INTRODUCING NEW BIOSIMILARS INTO CURRENT TREATMENT ALGORITHMS

Summary of a Biogen-sponsored symposium, held at the European League Against Rheumatism (EULAR) Congress 2016 in London, UK, on 9th June 2016

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MEETING SUMMARY

Three biosimilar products are now licensed for the treatment of rheumatic diseases in Europe. The European Medicines Agency (EMA) requires that similarity between a biosimilar and its reference product is demonstrated using a rigorous, stepwise process that includes extensive physicochemical and biological analytical testing, non-clinical pharmacology, clinical evaluations, and pharmacovigilance plans. Each step is highly sensitive to any differences between products and progressively reduces any uncertainty over similarity; all steps must be satisfied to demonstrate biosimilarity. The US Food and Drug Administration (FDA) requires a similar stringent biosimilar development process.

The etanercept biosimilar SB4 (Benepali®), recently approved for the treatment of rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis, non-radiographic axial spondyloarthritis), and plaque psoriasis, is herein used to demonstrate the detailed analytical characterisation and clinical testing that are required by the EMA before biosimilars are approved for use. A comprehensive characterisation study involving >55 physiochemical and >25 biological assays demonstrated that SB4 has highly similar structural, physicochemical, and biological quality attributes to reference etanercept. A Phase I study demonstrated pharmacokinetic equivalence between SB4 and reference etanercept in healthy male subjects. Furthermore, a Phase III, randomised, controlled trial performed in patients with

moderate-to-severe rheumatoid arthritis despite treatment with methotrexate (MTX) showed that SB4 was equivalent to etanercept in terms of efficacy, safety, and immunogenicity.

In conclusion, the biosimilar development process performed according to EMA or FDA guidelines is highly rigorous and comprehensive. Biosimilars such as SB4 are now available in clinical practice and are likely to improve access, reduce costs, and ultimately, improve health outcomes.

INTRODUCTION

A biosimilar is defined by the EMA as "a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product."[1] In developing a biosimilar, the aim is to create a highly similar product with no clinically meaningful differences from the reference biological in terms of safety, purity, and potency. Three biosimilar products are now licensed for the treatment of rheumatologic diseases in Europe: two infliximab biosimilars (CT-P13 and SB2) and one etanercept biosimilar (SB4). Biosimilars have considerable potential to offer cost savings and increased accessibility to effective biologic disease-modifying anti-rheumatic drugs (bDMARDs).[2] However, it is crucial that clinicians are confident that biosimilars have no meaningful differences compared with their reference products.

The comprehensive and stepwise assessment of the totality of evidence required by the EMA for biosimilar development was reviewed by international experts at a Biogen-sponsored, interactive symposium held during EULAR 2016, and illustrated through the example of the recently-approved etanercept biosimilar, SB4 (Benepali®). Furthermore, the expert faculty and audience discussed the practical benefits of introducing these new biosimilars into treatment algorithms for rheumatic diseases.

BIOSIMILARITY: AN INNOVATIVE REGULATORY AND DEVELOPMENT CONCEPT

Biological drugs are intrinsically complex proteins produced by living cells, and are highly sensitive to changes in manufacturing processes and storage conditions.[3] This complexity means that biosimilars cannot be generic or identical copies of the innovator biological because they are not created using exactly the same manufacturing conditions as the reference product. Thus, development of biosimilar products requires a rigorous and comprehensive set of comparability exercises and regulatory evaluation. According to the EMA, it needs to be demonstrated that the biosimilar is highly similar to its biological reference product, with no clinically meaningful differences in quality characteristics, biological activity, safety, and efficacy.[1] The active substance, posology, and route of administration for the biosimilar also need to be the same as for its reference product. Changes intended to improve efficacy are not considered part of the biosimilar approach.

"You can't apply the generic rules, because they [biosimilars] are not generics. You cannot make a generic biosimilar." (John D. Isaacs)

It is important to understand that currently used reference biologicals can themselves be considered as different versions of the original products at launch.[4,5] Because of the complexity of the products and their reliance on cell culture for production, it is impossible for any manufacturer to keep a biological perfectly consistent over time or across multiple production plants. Furthermore, the reference product may have undergone a number of intentional manufacturing changes since its approval. For example, reference etanercept (Enbrel®*) has undergone more than 20 post-approval changes.[4] Regulatory authorities have extensive experience in scrutinising and approving any such changes, with comparability exercises required when any critical changes are made to the manufacturing process, such as introducing a new purification step or setting up a new manufacturing site.

"We are fortunate in Europe that the EMA has long experience in their consideration of biosimilars… this is why many clinicians have a lot of trust in what the EMA is actually doing in their regulatory pathways." (Tore K. Kvien)

The EMA has pioneered the biosimilars development pathway (Figure 1), developing guidelines in 2005 and 2006 for approval of biosimilars using an abbreviated registration process. Of particular relevance to rheumatologists are the specific guidelines for monoclonal

antibodies, published in 2012,[6] and the guidelines for biotechnology-derived proteins, revised in 2015.[7] The World Health Organization (WHO), FDA, and regulatory authorities in Canada and Japan have produced similar guidance, as recently summarised.[2] In the European Union (EU), the EMA website provides a helpful overview of currently licensed biosimilars (www.ema.europa.eu)**. Biosimilars developed in countries with less rigorous regulatory pathways for such products are referred to as 'biocopies' or 'biomimics' and cannot necessarily be expected to have the same efficacy and safety profile as the reference biological.[8] Furthermore, biocopies may not be subject to rigorous pharmacovigilance processes to identify safety issues.

"We have to be very careful that we do not compare what is happening in countries with regulatory EMA and FDA pathways with other countries that do not scrutinise their products so carefully." (Arnold Vulto)

STEPWISE ASSESSMENT FOR TOTALITY OF EVIDENCE REQUIRED TO ESTABLISH BIOSIMILARITY

One of the goals of biosimilar development is to establish biosimilarity, not to re-establish benefit and safety.[1] Biosimilarity is demonstrated using a rigorous stepwise process to generate a totality of evidence that incorporates results from extensive physicochemical and biological analytical testing, non-clinical pharmacology, and clinical evaluations (Figure 2). All steps must be satisfied to confirm biosimilarity i.e. eventual differences have no relevance for clinical efficacy and safety.

"For the regular physician treating patients, it is sufficient to understand that EMA…are doing a comprehensive comparability exercise to look at analytical and in vitro data…Some of the details are very complex for regular clinicians, but this should not be a barrier to using these drugs." (Tore K. Kvien)

In the EU, this stepwise assessment is a comprehensive and transparent process with the assessment history for each product documented in detail in the European Public Assessment Report (EPAR), published by the EMA. At present, this detailed information is not fully documented in the product's Summary of Product Characteristics (SmPC), which is, instead, identical to the reference product SmPC. It has been argued that, as the SmPC is the primary source of information for the physician, it should contain all pertinent information on the biosimilar as well as the reference product.[10,11]

"The EMA is working on a third document… describing a summary of the EPAR for clinicians." (Arnold Vulto)

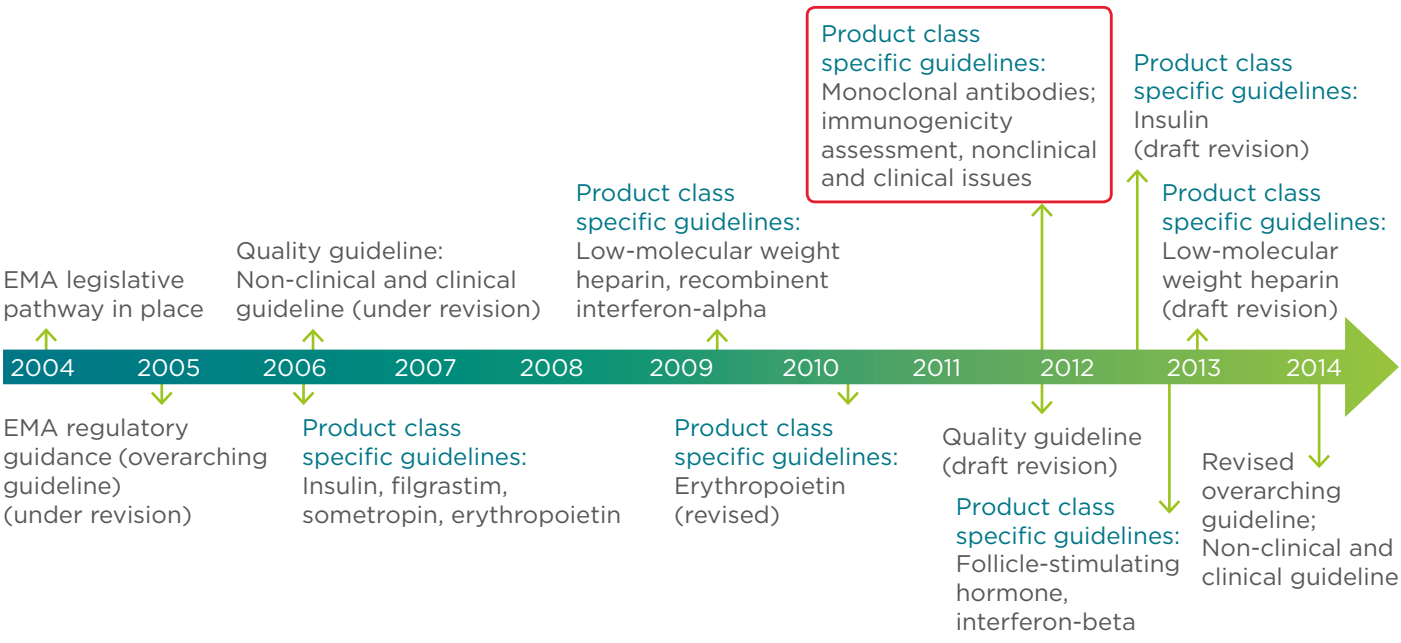

Figure 1: The European Medicines Agency (EMA) pioneered the biosimilars development pathway: timeline of guidelines issued by the EMA to guide the development of biosimilars.

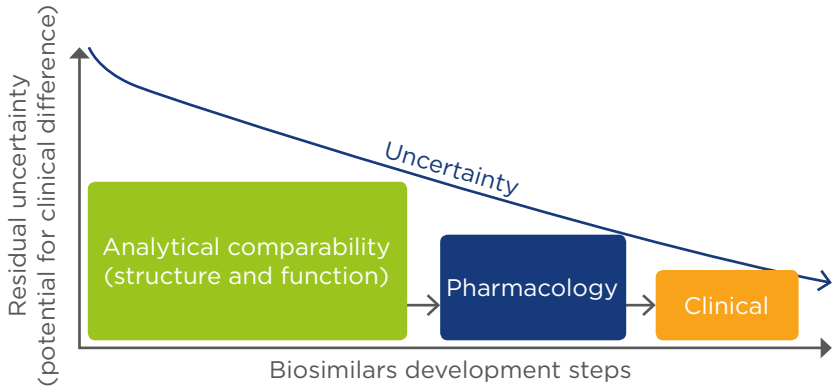

Figure 2: Stepwise assessment for the totality of evidence required to demonstrate biosimilarity.[9]

Analytical Comparability

The biosimilar development process places significant emphasis on analytical methods to exclude any relevant differences between the biosimilar and its reference biological. A biosimilar should be highly similar to the reference product in physicochemical and biological terms, with any observed differences justified in terms of their potential impact on safety and efficacy.[1] Natural and manufacturing variability means that biologicals often comprise a mixture of protein isoforms, with differences in higher order structure, post-translational modifications (such as glycosylation), and charge profile.[12] This may result in changes in biological activity including receptor binding, effector function, cytotoxicity, and signal transduction. Characterisation studies are required that are "sensitive, specific, and sufficiently discriminatory to provide evidence that observed differences in quality attributes are not clinically relevant."[7] The EMA notes that it is not expected that all quality attributes will be identical and minor differences may be acceptable, if appropriately justified.[7] However, it is most important that attributes which are critical to the efficacy and safety of a drug (referred to as critical quality attributes [CQAs]) are identified and maintained across products.[7]

"The rule for generic drugs is based only upon pharmacokinetic equivalence. Here we go far beyond that." (Arnold Vulto)

SB4 (Benepali®) is an etanercept biosimilar that has been developed by Samsung Bioepis Co., Ltd. (South Korea), a joint venture between Samsung BioLogics and Biogen. SB4 is the first etanercept biosimilar approved for use in the EU and is manufactured in Denmark. The analytical comparability of SB4 and reference etanercept was established in accordance with the International Conference of Harmonization comparability guideline[13] and the biosimilar guidelines of the EMA and FDA. Characterisation studies included >55 physiochemical tests and >25 biological assays to provide an extensive comparison of primary, secondary, and tertiary structure, purity and process-related impurities, glycan content and identity, and biological activities based on the mechanism of action.[14] These studies used sophisticated, state-of-the-art assays and are considered more sensitive than clinical measures at detecting small differences between molecules as they inherently exclude heterogeneous patient or disease factors. This comprehensive characterisation exercise clearly demonstrated that SB4 has highly similar structural, physicochemical, and biological quality attributes to reference etanercept.

"Altogether, there were 80 tests described in detail [for SB4]…these data have been submitted to EMA and have been scrutinised." (Arnold Vulto)

Clinical Pharmacology

Regulatory agencies typically require a Phase I pharmacokinetic comparability study of a biosimilar and its reference product as the first step in a biosimilar clinical development programme. While pharmacokinetic equivalence is necessary to demonstrate biosimilarity, it is insufficient of itself and must be coupled with analytic comparability and a Phase III clinical study. Generally, a single-dose, crossover study with full pharmacokinetic characterisation in a homogeneous population is recommended to demonstrate biosimilarity.[7]

To show pharmacokinetic equivalence, the confidence intervals (CIs) of the test-to-reference ratios of relevant pharmacokinetic parameters must be contained within a pre-specified equivalence margin, agreed upon with the regulatory agency.[7]

In the SB4 Phase I study, 138 healthy males were randomised to receive a single dose of SB4, reference etanercept sourced in the EU, or reference etanercept sourced in the US during Period 1, followed by crossover treatment in Period 2.[15] The crossover design allowed each subject to receive two treatments, so that a comparison between the two treatments could be made with each subject acting as their own control. The comparison between the EU- and US-sourced products also provided scientific justification for the use of EU-sourced etanercept as the only active comparator in the Phase III study.

The mean serum concentration-time profiles were superimposable between the SB4 and reference etanercept sourced in the EU, SB4 and reference etanercept sourced in the US, and reference etanercept sourced in the EU and US. The geometric least squares means ratios of AUC_{inf} (area under the concentration-time curve to infinity), AUC_{last} (AUC to the last quantifiable concentration) and C_{max} (maximum concentration) were close to 1 for all comparisons, and the corresponding 90% CIs were completely contained within the pre-specified equivalence margin of 80–125%.

"The study definitely met its expectations, showing that there were no pharmacokinetic differences between the biosimilar etanercept SB4 and the originator products." (Tore K. Kvien)

The incidence of treatment-emergent adverse events (TEAE) was similar between treatments, with no serious adverse events or deaths reported during the study. It is recognised that differences in impurities and/or breakdown products between biosimilars and their reference products can affect immunogenicity. Antidrug antibodies (ADAs) can limit drug bioavailability and shorten half-life through the formation of immune complexes that accelerate drug clearance and/or impair binding. In this Phase I study, immunogenicity was evaluated pre-dose and at Day 29 after the first treatment. While the incidence of ADAs was lower after SB4 exposure compared with reference etanercept exposure, the EMA did not consider this numerical imbalance clinically relevant and did not preclude biosimilarity.[16]

Clinical Assessment

Phase III, randomised, controlled trials designed to demonstrate equivalent efficacy and comparable safety, are the third step in removing uncertainty around the comparability of a biosimilar and its reference product. The EMA requires the trial to be performed in a sensitive population of patients with a disease for which the reference product is licensed and an equivalence margin should be pre-defined for the primary endpoint (American College of Rheumatology 20% [ACR20] response rate) based on the placebo-adjusted efficacy outcome derived from a meta-analysis of prior randomised controlled trials of the reference product.[1] Safety, including immunogenicity, should also be evaluated.

The clinical efficacy and safety of SB4 was compared with the reference product etanercept in a Phase III, multicentre, randomised, double-blind, parallel-group study performed in patients with moderate-to-severe rheumatoid arthritis despite treatment with MTX.[17,18] Patients receiving background MTX 10–25 mg/week were randomised to SB4 (n=299) or etanercept (n=297) administered as a weekly subcutaneous injection of 50 mg for 52 weeks. At the end of the double-blind treatment period, patients originally randomised to SB4 could continue in this treatment arm, while patients who were originally randomised to reference etanercept could be transitioned to SB4.[19] Only the EU-sourced version of reference etanercept was used in this study, which was considered acceptable as it had shown pharmacokinetic equivalence with the US-sourced version in the Phase I study.[15] The primary endpoint of the study was the ACR20 response rate at Week 24 in the per-protocol set. Although ACR20 is from a treatment perspective less relevant, it is established as the most sensitive endpoint to illicit any differences between the reference product and the biosimilar.

"You have a sensitive population, you have a sensitive primary endpoint, and you select the per-protocol population to increase the opportunity to find a difference." (Tore K. Kvien)

ACR20 response rates were 78.1% with SB4 and 80.3% with reference etanercept in the per-protocol set (Figure 3). The 95% CIs for the adjusted difference in ACR20 response rate

fell within the pre-specified equivalence margin of ±15% in both the per-protocol set (95% CI: -9.41 to 4.98%) and the full analysis set (95% CI: -5.24 to 9.07%), indicating therapeutic equivalence between products.[17] This equivalence was maintained over time, with the 95% CIs of the adjusted difference in ACR20 response rate at Week 52 also well-contained within ±15% in both the per-protocol set and full analysis set. Furthermore, the time-response curves of SB4 and etanercept in the full analysis set showed that ACR20, 50, and 70 response rates mirrored each other over the 52 weeks of the double-blind phase of the study.[18]

"It is reassuring that the response curves… before they plateau beyond Week 16–24, they are quite comparable…and maintain the effect up to Week 52." (Thomas Dörner)

Beyond clinical outcome measures, the modified Total Sharp Score was assessed at Week 52 in both groups.[18] The mean change from baseline in modified Total Sharp Score was comparable between the two treatment groups (0.45 for SB4 and 0.74 for reference etanercept).

The overall safety profile between SB4 and reference etanercept was comparable at Week 52.[18] There were minimal differences between SB4 and reference etanercept in terms of incidence of TEAEs (58.5% versus 60.3%, respectively), serious adverse events (6.0% versus 5.1%, respectively), TEAEs leading to study discontinuation (5.4% versus 6.7%, respectively), or serious infections (0.3% versus 1.7%, respectively). Injection-site reactions, grouped under the high-level term 'Administration-site reactions', occurred in fewer patients in the SB4 group at 52 weeks (3.7%) than the etanercept group (17.5%). The EMA concluded that this difference could have been at least partly due to an extensive split in the way that such reactions were reported and considered this numerical imbalance between the two arms of no clinical significance.[16] Malignancies were reported in four (1.3%) patients in the SB4 group (gastric adenocarcinoma, basal cell carcinoma, breast cancer, and metastatic lung cancer) and in one (0.3%) patient in the reference etanercept group (invasive ductal breast carcinoma). Two deaths were reported in the SB4 group, neither of which were considered related to treatment.

In the SB4 Phase III study, the incidence of ADAs at Week 24 was significantly lower in the SB4 group (0.7%) compared with the reference etanercept group (13.1%; p<0.001).[17] Only one sample from the reference etanercept group had neutralising capacity. The ADAs appeared early (between Week 2 and Week 8), and had mostly disappeared after Week 12. In a re-analysis excluding samples at Weeks 4 and 8, the overall ADA status at Weeks 24 and 52 was comparable and subgroup analyses by ADA status showed no apparent correlation between ADAs and clinical response or safety.[16] The evidence from this clinical trial confirmed the analytical and pharmacological data showing biosimilarity between SB4 and reference etanercept.

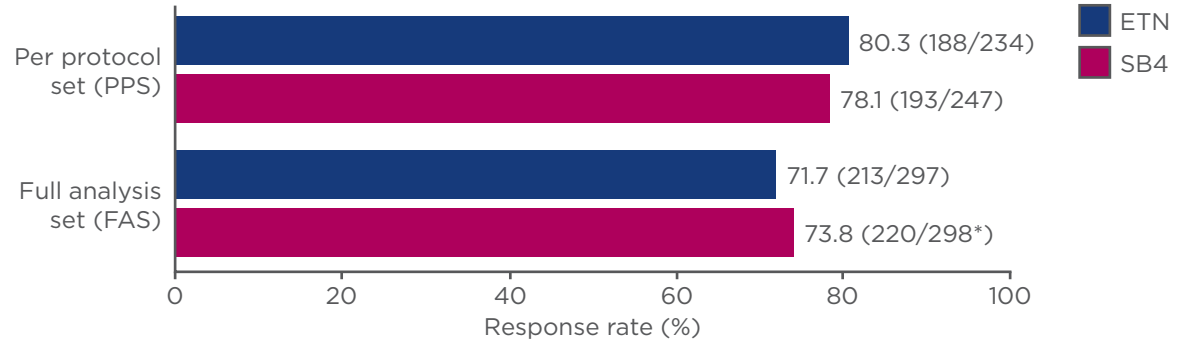

Figure 3: American College of Rheumatology response rates (ACR20) at Week 24 in patients treated with SB4 or reference etanercept.

PPS Adjusted difference: -2.22 (95% CI: -9.41 to 4.98), FAS Adjusted difference: 1.92 (95% CI: -5.24 to 9.07), [Predefined equivalence margin: -15 to 15%]

*One patient was excluded from the FAS due to missing efficacy data at baseline.

CI: confidence interval; PPS: per protocol set; FAS: full analysis set; ETN: reference etanercept.

Modified from Emery P et al.[17]

PHARMACOVIGILANCE

As with all pharmaceuticals, rare adverse events may occur in clinical practice that were not detected during clinical trials. Therefore, careful post-marketing pharmacovigilance is important for both biosimilars and reference products. The EMA requires a risk management plan for all biologicals, including biosimilars, and states that all appropriate measures should be taken to clearly identify any biological medicinal product which is the subject of a suspected adverse event report.[7]

"It is critical in terms of pharmacovigilance…that you as the clinician know what drug your patient gets…including the batch number…if there is a problem, we should be able to trace it back to which particular product was used." (Arnold Vulto)

TRANSITIONING BETWEEN BIOLOGICALS

Transitioning from a reference biological to a biosimilar is becoming an important consideration in rheumatology practice in the EU, particularly in terms of cost savings. Analysis of data from Week 52 to Week 100 of the SB4 Phase III clinical trial demonstrated that transitioning from reference etanercept to SB4 did not result in any loss of efficacy, increase in adverse events, or increase in immunogenicity.[19] At present, there is little evidence to guide transitioning to a biosimilar in clinical practice, although real-world data are being collected. For example, the NOR-SWITCH study[20] is a non-inferiority, randomised, controlled study being conducted in Norway that is evaluating the maintenance of efficacy following transition from reference infliximab to a biosimilar infliximab (CT-P13) compared with continued treatment with reference infliximab. It is imperative that high-quality pharmacovigilance and registry data are collected when transitioning to a biosimilar.

"We should be collecting more data directly from the patients, who are the real professionals here. They know their disease and their symptoms, and they will be the first to notice if there is a difference between what they have been receiving and what they have transitioned to." (John D. Isaacs)

As with all medicines, patients need to be able to make a fully informed decision about whether to transition from a reference biological to a biosimilar. This includes understanding what a biosimilar is, the pharmacovigilance plan for the product, and the financial implications of transitioning. Organisations such as the International Alliance of Patient Organizations (www.iapo.org.uk) provide clear and informative materials designed to educate patients on biosimilar medications and the implications for their disease management.

"Patients need to understand that if we can reduce the costs for some drugs, then we will have more resources available for new innovative products." (Tore K. Kvien)

CONCLUSIONS

"Hopefully, with the reduced costs of these drugs, accessibility will be better so that more patients can receive an effective treatment with biologic disease-modifying anti-rheumatic drugs (bDMARDs)." (Tore K. Kvien)

In the EU, the biosimilar development process is highly rigorous and comprehensive. Physicians can be confident that the EMA provides a thorough evaluation of each biosimilar that reaches regulatory review. Indeed, over the course of this symposium, the proportion of clinicians who would consider transitioning a patient from reference etanercept to a biosimilar increased from 54 to 73% (anonymous audience poll). Biosimilars, such as SB4, are now available in rheumatology clinical practice in the EU and are likely to improve access to rheumatology medicines, reduce costs, and, ultimately, improve health outcomes.

"We have at least the same quality of treatment, with better access for patients, at lower cost, so a win-win everywhere." (Arnold Vulto)

Footnotes

(*) Enbrel® is a registered trademark of Wyeth LLC

(**) Full URL for currently-licensed biosimilars in the EU: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&keyword=Enter%20keywords&searchType=name&alreadyLoaded=true&status=Authorised&jsenabled=false&searchGenericType=biosimilars&orderBy=name&pageNo=1

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