clinical, and clinical data; and a thorough scientific justification based upon an extensive understanding of the safety and efficacy profile of the reference product. Prof Peter Taylor explored the impact of biosimilars on the clinical landscape of rheumatology, the potential benefits of cost and access, and recommendations for their optimal use. The symposium concluded with a question and answer session.

Laying the Foundation: Analytical and Functional Characterisation of Protein Products and the Demonstration of Molecular Similarity

Doctor Emily Shacter

In the USA, a biosimilar is legally defined as a biological product that is highly similar to a US-licensed reference product, with no clinically meaningful differences between the biosimilar and the reference product in its safety, purity, and potency, notwithstanding minor differences in clinically inactive components.[1] Analytical studies of molecular and functional similarity form the foundation of the FDA biosimilarity assessment, followed by animal studies to show similarity in pharmacodynamics (PD) and toxicity, while clinical studies confirm the similarity in clinical performance and safety in patients.[1,2] The FDA can waive an element of the similarity assessment but they will not do so if there is any lack of certainty that the product will have clinical activity that is highly similar to the US-licensed reference product.

Protein products that are amenable to being developed and approved as biosimilars in the USA are large, complex molecules. The manufacture of a biosimilar biological protein product is extremely challenging and requires sophisticated manufacturing processes, starting with the development of a suitable cell line for synthesising the correct population of protein molecules. Today's analytical tools are powerful enough to detect even the smallest structural differences between proteins, such as those which can occur when manufacturing different lots of the same product. The challenge is to develop a molecule structurally and functionally similar to the reference product in all characteristics, accepting that small analytical differences are allowed if they will not affect clinical performance. Evaluation of the molecular structure and biological activities of a biosimilar protein leverages the scientific knowledge of the structure–function relationships of the reference product, only certain post-translational modifications and structural characteristics affect biological activity, immunogenicity, or pharmacokinetic (PK)/PD activity. Analyses to demonstrate biosimilarity focus on comparisons of amino acid sequence, which needs to be identical, post-translational amino acid modifications, glycoforms (for glycosylated proteins), higher order (three-dimensional) structure, and biological activity(ies) and antibody structure–function relationships, such as binding to the target antigen and Fc effector functions.[1,3]

The role of clinical studies in the FDA biosimilars assessment is to confirm that the biosimilar has the correct molecular structure and function as demonstrated by the absence of meaningful differences in safety, efficacy, and immunogenicity when compared with the US-licensed reference product; clinical studies for a biosimilar are not intended to re-establish the clinical safety and efficacy profile of the reference product in all conditions of use for which it is licensed. The reason is that the clinical safety and efficacy profile of the reference product is already well-known, based upon the large body of clinical experience that already exists for that product, so a product that has the same molecular structure as the reference product is expected to have the same clinical activity. Key confirmation that the biosimilar will have comparable clinical performance comes from the clinical PK/PD studies that are a required element for approval of most biosimilars in the USA. Clinical PK/PD studies are pivotal in the development of biosimilars[1,2] because the FDA considers them to be more sensitive than a clinical safety and efficacy study in detecting how the protein is interacting with the body. Highly similar PK/PD profiles in structurally similar molecules support the likelihood that clinical performance will also be highly similar. The current minimum FDA requirement is for one clinical PK/PD study that also demonstrates comparable immunogenicity of the biosimilar and its reference product. If possible, comparable immunogenic potential will be demonstrated in an immune-competent population. A comparative clinical safety study (or studies) to confirm equivalent efficacy and a comparable safety profile will be required if there is residual uncertainty about the biosimilarity to the reference product. For products that have multiple clinical indications that include oncology, emphasis is placed on demonstrating equivalence in the most vulnerable patient population; i.e., patients with cancer for whom suboptimal efficacy could be life-threatening. For rituximab, for example, efficacy would likely be tested in lymphoma patients rather than RA patients. If a reference product is licensed for several indications, and different mechanisms of action are relevant to the different indications, such as anti-tumour necrosis factors (TNF) acting primarily through TNF in RA but also possibly through antibody-dependent cell-mediated cytotoxicity in

inflammatory bowel disease (IBD), then the FDA expects demonstration of similarity in all possible functional activities.[4]

The extent of the analyses required to determine biosimilarity may vary depending on the complexity of the biological molecules. For the filgrastim biosimilar Zarxio®, a small (17 kDa) protein with minimal post-translational modifications, no glycosylation, and a single mechanism of action, requirements include the demonstration of similar PK, PD, and comparable immunogenicity, in addition to demonstrating a high degree of molecular similarity to its reference product (Neupogen®). A clinical safety and efficacy study may not have been necessary. In contrast, an anti-CD20 monoclonal antibody such as rituximab is a much larger (150 kDa) and complex glycoprotein with multiple functional domains. It is approved for use in a variety of indications and has multiple mechanisms of action that derive both from its target binding and its effector function. In this case, establishing biosimilarity would require molecular similarity studies, PK/PD studies in patients (e.g with RA), and also a safety and efficacy study in the more vulnerable population of patients with lymphoma.

A successful biosimilar is a product of sophisticated science, analytics, and biotechnology engineering, all of which are necessary to reverse-engineer and validate the consistent manufacture of a large, complex, biologically-produced molecule. The FDA has developed a thorough biosimilar assessment process, and will not approve a biosimilar unless certain that the product will have highly similar clinical performance in every indication for which licensure is sought. Clinicians can be confident that FDA-approved biosimilars will be among the most deeply-analysed and predictable products available.

Building the Totality-of-the-Evidence: Confirming Biosimilarity and Supporting Extrapolation

Professor Craig Leonardi

Confirmatory clinical studies of biosimilars aim to provide evidence that the biosimilar is not significantly different from the reference product; they are not aiming to independently establish safety and effectiveness. The work of demonstrating clinical efficacy and safety has already been done for the original approval of the reference product, and to achieve cost-effectiveness, producers of biosimilars aim to avoid unnecessary replication of clinical trials. Instead, smaller-scale direct comparisons and extrapolation provide the necessary evidence. For approved biosimilars, there should be no differences in safety and efficacy. In the development and approval of biosimilars, the largest part of the totality-of-the-evidence; the analytical, non-clinical, and clinical studies, is the analytical data, for quality assessment and a comprehensive comparison with the reference product. Clinical trials are a much smaller part of the similarity assessment compared with the studies carried out for the approval of the reference product where clinical studies in all potential indications of use must be carried out.

Confirmatory clinical studies for biosimilars focus on demonstrating equivalent safety, efficacy, and immunogenicity to the reference product. In equivalence trials, biosimilars must demonstrate activity within pre-established equivalence limits, having neither decreased nor increased activity in comparison with the reference products. For these trials, a suitably sensitive, homogeneous patient population should be chosen to detect any differences in activity, should they exist, and to assess immunogenicity, consistent with the population studied for the reference product to allow for comparison. The primary endpoint should be clinically relevant and ideally should have a large effect size (the difference in clinical response between the active product and the placebo) to allow for detection of small differences.

For rheumatologists interested in anti-TNF therapies for inflammatory diseases, the clinical model most sensitive for detecting differences in efficacy may well in fact be psoriasis. In IBD, the Crohn's Disease Activity Index (CDAI) for evaluating clinical symptoms[5] is a rather subjective assessment and does not appear to be a reliable measure of the actual disease status as measured by mucosal inflammation.[6] In RA, the American College of Rheumatology (ACR)'s ACR20 set of multidimensional outcome measures allows comparisons across different studies and therapies, but dichotomises continuous measures of response into 'responder' and 'non-responder' groups. Responder analyses, by cutting continuous measures into 'responder' and 'non-responder groups', can sacrifice statistical power while underestimating the differences between groups.[7]

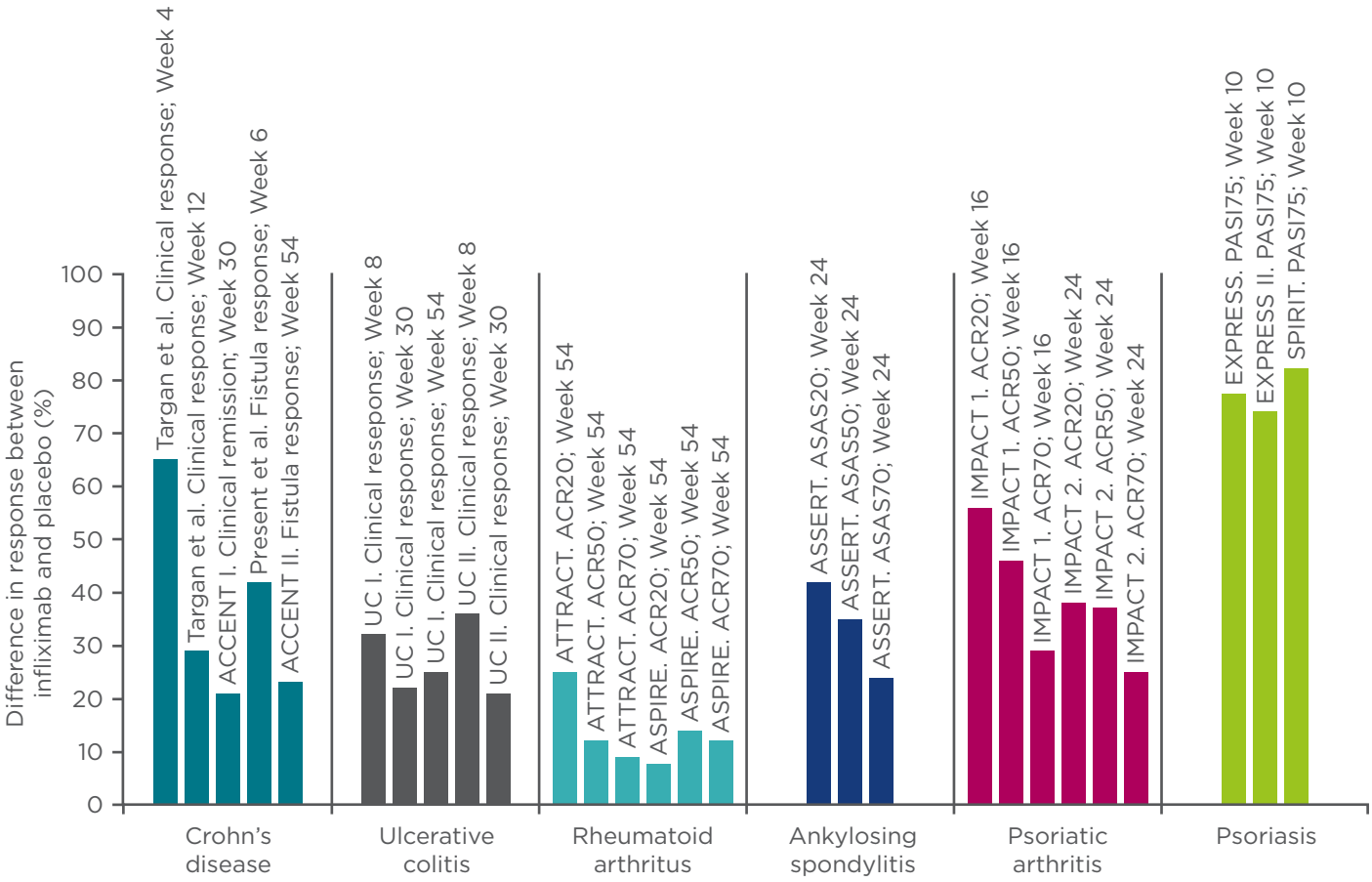

Figure 1: Placebo-adjusted differences in efficacy (infliximab–placebo) in inflammatory disease settings.[9]
ACR: American College of Rheumatology; PAS: Psoriasis Area Severity Index.

Additionally, the ACR20 does not always reflect disease response, as shown in the ATTRACT study, where infliximab-treated patients had a reduction in joint damage in both patients with and without an ACR20 response.[8] Across a variety of inflammatory diseases, as shown in Figure 1, psoriasis patients show the largest treatment effect size in response to the anti-TNF infliximab.[9] The Psoriasis Area Severity Index (PASI75) used to measure response[10] is sensitive (able to show statistically significant differences between treatment doses),[11] consistent across trials,[12] and linked to quality of life measures.[13] Other features that make patients with psoriasis a model of choice is the ease of assessment (no invasive testing is required), the speed of response (12–16 weeks, as opposed to 36 or 48 weeks in other inflammatory diseases),[14] the younger age and the relative lack of comorbidities, and concomitant medications.[15] Furthermore, biologics are usually used as monotherapy in psoriasis trials,[14] which avoids any potential bias that may be introduced from co-therapies.

Moreover, patients with psoriasis could be a sensitive clinical model for detecting differences in safety and immunogenicity. Data from trials of adalimumab in a variety of disease settings show that in patients with Crohn's disease or RA, serious adverse events of interest occurred at higher rates than in the patients with psoriasis, who were younger and relatively healthier than patients with Crohn's disease or RA.[16] Serious adverse events that do occur in patients with psoriasis may be more likely to be treatment-related than disease-related, improving the detection rate of relevant adverse events. Immunogenicity is a concern both for safety, in terms of hypersensitivity, anaphylaxis, and infusion reactions, and for efficacy, in terms of anti-drug antibodies (ADAs). Data on immunogenicity are an important part of the totality-of-the-evidence of biosimilarity. The most sensitive clinical model for detecting differences in immunogenicity should be an indication most relevant to the patient population and treatment regimen under which immune responses might occur. Patients with psoriasis are less likely to be immune-suppressed, as use of

disease modifying anti-rheumatic drugs (DMARDs) and immunosuppressants are typically not used in combination with anti-TNF and other biologic therapies,[14] in comparison with patients with RA, where guidelines recommend that biologics are used in combination with DMARDs and immunosuppressive drugs.[17] Thus, psoriasis could represent a more sensitive indication to detect differences in immunogenicity than RA.

As outlined here, patients with psoriasis are a sensitive population to test safety and efficacy equivalence for anti-TNF biosimilars. Extrapolation to other indications, e.g. RA or IBD, based on the totality-of-the-evidence of all analytical, non-clinical and clinical data, and understanding of the reference product, is a logical consequence of the biosimilar concept and avoids unnecessary studies for ethical and efficiency reasons.[18] Carrying out equivalence trials in each indication should not be necessary where the product's mechanism of action is the same for each indication. The structure–function relationships of the molecule mean that if the biosimilar has been shown to have the same structure and biological activity as the reference product, then it will have the same clinical function that has been demonstrated in each disease setting for the reference product. Where different disease settings are known to involve different mechanisms of action, then extrapolation may not be appropriate for a biosimilar and further clinical evidence may be required. Other factors to be considered in the scientific justification for extrapolation include target/receptor interactions, PK, and biodistribution between different patient populations, and differences in the safety or immunogenicity profile between indications.[1,18]

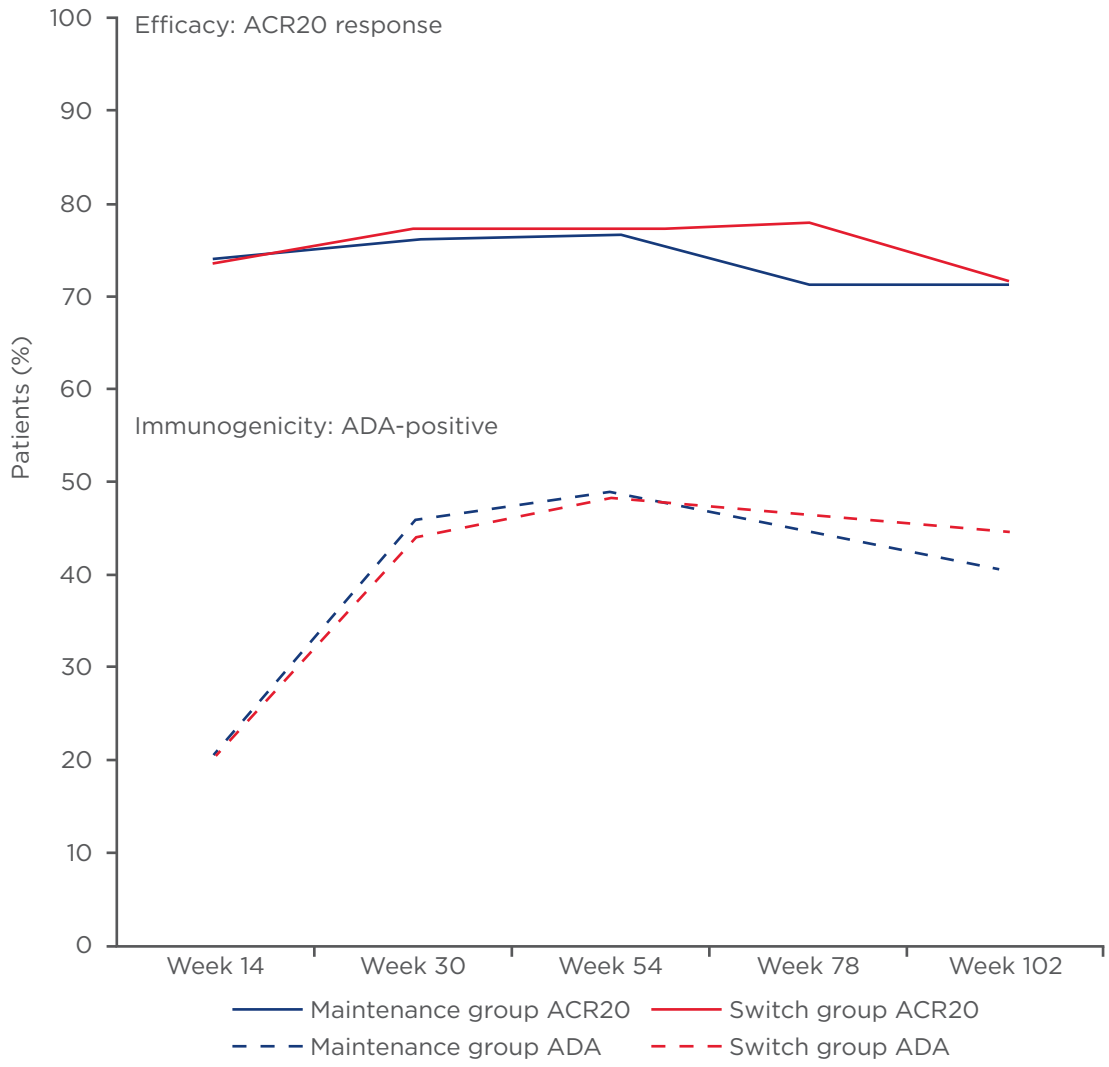

Figure 2: Long-term data from the extension phase of the PLANETRA study, where the originator arm was switched to biosimilar infliximab.[24]

ACR20: American College of Rheumatology 20% improvement criteria; ADA: anti-drug antibody.

In conclusion, the totality-of-the-evidence that supports the demonstration of biosimilarity includes structural and functional characterisation, non-clinical evaluation, clinical PK/PD data, a confirmatory clinical study demonstrating equivalent efficacy and safety, clinical immunogenicity data, and extensive understanding of the safety and efficacy profile of the reference product. It means that biosimilarity may be demonstrated even with minor structural or formulation differences, providing that the differences are not clinically meaningful in terms of safety, purity, or potency, and that the proposed product otherwise meets the statutory criteria for biosimilarity. Given that clinical studies do not form the major part of the biosimilar product characterisation, they will ideally be performed in the most sensitive clinically relevant population, and the totality-of-the-evidence of all data obtained support extrapolation to other indications.

Impacting the Clinical Landscape: The Role of Biosimilar Therapies in Rheumatology

Professor Peter Taylor

Biological therapies, especially monoclonal antibodies, have caused a dramatic change in the treatment landscape for rheumatology. Biosimilars of monoclonal antibodies have now entered into clinical use since the first approval by the European Medicines Agency (EMA) in June 2013.[19] To incorporate biosimilars in their clinical practice, rheumatologists want to be confident that biosimilars will have the same safety and efficacy profile as the originator drug for all approved indications, and the same durability of response (i.e. no higher immunogenicity and associated loss of response). Barriers to prescribing biosimilars identified in a 2013 survey of rheumatologists were predominantly doubts on similarity, safety, and efficacy.[20] The quality control in biosimilar development processes and the rigorous assessment procedures followed by the FDA and the EMA can go some way to providing reassurance in these areas. Lack of long-term data and lack of data from local countries were also concerns.[20] As several of the biosimilar monoclonal antibodies have been available for several years now, these concerns are beginning to be addressed through post-marketing studies, and can also be addressed by guidelines for incorporating biosimilars into rheumatology practice.

Optimal use of biosimilars can be ensured by addressing the perceived gaps in the evidence. Concerns over immunogenicity can be addressed through studies such as that for the infliximab biosimilar CT-P13, which showed that antibodies to the originator product recognised the biosimilar and cross-reacted with it to a similar level as with the originator product.[21] Concerns over long-term safety and efficacy of biosimilars can be addressed through pharmacovigilance, good prescribing practice, and registry studies. In particular, traceability is an important issue for pharmacovigilance of biosimilars, and the use of brand names in prescribing is necessary to identify each biosimilar uniquely. Registry data are invaluable for providing essential long-term evidence of the safety and effectiveness of therapeutic agents in clinical practice. A variety of registries have been set up in rheumatology, and the British Society of Rheumatology (BSR) Biosimilars Registry (BSRBR) is currently recruiting participants with RA to record data on all patients newly starting or switching to biosimilars and to monitor adverse events. The BSR is also recommending that patients with psoriasis, ankylosing spondylitis (AS), or other non-RA diseases who are prescribed a biosimilar have information collected on the BSRBR forms by their consultants and stored locally.

Concerns over the safety and effectiveness of switching from an originator to biosimilar products are being addressed through studies. For epoetins, where biosimilars have been available for some time, multiple studies have shown that substituting epoetins is not associated with the occurrence of adverse events.[22] For monoclonal antibodies, clinical data indicate equivalent efficacy, safety, and immunogenicity after switching from originator product to biosimilar infliximab in patients with RA (Figure 2). Additionally, clinical studies of biosimilars are now incorporating an interchangeability of study design, with multiple switches between the reference product and the biosimilar.[23]

The BSR have produced a position statement on biosimilar medicines to enable rheumatologists to incorporate biosimilars into practice. They recommend prescription by brand name for traceability and in response to clinical reasons, not solely economic considerations. Decisions on

starting biosimilars should be made in partnership with the patient and substitution should only be with the consent of the prescribing clinician. Patients should be registered with the BSRBR. Biosimilars should undergo robust technology appraisals and local tenders involving biosimilars should seek to source a range of products. Importantly, the BSR identified a need for raising awareness on biosimilars and better information sharing across the care pathway.[25]

The underlying reasons for incorporating biosimilars into rheumatology practice are to address inequities of access and the sustainability of healthcare systems. The economic burden of RA is considerable, and despite major advances in the management of RA, unmet medical needs remain.[26] Patient access to biologic therapies varies across Europe, with currently approved biologics either not reimbursed or only partially reimbursed for a restricted subset in many countries, while the cost of biologics is not affordable in over half of the 46 European countries investigated in one study.[27,28] Patients with limited access to biologics have poorer clinical outcomes.[29] Biosimilars offer the potential to broaden patients' access to treatment, which has already been demonstrated in Europe with filgrastim.[30] Significant savings for payers can be achieved, as in the case of Germany's healthcare system, where €655 million cumulative savings were attained from the use of biosimilar epoetin.[31] Savings generated through biosimilars could be used to increase patient access to biological medicines, although access will depend on the country, the product, eligibility criteria, and current clinical practice. In the UK, for example, the National Institute for Health and Care Excellence (NICE) has widened access to AS therapy due to biosimilar infliximab being available at a significant cost discount.[32] With the more favourable cost-effectiveness ratio of biosimilars, there is also the potential to introduce biologics earlier in the treatment paradigm, which could potentially prevent or slow disease progression. The potential health economic benefits of biosimilars will depend on many factors, including education of all stakeholders, experience in the use of biologics to address concerns and demonstrate value, sustainable pricing, and rational decision-making.[33]

In summary, confidence in biosimilar use in rheumatology can be established through optimal use and the collection of real-world evidence, in addition to high-quality, comprehensive data on the effectiveness, safety, immunogenicity, and value for money of biosimilars and originator drugs. Biosimilars have the potential to expand treatment options for patients, but healthcare providers and payers should introduce them responsibly, taking all the issues of efficacy, safety, tolerability, immunogenicity, convenience, and value for money into account.

Question and Answer Session

Although the rationale for testing biosimilar immunogenicity on a population that is not immune-suppressed, i.e. patients with psoriasis, has been explained here, it has been observed that patients with RA have a different immunological response to biologics than those with psoriasis or AS. Does this affect the determination of biosimilarity?

Dr Emily Shacter replied that the recommended approach would be to compare immunogenicity in a sensitive population. Whenever clinical studies are performed, whether in healthy volunteers or patients, immunogenicity testing is performed, and all of the results contribute to the body of evidence for the determination of biosimilarity.

If a proposed biosimilar differs in its immunogenicity profile from the reference product, can it still really be considered biosimilar?

Dr Emily Shacter replied that it depended on whether the totality-of-the-evidence was in support of biosimilarity. With the infliximab biosimilar CT-P13, for example, although there were differences in the incidence of ADAs between the biosimilar and the reference product, the epitopes recognised by the ADAs to CT-P13 and the reference product in patients with IBD were the same, and no significant differences in ADAs were observed in the two clinical studies that were performed in AS and RA. This implies that the biosimilar had molecular similarity to the reference and was seen in the same way in the body, and that the differences that were seen were likely random due to the small sample size.

The use of low-dose (i.e. subclinical doses) of methotrexate reduces the immunogenicity of biologics in RA and is used to improve the durability of response, is this also true in psoriasis?

Prof Craig Leonardi replied that this was also true in psoriasis, but that dermatologists tried to avoid the use of methotrexate in their patients.

Given the discussion here of the importance and precision of analytical tests to provide the evidence of biosimilarity, is it possible that analytical tests in the future will be so sophisticated that a clinical trial will not be needed?

Dr Emily Shacter replied that the preference will always be to have a clinical trial, at least to evaluate PK and, if relevant, PD to confirm that the drug is behaving in the body as expected.

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

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INTRODUCTION

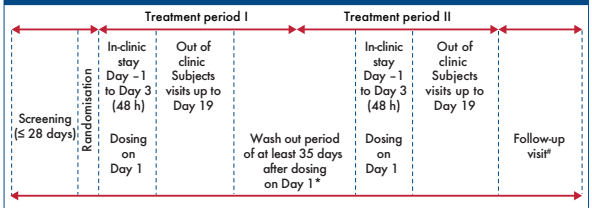
- A biosimilar is a biologic product that is 'comparable' (EMA) or 'highly similar' (US FDA) to an approved biological drug, i.e. the originator
- GP2015 is a proposed etanercept biosimilar
- Here, we present results from a study conducted in healthy male subjects to compare the pharmacokinetics (PK) 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/m^2 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

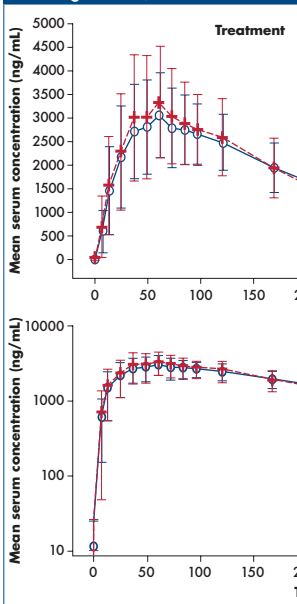
- 54 subjects were randomised, 27 each to the treatment sequences GP2015/etanercept originator and etanercept originator/GP2015 and all completed the study without major protocol deviations. All 54 subjects were included in the safety and PK analysis sets. The demographic and baseline characteristics 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 baselin

Demographic variables	GP2015, etanercept originator N=27
Age, years, mean (SD)	35.2 (8.4
Race, n (%)	
White	15 (55.6
Asian	7 (25.9
Black/African American	3 (11.1
Other	2 (7.4)
Weight, kg, (mean SD)	75.51 (10.
BMI, kg/m², (mean, range)	24.58 (19.0–29

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

Figure 2. Mean serum concentration semi-logarithmic) of GP2015 and et



ETN, etanercept originator; PK, pharmacokinetic

Biosimilar, and Etanercept Originator
-over Study

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e characteristics (safety set)

	Etanercept originator/GP2015 N=27	Total N=54
5)	30.6 (7.55)	32.9 (8.27)
)	14 (51.9)	29 (53.7)
	6 (22.2)	13 (24.1)
	5 (18.5)	8 (14.8)
	2 (7.4)	4 (7.4)
08)	76.71 (9.48)	76.11 (9.71)
.4)	25.11 (20.5–29.4)	24.85 (19.0–29.4)

GP2015 during treatment period 1 and
rcept originator/GP2015, subjects received
nd GP2015 in treatment period 2

-time profiles (linear and anercept originator (PK set)

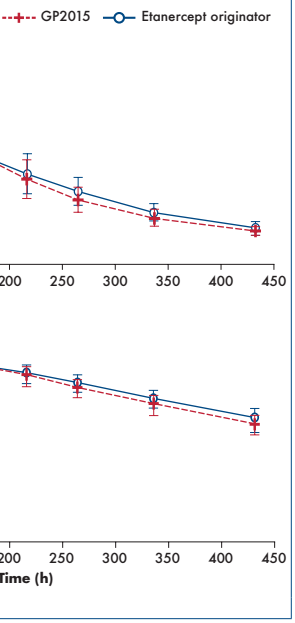

Table 2. Mean ratio and 90% CI for primary PK parameters based on nominal dose

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-last}, 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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Poster presented at EULAR Congress 2016 (08–11 June), London, UK

Pharmacokinetics and Safety of GP2015, a Proposed Etanerc Subcutaneously by Autoinjector or Prefilled Syringe in Health

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INTRODUCTION

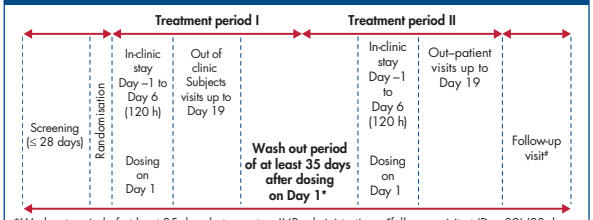
- Joint-destructive diseases, such as rheumatoid arthritis, are often associated with impaired dexterity
- The use of an autoinjector (AI) for drug delivery has been shown to increase patient adherence, acceptability and convenience, in comparison to conventional or pre-filled syringes (PFS)[1,2]
- GP2015, 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**

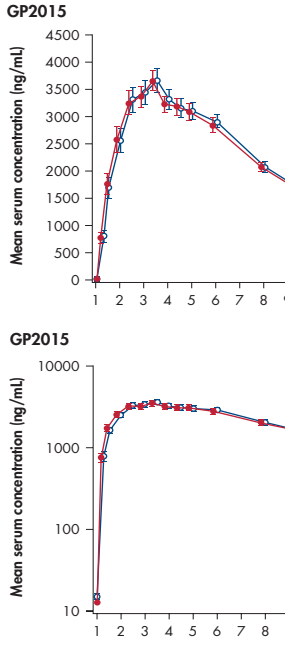
Table 1. Demographic and baseline characteristics (safety set)

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 administered by an AI or a PFS (**Figure 2**

Figure 2. Mean serum concentration- semi-logarithmic) of GP2015 AI and



AI, autoinjector; PFS, pre-filled syringes

- The 90% CIs for the ratio of the geometri were within the pre-defined bioequivaler

Table 2. Geometric means and 90% co

PK Parameter	Geome
	AI
C_{max} (µg/mL)	3.7
AUC_{0-last} (h*µg/mL)	684.1
AUC_{0-inf} (h*µg/mL)	745.2

AUC_{0-inf}, area under the serum concentration-tir extrapolated to infinity; AUC_{0-last}, measured fr concentration; AI autoinjector; C_{max}, maximum interval; PK, pharmacokinetic; PFS, pre-filled sy

ept Biosimilar, Administered y Male Subjects

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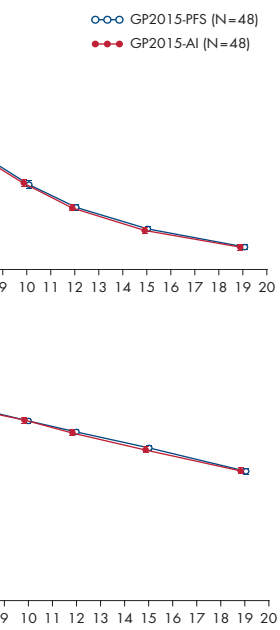
of GP2015 were comparable when
2)

time profiles (linear and PFS



ic means for the primary PK parameters
nce range of 0.80–1.25 (**Table 2**)

nfidence intervals for PK parameters

etric Means		Mean Ratio (%)	90% CI of Ratio
	PFS		
	3.6	1.01	0.94–1.08
	678.4	1.01	0.95–1.07
	737.4	1.01	0.96–1.07

me curve measured from the time of dosing and
om the time of dosing to the last measurable
observed serum concentration; CI, confidence
ringe

- 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

References

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

Acknowledgment

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