



# Biosimilars for psoriasis

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## Biosimilars for Psoriasis: Clinical Studies to Determine Similarity

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Biosimilars for Psoriasis

## Biosimilars for Psoriasis: Clinical Studies to Determine Similarity

A. Blauvelt<sup>1</sup>, L. Puig<sup>2</sup>, S. Chimenti<sup>3</sup>, R. Vender<sup>4</sup>, M. Rajagopalan<sup>5</sup>, R. Romiti<sup>6</sup>, L. Skov<sup>7</sup>, C. Zachariae<sup>7</sup>, H. Young<sup>8</sup>, E. Prens<sup>9</sup>, A. Cohen<sup>10</sup>, J. van der Walt<sup>11</sup> and J.J Wu<sup>12</sup>

<sup>1</sup>Oregon Medical Research Center, Portland, Oregon; <sup>2</sup>Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; <sup>3</sup>University of Rome Tor Vergate; <sup>4</sup>Director of Dermatrials Research Inc. & Venderm Innovations in Psoriasis; <sup>5</sup> Head of Dermatology, Apollo Hospitals, Chennai, India; <sup>6</sup> Department of Dermatology, University of São Paulo, Brazil <sup>7</sup>Herlev and Gentofte Hospital, University of Copenhagen, Denmark; <sup>8</sup>University of Manchester, Manchester Academic Health Science Centre, Department of Dermatology, Salford Royal Hospital Manchester, UK; <sup>9</sup>Erasmus University Medical Center, Dept. of Dermatology; <sup>10</sup>Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva and Department of Quality Measurements and Research, Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel; <sup>11</sup>International Psoriasis Council, St. Louis, MO, <sup>12</sup>Department of Dermatology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA

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11 **Corresponding Author:**

12 Andrew Blauvelt, M.D., M.B.A., President and Investigator, Oregon Medical Research Center,  
13 9495 SW Locust Street, Suite G, Portland, Oregon 97223; phone: 503-245-1525; fax: 503-245-  
14 0315; email: [ablauvelt@oregonmedicalresearch.com](mailto:ablauvelt@oregonmedicalresearch.com)

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Biosimilars for Psoriasis

### What's already known about this topic?

- Clinical studies, in addition to preclinical data, are required for regulatory approval of biosimilars.
- Biosimilar clinical trials are designed with smaller sample sizes than those required for approval of new biologic agents, and are not required for every indication of the originator.

### What does this study add?

- The International Psoriasis Council provides suggestions for biosimilar clinical trial design and describes psoriasis as the best disease model for TNF blocker biosimilar studies.

### Abstract

Biosimilars are drugs that are similar, but not identical, to originator biologics. Pre-clinical analytical studies are required to show similarity on a molecular and structural level, but efficacy and safety studies in humans are essential to ultimately determine biosimilarity. In this review written by members of the International Psoriasis Council, we discuss how biosimilars are evaluated in a clinical setting, with emphasis on extrapolation of indication, interchangeability, and optimal clinical trial design.

Biosimilars for Psoriasis

## Introduction

Biosimilars are drugs that are similar, but not identical, to original marketed biologic products.<sup>1</sup>

This basic definition of biosimilars urges the question of “How is similarity defined?” Different biosimilar manufacturers and drug regulating authorities are answering this question in different ways (Table 1). Although pre-clinical analytical studies represent the scientific foundation for biosimilars, efficacy and safety studies in humans remain the gold standard to confirm clinical equivalence and therefore biosimilarity.<sup>2</sup> Here, we discuss how biosimilarity is being defined on a clinical level.

Perhaps the biggest and most significant problem related to biologic prescribing and use for psoriasis patients has been the high cost of these products.<sup>3</sup> The signature promise of biosimilars is that they will decrease cost and increase access to biologic drugs for individuals who suffer from psoriasis, greatly improving the larger problem of under-treatment of this disease by dermatologists.<sup>4</sup> In order to reduce clinical development costs, clinical study requirements for regulatory agency approval of biosimilars are designed to be done with smaller sample sizes than those required for approval of new biologic agents, and need not be repeated for every indication of the originator. In other words, the amount and type of clinical data generated in clinical studies involving biosimilars will inherently be less than the clinical data obtained for originator biologics. Regarding this point, another purpose of this paper is to provide suggestions for optimal clinical study design as biosimilars proceed through development and regulatory hurdles.

## Extrapolation in Biosimilar Clinical Studies

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3 Clinical trials are critical in gaining approval and subsequent use of biosimilars in clinical  
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5 practice (Table 2). Both the U.S. Food and Drug Administration (FDA) and the European  
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7 Medical Agency (EMA) have published trial design guidelines for biosimilars.<sup>5,6</sup> *Extrapolation*  
8  
9 is defined as the ability to utilize clinical study data for one disease to gain agency approval for  
10  
11 another disease not explicitly studied in clinical trials.<sup>7,8</sup> For example, using the principle of  
12  
13 extrapolation, the EMA recently approved a biosimilar infliximab product (marketed as  
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15 Remsima® and Inflectra®) for psoriasis, psoriatic arthritis, and inflammatory bowel diseases  
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17 when this biosimilar drug had undergone clinical testing in only two disease types: rheumatoid  
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19 arthritis and ankylosing spondylitis (Table 3).<sup>9</sup> Of note, showing similar clinical study results for  
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21 biosimilar infliximab and Remicade® in these latter two diseases does not necessarily mean that  
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23 similar clinical results would be documented in other head-to-head studies with these same drugs  
24  
25 when used in patients with psoriasis or psoriatic arthritis. As a result of this decision by the  
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27 EMA, the dermatology community may find it difficult to interpret data collected from  
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29 biosimilar trials done in dissimilar disease states.<sup>10</sup>

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39 Health Canada, the drug regulating authority in Canada, has recently reached a somewhat  
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41 different conclusion than the EMA regarding Remsima®/Inflectra®. These drugs were  
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43 approved for use in inflammatory diseases of the skin (e.g., psoriasis) and joints (e.g.,  
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45 rheumatoid arthritis and psoriatic arthritis), but not for inflammatory bowel diseases. Health  
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47 Canada argued that extrapolation of data from rheumatoid arthritis/ankylosing spondylitis to  
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49 psoriasis/psoriatic arthritis could be done, but not from the former diseases to Crohn's  
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51 disease/ulcerative colitis.<sup>11</sup> They stated that differences in the results of an assay for antibody-  
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53 dependent cell-mediated cytotoxicity, a function of TNF blockers believed to be critical for  
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3 efficacy in inflammatory bowel diseases, might have implications in regard to the efficacy in  
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5 Crohn's disease/ulcerative colitis that prevented extrapolation to this indication (in the absence  
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7 of a specific clinical trial) of the biosimilar infliximab product that underwent review. This case  
8  
9 highlights that disease extrapolation can be controversial and that different regulatory authorities  
10  
11 may take different stances as they review applications for biosimilars.  
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18 In order to keep costs down, regulatory agencies have firmly endorsed the concept of  
19  
20 extrapolation for biosimilar approvals.<sup>12</sup> Thus, utilizing biosimilars in practice for diseases  
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22 where little or no clinical data exist is a reality that clinicians must learn to accept. Moving  
23  
24 forward, biosimilar companies will continue to choose the most appropriate disease(s) to perform  
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26 clinical trials designed to acquire data for agency approvals. The FDA recommends that a  
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28 sponsor should choose a disease condition to study that would be sensitive enough to identify  
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30 any clinically meaningful differences between the originator product and the biosimilar product.  
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37 *For TNF blockers, we suggest that future biosimilar trials be performed in psoriasis.* First, the  
38  
39 treatment effect size is large in psoriasis clinical trials, that is the difference between active drug  
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41 response rates and placebo response rates (often very low) are greater for psoriasis than in all  
42  
43 other inflammatory diseases treated with TNF blockers. For example, in the EXPRESS trial,  
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45 80% of patients treated with infliximab achieved PASI 75 at week 10 versus 3% of the placebo  
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47 group<sup>13 14</sup> Second, psoriasis trials can be performed without the confounding presence of other  
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49 immunosuppressive drugs, such as prednisone and methotrexate, which are often concomitantly  
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51 used by patients with other inflammatory diseases;<sup>15</sup> these drugs could interfere with both  
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53 efficacy and immunogenicity results during a clinical trial.<sup>16</sup> Third, psoriasis is a common  
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Biosimilars for Psoriasis

disease and thus recruitment of study subjects and execution of the biosimilar TNF inhibitor trials can be quickly and readily accomplished.

## Interchangeability in Biosimilar Clinical Studies

Interchangeability is the concept that a biosimilar drug and its parent biologic compound are so similar that a patient could be switched from one originator drug to another biosimilar drug and back during chronic therapeutic use, perhaps an indefinite number of times, without any untoward clinical side effects occurring due to this interchange of products.<sup>17 18</sup>

The FDA defines interchangeability when a biosimilar “can be expected to produce the same clinical result as the reference product in any given patient; and for a product administered more than once, the safety and reduced efficacy risks of alternating or switching are not greater than with repeated use of the reference product.”<sup>5</sup> The EMA defines interchangeability as the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting in any one patient, on the initiative, or with the agreement of the prescriber,<sup>19 20</sup> whereas automatic substitution, occurs when a prescribed medicine is substituted with another product by a pharmacist in the absence of physician notification.<sup>20 21</sup> Furthermore, each individual U.S. state will have laws regarding interchangeability. Pharmaceutical companies will likely wait until after the initial biosimilar approval occurs before determining whether or not to pursue clinical studies addressing interchangeability for their products. Until this occurs, payers may authorize the substitution of biosimilars for original biologics. Thus, dermatologists may lose control over what drug is actually chosen (e.g., parent drug vs. biosimilar #1 vs. biosimilar #2, etc.) after a prescription is written.

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6 The EMA does not have legal authority on whether a biosimilar should be used interchangeably  
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8 with its reference medicine; interchangeability and substitution are regulated by individual  
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10 member states.<sup>22</sup> Likewise, Health Canada does not recommend substitution of a biosimilar with  
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12 its reference biologic.<sup>23</sup> Some European countries prohibit automatic switching by the  
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14 pharmacist (Austria, Ireland, Czech Republic, Luxembourg, Belgium, Denmark, Finland,  
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16 Hungary, Norway, Portugal, Germany, Greece, Italy, Slovenia, Spain, Sweden, Switzerland and  
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18 the United Kingdom).<sup>24</sup> In France, automatic substitution (by community pharmacists) of a  
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20 biologic with another belonging to the same biosimilar group is allowed to initiate or allow  
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22 continuation of treatment, provided this possibility has not been ruled out by the prescriber. In  
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24 the Netherlands automatic switching is allowed with patient's informed consent.  
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32 *We suggest that biosimilars and originator biologics should not be randomly interchanged, since*  
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34 *it would be impossible to accurately assess loss of efficacy and adjudicate adverse effects in the*  
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36 *setting where drug switching is occurring haphazardly.* Rigorous clinical evidence is needed to  
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38 assess the safety and efficacy of switching from an originator to a biosimilar product. In an  
39  
40 extension study of PLANETRA, rheumatoid arthritis patients switched from infliximab to CT-  
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42 P13 (Remsima) did not demonstrate loss of efficacy or increase in immunogenicity over two  
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44 years compared to the group of patients that were started and maintained on CT-P13.<sup>25,26</sup> Similar  
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46 findings were reported in the extension study (PLANETAS) in ankylosing spondylitis patients.<sup>27</sup>  
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48 However, it is important to note that these studies were not designed to test equivalency or non-  
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50 inferiority. Data from an Italian observational cohort study of inflammatory bowel disease  
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52 patients demonstrated no differences in safety between patients switched from reference  
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Biosimilars for Psoriasis

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3 infliximab to patients starting on Remsima. However, a five-fold increase of loss of response  
4 was observed in the switch group (12.2%) compared to the patients starting on Remsima (2.3%;  
5 combined biologic treatment naive patients and previous biologic treatment group) and a trend  
6 for poorer outcomes (loss of response and primary failure) in the ulcerative colitis group versus  
7 the Crohn's disease response group.<sup>28</sup> By contrast, other observational studies, also presented at  
8 the 11<sup>th</sup> Congress of the European Crohn's and Colitis Organisation, demonstrated evidence on  
9 the comparable outcomes of inflammatory bowel patients treated with the biosimilar  
10 Remsima.<sup>29,30</sup> The findings described above should be interpreted with caution due to the small  
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Currently, in the NOR-SWITCH study, approximately 500 patients are being enrolled to assess the safety and efficacy of switching Remicade (originator) to Remsima (biosimilar) in patients with rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, spondyloarthritis, ulcerative colitis, and Crohn's Disease. The primary outcome measure is worsening of disease over 52 weeks. By definition, this clinical design is assessing substitution or transitioning (single switch) of the originator with the biosimilar, and not directly assessing the interchangeability with multiple switches.

### **Optimal Clinical Study Design for Biosimilars**

A biosimilar trial that aims to show both biosimilarity and interchangeability must address additional regulations and design specifications.<sup>31</sup> There are two conditions that are equally possible for a patient to encounter as outlined by Anderson and Hauck:<sup>32</sup> 1) the patient may have no prior exposure to both the reference product (R) and biosimilar (B) or 2) the patient may have

Biosimilars for Psoriasis

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3 had prior exposure to either and switching back and forth may occur, perhaps for economic  
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5 reasons. *We suggest that a consideration for a biosimilar/interchangeable clinical trial would be*  
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7 *to include both elements of crossover and parallel design.* The minimum number of periods that  
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9 would allow for switching back and forth is three, and so the possible sequences of exposure are:  
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11 RRR, BBB, RBR, BRB, RRB, RBB, BRR, and BBR (Figure 1). This is the ideal, 8-sequence, 3-  
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13 period (8 x 3) clinical trial design that would incorporate all potential situations a patient may  
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15 encounter, but it may be less feasible than a RR, BB, RB, BR design.  
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22 Such a clinical trial design would also greatly aid in determining causality for an adverse event  
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24 when drug switching is occurring.<sup>33</sup> Determining causality for an adverse event is potentially  
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26 variable upon the half-life of the products, and any design chosen should allow for comparison to  
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28 a cohort that does not switch. Since in the 8x3 design there are three cases in which a crossover  
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30 occurs in the same direction, but at varying times, for both the reference product and the  
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32 biosimilar group, how close an adverse event occurs to a switch could indicate whether  
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34 accumulation of the initial product is the cause for the adverse event or not.  
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41 *We suggest that a biosimilar trial should also be at least as long as the primary endpoint in the*  
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43 *reference product's pivotal trials, and be based on the same safety measures collected during*  
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45 *these original trials.* For example, TNF blocker biosimilar trials should include safety outcomes  
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47 such as deaths, malignancies, opportunistic infections, reactivation of tuberculosis and hepatitis  
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49 B virus, major adverse cardiac events, and injection site reactions.  
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## 55 **EMA and FDA Guidelines on Biosimilar Clinical Studies**

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## Biosimilars for Psoriasis

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3 The EMA stated they made the decision on biosimilar infliximab (CT-P13), and will continue to  
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5 make approval and extrapolation decisions on future biosimilars, based on the totality of  
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7 evidence presented by biosimilar companies. In other words, the biosimilar product should not  
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9 show any meaningful differences from the reference medicine in terms of its quality, safety, and  
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11 efficacy. Biosimilar applications must include extensive pre-clinical analytical data on the  
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13 structure and function of the drugs, pharmacokinetics/pharmacodynamics information, and  
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15 clinical studies on efficacy and safety (benefits/risks ratio, risk of immune reactions,  
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17 immunogenicity) equivalence.<sup>34</sup> Additionally, in terms of efficacy, it is necessary to demonstrate  
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19 clinical equivalence on efficacy and safety of the biosimilar and the reference biologic in  
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21 adequately powered, randomized, parallel group, preferably double-blinded, comparative clinical  
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23 trials.<sup>35</sup> The European Commission recently approved a second TNF- $\alpha$  infliximab biosimilar  
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25 (Flixabi) for all indications in the 28 European Union member states and also the European  
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27 Economic Area member countries of Norway, Liechtenstein, and Iceland. Although the EMA  
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29 has demonstrated their support for indication extrapolation in the case of TNF blockers, the  
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31 concern is that similar efficacy or safety between biosimilar and originator biologic may not be  
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33 demonstrated in diseases that are not directly studied.  
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43 The Patient Protection and Affordable Care Act provided U.S. guidelines for biosimilar  
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45 approvals.<sup>36</sup> Clinical data needed for FDA approval of biosimilar drugs require less extensive  
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47 studies than for the originator drugs.<sup>5</sup> Either a phase I or phase III trial in patients with a disease  
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49 for which the originator product is licensed is needed to establish biosimilarity.<sup>37</sup> A  
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51 pharmaceutical company producing a biosimilar stated at an investigator meeting that they  
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53 intended to have one phase 1 trial for pharmacokinetics and a single pivotal phase 3 trial  
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3 involving 400-500 patients in order to obtain FDA approval. This is in contrast to branded  
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5 etanercept and adalimumab that each underwent more than one phase 3 trial with approximately  
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7 1,000 psoriasis patients;<sup>13 38</sup> by even greater contrast, multiple 5-year psoriasis trials involving  
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9 2000-3000 study subjects are required for new originator biologics that block function of IL-  
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11 17<sup>39-41</sup> or IL-23.<sup>42-44</sup> The explanation resides in the fact that for any given type I and II statistical  
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13 errors, sample sizes required to demonstrate clinical equivalence (or non-inferiority and non-  
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15 superiority) of a biosimilar to its originator are smaller than those required to demonstrate  
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17 superiority of a biologic to placebo or a comparator.  
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25 Recently, one biosimilar infliximab application, Inflectra (Celltrion, Inc.), has been approved by  
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27 the FDA for multiple indications including psoriasis and psoriatic arthritis. Several phase 3  
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29 biosimilar etanercept and biosimilar adalimumab clinical trials are currently underway for  
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31 psoriasis and rheumatoid arthritis. Rheumatologists may soon need to extrapolate data, being  
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33 faced with drugs approved for psoriatic arthritis that were only studied in psoriasis.<sup>45</sup> The  
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35 primary endpoints of equivalence trials must not be the same that were used in clinical trials of  
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37 the originator biologics. The FDA requires biosimilars to show similar efficacy to originator  
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39 biologics, namely that the proposed product has neither decreased nor increased activity  
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41 compared to the reference product.<sup>36</sup>  
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## 48 **Summary**

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50 Biosimilars can potentially reduce medical costs compared to originator biologics, but there are  
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52 many clinical issues that have to be closely watched. Regulatory agencies will have to decide  
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54 whether clinical trials of a biosimilar in one condition should be extrapolated to other conditions.  
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Biosimilars for Psoriasis

We take the stance that psoriasis is the best disease model that should be used for TNF blocker biosimilar clinical trials, and extrapolation can then be extended to other inflammatory conditions where the originator biologic is indicated. We are hopeful that approval agencies will more specifically define interchangeability. For the sake of accurate safety monitoring and tracking of loss of efficacy, we argue that the substitution of interchangeable biosimilars for original biologics should not be done without the knowledge of the prescribing physician.

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Biosimilars for Psoriasis

## Acknowledgments

Sergio Chimenti passed away prematurely at the end of February 2016. He spent his successful career as a clinician, teacher, and researcher with a special focus on dermatology and psoriasis. Dr. Chimenti was Chairman and Professor in Dermatology at the University of Rome “Tor Vergata”, Italy as well as a long-time member of the International Psoriasis Council. Sergio was also a marvelous team leader, being able to motivate and to promote excellence among his colleagues and trainees. One of his final achievements was his successful bid to host the next World Congress of Dermatology in Italy in 2019. Sergio Chimenti will never be forgotten.

## Figure Legends

### **Figure 1. Biosimilar interchangeable clinical trial design including both elements of crossover and parallel design**

The study design is comprised of 8 parallel sequences with 3 switch periods. Each period will run according to the length of time scheduled for the primary endpoint of the reference product's pivotal trial. Example: 12 weeks for etanercept (primary endpoint PASI 75).

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**Table 1 – Biosimilars that are approved or are in the process of approval for chronic inflammatory disorders**

Biosimilar	Indication	Clinical studies conducted for approval	Company	Approval Year	Comment	Reference
<b>Etanercept</b>						
<b>GP2015</b> <sup>46</sup>	RA, PsA, PsO, AS, JIA	PsO	Sandoz	Anticipated 2016 USA	FDA accepted the BLA submission in Oct 2015; EMA accepted submission Dec 2015	<a href="http://www.gabionline.net/layout/set/print/Biosimilars/News/FDA-accepts-application-for-etanercept-biosimilar">http://www.gabionline.net/layout/set/print/Biosimilars/News/FDA-accepts-application-for-etanercept-biosimilar</a>
<b>Brenzys (SB4)</b> <sup>47</sup>	RA, PsA, PsO, AS	RA	Merck and Samsung Bioepsis	2015 South Korea	Brenzys approved in South Korea September 2015. Approved by EMA 2016 for approval in Europe	<a href="http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-South-Korea">http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-South-Korea</a>
<b>Intacept</b> <sup>48</sup>	RA, JIA, AS, PsO, PsA	NA	Intas Pharmaceuticals	2015 India	No peer-reviewed publications	<a href="http://www.pnnewswire.co.in/news-releases/intas-pharmaceuticals-launches-intacept-the-first-etanercept-biosimilar-497747161.html">http://www.pnnewswire.co.in/news-releases/intas-pharmaceuticals-launches-intacept-the-first-etanercept-biosimilar-497747161.html</a>
<b>Davictrel (HD203)</b> <sup>47</sup>	RA, PsA, PsO, AS	RA	Hanwha Chemical, South Korea / Merck	2014 South Korea	Approved by South Korea	<a href="http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-">http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-</a>

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						in-South-Korea
<b>Qiangke</b> <sup>49</sup>	RA, JIA, AS, PsO, PsA	NA	Shanghai Celgen Biopharmaceuticals	2014 China	No peer-reviewed publications	<a href="http://gabionline.net/Biosimilars/News/TNF-copy-biological-approved-in-China">http://gabionline.net/Biosimilars/News/TNF-copy-biological-approved-in-China</a>
<b>Adalimumab</b>						
<b>Exemptia</b> <sup>50</sup>	RA, JIA, PsA, AS, adult UC, adult and pediatric CD	RA	Cadila Healthcare Ltd. Zydus Cadila (India)	India 2014	Clinical trial published after launch	Jani et al. 2015
<b>Infliximab</b>						
<b>CT-P13 Remsima/ Inflectra/ Flammegis</b> <sup>51</sup>	RA, PsO, PsA, AS, adult and juvenile UC and adult and juvenile CD	AS, RA	Celltrion	South Korea 2012 70 countries; extrapolation differences according to country; approved in the the US February 2016	Health Canada did not allow extrapolation to ulcerative colitis or Crohn's disease; JPMDA of Japan did allow extrapolation to AS, PsA or PsO	Dorner and Kay 2015
<b>Infimab (BOW015)</b> <sup>52</sup>	RA	RA	Epirus Biopharmaceuticals	India 2014	Published phase III data in ACR/ARHP abstract by Kay et. 2014	<a href="http://www.gabionline.net/layout/set/print/Biosimilars/News/Infliximab-similar-biologic-receives-Indian-approval">http://www.gabionline.net/layout/set/print/Biosimilars/News/Infliximab-similar-biologic-receives-Indian-approval</a>

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- AS = ankylosing spondylitis, CD = Crohn’s disease, JIA = juvenile idiopathic arthritis, PsA = psoriatic arthritis, PsO = psoriasis, RA = rheumatoid arthritis, UC = ulcerative colitis  
NA= not available

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Biosimilars for Psoriasis

Table 2 – Published clinical studies in biosimilars

Disease - Innovator	Product	Company name, country	Phase	Trial design	Status	No. of subjects	Start/end dates	Primary outcome(s)
<b>Psoriasis - Etanercept</b>								
2014-000444-14	CHS-0214	Coherus Biosciences, USA	III	2-arm, parallel	Ongoing	424	Jan 2015/-	PASI % improvement, PASI75
NCT02134210	CHS-0214	Coherus Biosciences, USA	III	2-arm, parallel	Ongoing	496	Jun 2014/ May 2016	PASI75
NCT02486939	CHS-0214	Coherus Biosciences, USA	III	1-arm (extension study)	Recruiting	400	Jul 2015/ Apr 2017	AE, Labs, Vital signs, Physical examinations, Immunogenicity
2012-002011-26	GP2015	Sandoz, Switzerland	III	2-arm, parallel	Completed	546	May 2013/ Mar 2015	PASI75
NCT01891864	GP2015	Sandoz, Switzerland	III	2-arm, parallel	Completed	531	Jun 2013/ Mar 2015	PASI75
<b>Psoriasis - Adalimumab</b>								
NCT01970488	ABP 501	Amgen, USA	III	2-arm parallel	Completed	350	Oct 2013/ Mar 2015	PASI % improvement
2013-000537-12	ABP 501	Amgen, USA	III	2-arm, parallel	Completed	340	Sep 2013/- March 2015	PASI % improvement
NCT02581345	M923	Baxalta/Momenta	III	3-arm parallel	Recruiting	516	Sep 2015/Sep 2016	PASI75
NCT02016105	GP2017	Sandoz, Switzerland	III	2-arm, parallel	Ongoing	448	Dec 2013/ Apr 2016	PASI75
<b>Rheumatoid arthritis - Etanercept</b>								
NCT02115750/2014-000443-33	CHS-0214	Coherus Biosciences, USA	III	2-arm, parallel	Ongoing	620	May 2014/ May 2016	ACR20
NCT02486939	CHS-0214	Coherus Biosciences, USA	III	1-arm (extension study)	Recruiting	400	Jul 2015/ Apr 2017	AE, Labs, Vital signs, Physical examinations, Immunogenicity
NCT01270997	HD203	Hanwha Chemical,	III	2-arm, parallel	Completed	294	Dec 2010/ May 2012	ACR20

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		South Korea						
2012-005026-30	SB4	Samsung Bioepsis, South Korea	III	2-arm, parallel	Ongoing	498	Aug 2013/ -	ACR20
<b>Rheumatoid arthritis- Adalimumab</b>								
NCT01970475	ABP 501	Amgen, USA	III	2-arm, parallel	Completed	526	Oct 2013/ Nov 2014	ACR20
2013-004654-13	ABP 501	Amgen, USA	III	1-arm (extension study)	Ongoing	425	Feb 2014/-	AEs, SAEs, AE, Labs, Immunogenicity
2013-000525-31	ABP 501	Amgen, USA	III	2-arm, parallel	Completed	500	Aug 2013/ Nov 2014	ACR20
NCT02137226 2012-002945-40	BI 695501	Boehringer Ingelheim, Germany	III	2-arm, parallel	Ongoing	650	Jan 2015/ Dec 2016	ACR20
2014-000352-29	PF-06410293	Pfizer, USA	III	2-arm, parallel	Ongoing	560	Oct 2014/-	ACR20
2013-005013-13	SB5	Samsung Bioepsis, South Korea	III	2-arm, parallel	Completed	490	Apr 2014/-Oct 2015	ACR20
NCT02167139	SB5	Samsung Bioepsis, South Korea	III	2-arm, parallel	Ongoing	490	May 2014/ May 2015	ACR20
<b>Crohn's disease - Infliximab</b>								
NCT02096861 2013-004497-10	CT-P13	Celltrion/Hospira, South Korea/USA	III	4-arm, parallel: 2 continuous, 2 cross-over	Recruiting	214	Jul 2014/Mar 2017	CDAI-70
<b>Rheumatoid arthritis-Infliximab</b>								
NCT01217086	CT-P13	Celltrion/Hospira, South	III	2-arm, parallel	Completed	617	Oct 2010/ Jul 2012	PK equivalence

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		Korea/USA						
NCT01571219	CT-P13	Celltrion/H ospira, South Korea/USA	III	1-arm (extension study)	Completed	302	Mar 2012/Jul 2013	Long-term efficacy ACR
NCT01927263	NI-071	Nichi-Iko, Japan	III	2-arm, parallel	Unknown*	230	Jul 2013/ Mar 2015	DAS28-ESR
NCT02222493 2013-004148-49	PF- 064381 79	Pfizer, USA	III	2-arm, parallel	Recruiting	614	Aug 2014/Sep 2017	ACR20
NCT01936181	SB2	Samsung Bioepis, South Korea	III	4-arm, parallel, cross-over	Active, not recruiting	584	Aug 2013/ Aug 2014	ACR20
<b>Other study - Infliximab</b>								
NCT02148640	CT-P13	Norway Health Authority	IV	2-arm, parallel (switch)	Recruiting	500	Oct 2014/Apr 2016	Occurrence of disease worsening PsA, AS, RA, PsO, UC, CD

AE: adverse event; ACR20: 20% improvement in ACR (American College of Rheumatology) core set measurements; CDAI-70: Crohn's disease activity index -70 response; DAS28-ESR: Disease Activity Score for 28 joints - erythrocyte sedimentation rate; PK: pharmacokinetic.

PASI: Psoriasis Area and Severity Index; PASI75: 75% or greater improvement in PASI score; SAE: serious adverse event.

\*Last verified August 2013

All data taken from following websites:

<http://gabionline.net/layout/set/print/Reports/Pivotal-clinical-trials-for-etanercept-biosimilars>

<http://www.gabionline.net/Reports/Pivotal-clinical-trials-for-adalimumab-biosimilars>

<http://gabionline.net/Reports/Pivotal-clinical-trials-for-infliximab-biosimilars>

Data was verified on clinicaltrials.gov and clinicaltrialsregister.eu (accessed on Nov. 18, 2015)

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Table 3 – Extrapolation for the use of Remsima® and Inflectra® as infliximab biosimilar by health authorities

<b>Diseases in which infliximab biosimilar has been studied in clinical trials</b>	<b>Examples for extrapolation by European Medical Agency (EMA)</b>	<b>Examples for extrapolation by Health Canada *</b>
Rheumatoid arthritis <sup>+</sup>	Psoriasis	Psoriasis
Ankylosing spondylitis <sup>^</sup>	Psoriatic arthritis	Psoriatic arthritis
	Crohn's disease	
	Pediatric Crohn's disease	
	Ulcerative colitis	
	Pediatric Ulcerative colitis	

<sup>+</sup>EMA authorization: pivotal efficacy and safety trial in patients with active rheumatoid arthritis; Health Canada authorization: efficacy and safety trials conducted in patients with rheumatoid arthritis and ankylosing spondylitis<sup>53 54</sup>

<sup>^</sup>EMA pivotal pharmacokinetic study in patients with ankylosing spondylitis; Health Canada pharmacokinetic study in patients with ankylosing spondylitis

\*Health Canada did not approve for the extrapolation to inflammatory bowel diseases as antibody-dependent cell-mediated cytotoxicity had not been adequately demonstrated for the biosimilar infliximab according to Health Canada opinion<sup>55</sup>

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For Peer Review

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Figure 1. Biosimilar interchangeable clinical trial design including both elements of crossover and parallel design



The study design is comprised of 8 parallel sequences with 3 switch periods. Each period will run according to the length of time Scheduled for the primary endpoint of the reference product's pivotal trial. Example: 12 weeks for etanercept (primary endpoint PASI 75).

Review