The Portuguese Society of Rheumatology position paper on the use of biosimilars – 2017 update

ABSTRACT

Biosimilars are new and more affordable similar versions of previously approved reference biological drugs. Following the approval of the first monoclonal antibody biosimilar in 2013, the Portuguese Society of Rheumatology issued a position paper on the use of biosimilars in rheumatic conditions covering efficacy, safety, extrapolation, interchangeability, substitution and pharmacovigilance. However, as this is a rapidly evolving field, it was felt that the knowledge and evidence gathered since then justified an update of these statements. Literature searches on these issues were performed and the search results were presented and discussed in a national meeting. Portuguese rheumatologists considered that affordability should be taken into consideration when initiating a biological drug, but other factors were equally important. In patients already on reference biological treatment, switch to a more affordable biosimilar is desirable, provided a set of conditions is rigorously met. Automatic substitution is not acceptable and current evidence is insufficient to support interchangeability. Extrapolation of clinical indications is endorsed by Portuguese rheumatologists, and the statements on safety, pharmacovigilance and traceability are in accordance with the previous position paper.

Keywords: Ankylosing spondylitis; Biosimilar; Anti-tumor necrosis factor-alpha therapy; Rheumatoid arthritis.

INTRODUCTION

Biosimilars are biological medicinal products containing a version of the active substance of an already authorized original biological medicinal product (reference product)1, for which they are required to have similar efficacy, safety and immunogenicity. Biosimilars were created for the sole purpose of mitigating the economic burden put on healthcare systems by biological therapies, which are currently the main driver for direct costs with rheumatic patients - in 2014, these drugs represented four of the five top selling drugs in the world with a combined value of US$38.9 billion in sales2. Importantly, biosimilar-related savings could hypothetically increase the number of patients treated with biologicals, allow an earlier initiation of biological

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therapies upon conventional drug failure and possibly mitigate inequities in treatment access between low and high-income countries.\textsuperscript{2,3}

Biosimilars are, by definition, similar but not identical to their reference products. As opposed to generics, it is not possible for biosimilar developers to produce an exact copy of the originator drug due to its intricate molecular structure and to the inherent, yet controlled, variability associated with specificities in the manufacturing processes.\textsuperscript{4} The development of a biosimilar candidate is a highly regulated process with rigorous analytical, preclinical and clinical testing and an extensive body-of-evidence required before drug approval.\textsuperscript{5} Until January 2017, twenty-three biosimilars were granted marketing authorization by the European Medicines Agency (EMA), making the European market the most experienced in biosimilar regulation and approval.\textsuperscript{6} Up to 2013, all approved biosimilars were hormones and growth factors, with simpler chemical structures and lower molecular weights (the first, somatropin [Omnitrope\textsuperscript{®}], was approved in 2006). In 2013, the marketing of the first infliximab (INF) biosimilar (CT-P13, Remsima\textsuperscript{®}/Inflectra\textsuperscript{®}) raised lively debate among physicians due to the structural complexity of monoclonal antibodies, much more difficult to replicate, and the fear of consequent unexpected events. The discussion around biosimilars broadened to all healthcare stakeholders and focused not only on clinical practice (immunogenicity, extrapolation of clinical indications, interchanging and automatic substitution), but also on regulatory requirements (preclinical and clinical assessment standards and proper pharmacovigilance) and ethical issues (fair distribution of health resources and healthcare system sustainability).

Soon after the endorsement of CT-P13 (Remsima\textsuperscript{®}/Inflectra\textsuperscript{®}), the Portuguese Society of Rheumatology published in early 2014 the position paper on the use of biosimilars in rheumatic conditions, after a national meeting where the results of two systematic literature reviews were presented and discussed\textsuperscript{7}. Briefly, Portuguese rheumatologists decided that: i) factors other than economic should be considered when starting biological therapies; ii) automatic substitution was not acceptable; iii) switching should be based on the attending physician decision and only after 6 months of treatment and adequate patient information; and iv) extrapolation to conditions or patient populations not studied during the clinical evaluation of a biosimilar candidate should not be performed\textsuperscript{7}.

This was the first position paper of a Portuguese medical society on the use of biosimilars. The concept of biosimilarity, the highly complex and regulated developmental process and the implications of using biosimilars in everyday practice were new to most rheumatologists. Even so, important statements on controversial matters were made in a time of limited trial data and nonexistent daily life clinical experience. In the past years, this reality has changed: the implementation of CT-P13 (Remsima\textsuperscript{®}/Inflectra\textsuperscript{®}) in Portugal has grown slowly, but steadily; reports from other countries on biosimilar use, interchangeability and extrapolation have been released; several observational studies have been published on the safety in rheumatic and non-rheumatic conditions; and five new anti-rheumatic biosimilars were approved in Europe (but only two by the time our literature review was performed): etanercept (ETN) biosimilars SB4 (Benepla\textsuperscript{®}) and GP2015 (Erelzi\textsuperscript{®}), INF biosimilar SB2 (Flixbi\textsuperscript{®}), rituximab biosimilar CT-P10 (Truxima\textsuperscript{®}) and lastly adalimumab biosimilar ABP 501 (Amgevita\textsuperscript{®}/Solymbic\textsuperscript{®}). For these reasons, the Portuguese Society of Rheumatology considered timely to update the position paper on the use of biosimilars in rheumatic patients.

### MATERIAL AND METHODS

The update of the position paper of the Portuguese Society of Rheumatology on the use of biosimilars was based on evidence in the literature and on expert opinion. Six fellows (AS, FT, DJ, TMR, PM, CT) performed literature searches on biosimilar relevant topics, namely efficacy, safety and immunogenicity, interchangeability, extrapolation of clinical indications, automatic substitution and pharmacovigilance. Clinical studies on rheumatic patients, including randomized controlled trials (RCTs), long-term extensions (LTE) and observational studies were searched in the Medline database from 2013 to November 2016; evidence previous to 2013, used to support the 2014 position paper, was also considered. Studies on patients with dermatological or gastrointestinal conditions were assessed when relevant. Position statements of scientific societies, pharmaceutical industry and patient associations were hand searched.

The search results were presented to the Portuguese rheumatologists in an open meeting held in December 2016. Evidence was presented and discussed, and each
of the 2014 position statements was reviewed and reformulated when appropriate.

**POSITION STATEMENTS**

The updated statements can be found below, followed by the supporting evidence and experts’ opinion. Table I presents a glossary of biosimilar-related terms for a better understanding of the discussion, and Tables II (English version) and III (Portuguese version) summarize the updated statements.

**DRUG SELECTION**

- In a patient starting any biological therapy, treatment choice should be based on individual, disease and drug-related factors, and not only on economic aspects.
- Whenever the physician chooses to prescribe a biological drug with an available biosimilar version, the more affordable drug should be used.

All biosimilars currently approved in the European Union have demonstrated a high degree of similarity to their reference products on a quality, non-clinical and clinical level, the latter in phase I and III RCTs assessing efficacy, safety and immunogenicity. The clinical efficacy of INF biosimilar CT-P13 (Remsima®/Inflectra®) was supported by the results of the phase I trial PLANETAS® in patients with ankylosing spondylitis (AS) and the phase III trial PLANETRA in patients with rheumatoid arthritis (RA)⁹. These studies demonstrated that CT-P13 has comparable efficacy to reference INF up to week 54. Two phase III trials have shown comparable efficacy of INF biosimilar SB2 and ETN biosimilar SB4 to their respective reference products up to 54 weeks, in patients with moderate to severe RA despite methotrexate therapy¹⁰⁻¹². CT-P13, SB2 and SB4 have also shown similar positive effects on radiographic progression in RA, comparing to their reference products⁹,¹¹,¹³.

All safety outcomes, including treatment-related adverse events, serious adverse events, serious infections, discontinuations due to adverse events, malignancies and deaths, were similar between CT-P13, SB2 and SB4.
and their reference counterparts8-10,12. The only exception was the lower incidence of injection-site reactions (3.7% vs 17.5% at 52 weeks) and antidrug antibodies (1.0% vs 13.2% at 52 weeks) of SB4 compared to reference ETN12. EMA considered that these differences didn’t preclude biosimilarity since no apparent correlation between antidrug antibodies and clinical response or safety was observed.

During the time between the presentation of the search results and the publication of this manuscript, the EMA endorsed three other biosimilars based on similar efficacy and safety profiles: rituximab and adalimumab biosimilars CT-P10 (Truxima®) and ABP 501 (Amgevita®/Solymbic®), respectively, both assessed in RA patients14,15, and ETN biosimilar GP2015 (Erelzi®), assessed in patients with plaque-type psoriasis16.

Portuguese rheumatologists understand that the process leading to the approval of biosimilars in Europe is highly regulated and allowed new and more affordable versions of originator products to enter the market. Keeping that in mind, they agreed, however, that the selection of a biological drug to use in a patient unresponsive or intolerant to conventional treatment is complex and should take into consideration patient, disease and drug-related factors. The attending rheumatologist decides on the biological drug to prescribe considering efficacy, safety and cost-effectiveness in a case-by-case scenario, supported by a risk-benefit assessment and individual clinical reasoning (age, comorbidities, infectious risk, concomitant treatments and functional status, among many others). On the other hand, it is also the rheumatologist’s responsibility to strive for the sustainability of healthcare systems. This means that whenever two or more versions of the same biological drug are available, the more affordable should preferably be used, except when the rheumatologist considers that patient, disease or drug-related factors dictate otherwise.

**EXTRAPOLATION OF CLINICAL INDICATIONS**

- The extrapolation of clinical indications approved according to the current European Regulations is ac-

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**TABLE II. POSITION STATEMENTS OF THE PORTUGUESE SOCIETY OF RHEUMATOLOGY ON THE USE OF BIOSIMILARS IN RHEUMATIC CONDITIONS (ENGLISH VERSION)**

<table>
<thead>
<tr>
<th>Biosimilar topic</th>
<th>Position Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug selection</strong></td>
<td>In a patient starting any biological therapy, treatment choice should be based on individual, disease and drug-related factors, and not only on economic aspects. Whenever the physician chooses to prescribe a biological drug with an available biosimilar version, the more affordable drug should be used.</td>
</tr>
<tr>
<td><strong>Extrapolation of clinical indications</strong></td>
<td>The extrapolation of clinical indications approved according to the current European Regulations is acceptable. All biosimilars used in extrapolated indications should be the object of rigorous registry to serve pragmatical scientific comparisons.</td>
</tr>
<tr>
<td><strong>Interchangeability</strong></td>
<td>Interchangeability, understood as the similarity between biosimilars to a level that allows the indistinctive use and change between products in the same patient, cannot be established on the basis of currently available evidence and thus is not acceptable.</td>
</tr>
<tr>
<td><strong>Automatic substitution and non-medical switch</strong></td>
<td>Automatic substitution of an original biological product for a biosimilar, by either a pharmacist or by legal determination, without information and consent of the attending rheumatologist, is unacceptable. However, judicious switching for a more affordable biological product (non-medical switch) is desirable, provided that a set of conditions described in the main text is conjunctly met.</td>
</tr>
<tr>
<td><strong>Safety, pharmacovigilance and traceability</strong></td>
<td>Regulatory authorities, marketing authorization holders (former product license holder) and healthcare professionals must assure rigorous pharmacovigilance mechanisms. The brand name, batch number and date of administration must be registered in the Reuma.pt database upon every biosimilar drug administration. If biosimilars have the same INN as the originator molecule, prescription should be performed by brand name.</td>
</tr>
</tbody>
</table>
**TABLE III. POSITION STATEMENTS OF THE PORTUGUESE SOCIETY OF RHEUMATOLOGY ON THE USE OF BIOSIMILARS IN RHEUMATIC CONDITIONS (PORTUGUESE VERSION)**

<table>
<thead>
<tr>
<th>Tópico</th>
<th>Posicionamento</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seleção de fármaco</td>
<td>Num doente que inicia tratamento biológico, a escolha do fármaco deve basear-se em factores relacionados com o indivíduo, com a doença e com o próprio fármaco, e não apenas em factores económicos. Sempre que o médico decida prescrever um fármaco biológico que tenha disponível uma versão biossimilar, o fármaco mais económico deverá ser escolhido.</td>
</tr>
<tr>
<td>Extrapolação de indicações clínicas</td>
<td>A extrapolação de indicações clínicas, aprovadas de acordo com a regulamentação Europeia atual, é aceitável. Todos os biossímulares utilizados em indicações extrapoladas devem ser objecto de registo rigoroso para permitir comparações científicas pragmáticas.</td>
</tr>
<tr>
<td>Interpermutabilidade</td>
<td>Interpermutabilidade, entendida como a semelhança entre biossímulares a um nível suficiente para permitir o uso e troca indiscriminados destes produtos no mesmo doente, não pode ser estabelecida à luz da evidência atual e não é, por isso, aceitável.</td>
</tr>
<tr>
<td>Substituição automática e switch não-médico</td>
<td>A substituição automática de um biológico original por um biossimilar, por parte do farmacêutico ou por determinação legal, sem informação e consentimento do reumatologista assistente, é inaceitável. Contudo, a troca judiciosa por um biológico mais económico (switch não-médico) é desejável, desde que as condições descritas no texto principal sejam preenchidas na totalidade.</td>
</tr>
<tr>
<td>Segurança, farmacovigilância e rastreabilidade</td>
<td>As autoridades reguladoras do medicamento, os detentores da autorização de introdução no mercado e os profissionais de saúde devem garantir mecanismos rigorosos de farmacovigilância. O nome comercial, o número do lote e a data de administração devem ser registados na base de dados Reuma.pt a cada administração de biossimilar. Se os biossímulares tiverem a mesma denominação comum internacional que o biológico original, a prescrição deve ser feita pelo nome comercial.</td>
</tr>
</tbody>
</table>

ceptable.

– All biosimilars used in extrapolated indications should be the object of rigorous registry to serve pragmatical scientific comparisons.

Extrapolation of clinical indications is a well-known scientific principle in manufacturing and licensing of biological drugs. Extrapolation occurs whenever a clinical indication of a reference drug is granted to the new drug without the requirement for clinical studies to support that indication, working on the assumption that if two molecules have similar characteristics and mechanisms of action their clinical efficacy and safety will be equivalent.

From a regulatory perspective, extrapolation relies on the extensive quality and non-clinical assessment, which uses state-of-the-art analytical assays to demonstrate a high degree of similarity in critical structural and physicochemical attributes between the biosimilar candidate and the originator. This analytical fingerprint is monitored and tightly controlled throughout the whole manufacturing process to ensure that similarity remains within prespecified limits. Biological activity is compared using functional tests that should cover all known antigen receptor(s) and mechanism(s) of action of the reference drug in the different clinical indications, duly justified by a comprehensive literature search provided by the biosimilar sponsor. An abbreviated clinical phase then follows, in which the sponsor selects a patient population sensitive enough to allow the detection of possible differences in efficacy, safety and immunogenicity between biosimilar candidate and originator. However, it should be noted that there is yet no consensus concerning the definition of the most sensitive population to be used in clinical trials of biosimilars, and standards on this matter are still lacking. As an example, the two currently approved biosimilars of ETN were assessed in two distinct patient populations, namely RA (SB4, in Europe) and plaque psoriasis (GP2015, in the USA). Whenever the reference drug has distinct clinical indications (for ins-
Interchangeability, understood as the similarity between biosimilars to a level that allows the indistinctive use and change between products in the same patient, cannot be established on the basis of currently available evidence and thus is not acceptable.

An interchangeable biosimilar product can be defined as a biological drug that has demonstrated biosimilarity to a reference product and, when administered to a patient more than once, alternating between the reference product and the biosimilar does not compromise safety or efficacy. Evidence supporting alternation between biosimilar and reference product has, thus far, stemmed from two types of studies (all including patients with long-standing disease): randomized placebo controlled (non-inferiority) trials and LTE of RCTs. Switching from INF originator to CT-P13 has been evaluated in a large (N=481), non-inferiority RCT (NOR-SWITCH)\(^ {20}\). Patients with inflammatory systemic diseases (including RA, spondyloarthritis and PsA) with stable treatment with originator INF for \(\geq 6\) months were randomized to maintain treatment with the originator INF or switch to CT-P13. The primary endpoint was defined as disease worsening according to disease-specific outcomes and/or a consensus between investigator and patient leading to major change in treatment. The study, powered to detect a 15% non-inferiority margin in the entire population, has shown no difference between the treatment groups for the primary endpoint (95% CI of group difference after 54 weeks: -12.7%; 3.9%), thus supporting non-inferiority for those switching to CT-P13. However, in possibly underpowered subgroup analyses within each disease-groups, the non-inferiority margin was not achieved.

The EGALITY study, a 52-week RCT, compared the ETN biosimilar candidate GP2015 to originator ETN in patients with moderate to severe chronic plaque-type psoriasis\(^ {16}\). This is the only study comparing a multiple-switch strategy. After the initial 12-week parallel-group period, patients changed treatment for 3 times in 6-week intervals or maintained treatment with the original allocated drug. After 52 weeks the maintenance arms have shown no efficacy or safety differences as compared to the multiple-switch arms.

In a phase 3 study of the INF biosimilar candidate SB2 in RA patients, after the initial 54-week parallel-group period, the INF arm was re-randomized to either maintain INF or switch to SB2, while the SB2 arm was kept on SB2, up to week 70. This study showed similar efficacy, safety and immunogenicity results between the 3 arms\(^ {21}\). Three open-label LTE (two on CT-P13\(^ {22, 23}\) and one on SB\(^ {24}\)) in patients with RA and AS compared treatment switch from originator to biosimilar with biosimilar maintenance without randomized treatment re-allocation, showing no significant differences in efficacy and safety between treatment-arms.

Taken altogether, the available evidence, though suggesting that interchangeability may be feasible in patients with longstanding disease, is yet scarce and not without bias, thus insufficient to support a positive recommendation. Issues were raised on study design, lack of standards to assess interchangeability and consequences of multiple switches between originators and biosimilars and biosimilars themselves. More data stemming from RCTs in well-defined populations, preferably with multiple and bi-directional switches from originators and biosimilars, were considered necessary.
AUTOMATIC SUBSTITUTION AND NON-MEDICAL SWITCH

Automatic substitution consists in a legal determination allowing pharmacists or other health professionals to switch a biological product to a biosimilar version without consulting the prescribing rheumatologist. This principle is considered unacceptable by Portuguese rheumatologists. However, there is currently no clinical reason to prefer a reference product over its biosimilars approved for the same disease, provided that similarity is demonstrated according to the EMA standards. The choice for the most affordable product should be the rule as an ethical imperative for society, as long as equal benefit and risk for the patient are assured. As previously mentioned in the Drug Selection statement, there was agreement in this matter regarding biological treatment initiation. However, in rheumatic patients already in stable biological treatment, this question is more complex. The switch of the reference biological to a biosimilar (or vice versa) due to reasons other than efficacy or safety is known as non-medical switch. The main driver for non-medical switch is economical, aiming at cost-containment. However, in exceptional cases, the option for a particular biological product, either the reference biological or its approved biosimilars, may be warranted owing to particular circumstances of the patient. This decision can only be made by the rheumatologist. These exceptional circumstances must be clearly documented in order to facilitate the standardization and streamlining of these procedures.

For the sake of pharmacovigilance, it is important to continue monitoring all biological products. Studies carried out so far are reassuring, but they do not provide absolute and definitive guarantees that discrepancies do not become apparent over time (especially on long-term safety). It is an ethical imperative, for physicians and health authorities, to increase the knowledge in this matter. For this reason it is indispensable to assure traceability of drugs and batches used. Each new drug should be administered during a sufficient time period to allow its “pharmacovigilance” (interchanging between biological products, even biosimilars, in the same patient, constitutes a potential untraceable safety risk and an ethically unacceptable loss of opportunity to increase knowledge in this field) and when a non-medical switch is made, the clinical status of the patient should be accurately documented (blood sample collection for biological characterization should be performed whenever feasible). Every time a non-medical switch occurs, the rheumatologist should be involved in the process.

The judicious switch of a biological product for a more affordable biosimilar is desirable, provided that the all following conditions are strictly observed and complied:

A. Biosimilars must have been approved for the disease under consideration. Only biosimilars approved for the concerning disease, either by direct assessment or extrapolation of indications, may be switched.

B. Traceability

B.1. Registration: Official records must be kept of which product is administered, through its unique name (trade name if it has the same International Nonproprietary Name [INN]) and batch number.

B.2. Permanence in therapy: a new product can only be started if there is guarantee that it will be available for that patient for the following 12 months.

C. Standardized protocol

C.1. Defined exceptions: consensual definition, with participation of rheumatologists, of the conditions that may justify the physician’s objection to non-medical switching.

C.2. Prior notification: The attending rheumatologist should be involved in the non-medical switching process and required to issue a clinical report (described in the next point) that supports his decision to oppose or approve this switching, in the face of consensual exceptions.

C.3. Clinical and Biological Registry: Non-medical switching is oblitoriely preceded by a detailed and protocoled clinical record made by the rheumatologist at the Rheumatic Diseases Portuguese Registry, Reuma.pt. The administration of the new product is ideally preceded by a blood sample collection and storage in a biobank.

C.4. Conflict resolution: The objection of a rheumatologist to non-medical switching shall, in all cases, be submitted to the approval of the Pharmacy and Therapeutics Committee of the hospital or
equivalent body.

C.5. Patient information: The patient must be informed before non-medical switching.

SAFETY, PHARMACOVIGILANCE AND TRACEABILITY

- Regulatory authorities, marketing authorization holders (former product license holder) and healthcare professionals must assure rigorous pharmacovigilance mechanisms.
- The brand name, batch number and date of administration must be registered in the Reuma.pt database upon every biosimilar drug administration.
- If biosimilars have the same INN as the originator dates has been highly similar to their reference products during the stepwise comparability exercise required for approval. Nevertheless, the clinical confirmatory phase of biosimilar development is performed in a limited patient population, during a limited follow-up and only in one (or just a few) clinical indication(s) of the reference product. This means that robust pharmacovigilance plans are of the utmost importance to assure that the comparable safety profile in clinical trials persists in everyday practice, and all stakeholders should be involved. Methods of pharmacovigilance include passive methods, such as spontaneous reporting systems, active surveillance, such as electronic healthcare databases, comparative observational studies and targeted clinical investigations. The different existing national registries have proved to effectively monitor patients with rheumatic diseases on biologicals. Since 2008, Reuma.pt presents as an essential tool for pharmacovigilance and traceability of biological-treated patients, and Portuguese rheumatologists consider that its use should also be applied in biosimilar-treated patients.

As part of the pharmacovigilance strategy, effective drug traceability is warranted so that timely detection of safety issues and appropriate intervention are ensured. The pharmaceutical supply chain of biologicals contains several steps of potential incomplete tracing, namely in medical prescription, pharmacy dispensing and biological administration. In a cross sectional study, the batch number was reported along with the drug name in only 19.9% of all biopharmaceutical drug reports. It is feasible and advisable for the attending rheumatologist to register the batch number in Reuma.pt when the patient is treated in the day care unit. As the majority of rheumatic patients are treated as outpatients, the rheumatologist has no access to the biosimilar batch number, and thus the hospital pharmacist should be responsible for registering that information.

The approval of various biosimilars for the same reference product increases the likelihood of a misattribution of an adverse event, so biosimilar nomenclature is key. According to EMA guidelines, correct naming of biological drug should include the brand name or the INN together with a trademark. Portuguese rheumatologists were also in agreement with this recommendation.

CONCLUSION

The 2017 update of the Portuguese Society of Rheumatology position paper on the use of biosimilars convenes both expert opinion and evidence gathered since the publication of the first paper. Portuguese rheumatologists considered that affordability should be taken into consideration when prescribing a biological drug for the first time, but other patient- and disease-related factors were deemed equally important. In patients already on biological treatment with a reference product, switch for a more affordable biosimilar was also desirable, provided a set of conditions was rigorously met. Automatic substitution was considered not acceptable and current evidence is insufficient to support interchangeability. Extrapolation of clinical indications was endorsed by Portuguese rheumatologists, provided that European regulations were followed. The statements on safety, pharmacovigilance and traceability were in accordance with the previous paper.

With this position paper, the Portuguese Society of Rheumatology reinforces its role as a key stakeholder in the quality of care of Portuguese rheumatic patients, striving for more affordable and more accessible biological treatments, but keeping as a priority the patient’s best interest.

CONFLICT OF INTERESTS

Filipe Araújo, Cátia Duarte, Helena Canhão, Helena Santos, José António Pereira da Silva, José Bravo Pimentão, Luís Cunha Miranda, João Eurico Fonseca, as well as the Portuguese Society of Rheumatology itself, have collaborated throughout the years with most Pharmaceutical Companies involved in the marketing of either reference biologics or biosimilars, for which they have received honoraria or other forms of compensation. It is their strong belief, however, that this cooperation has not influenced either the indivi-
dual opinions or the adopted position statements, which were collectively endorsed. Pharmaceutical companies had no direct or indirect intervention in the elaboration of this Position Paper.

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REFERENCES


