Authors' Reply to Pires et al.: “Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes”

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Dear Editor,

We thank Pires et al. for their interest in our publication [1, 2]. However, their comments do not change the basic conclusion that switching from reference biologics to biosimilars shows that clinical outcomes are unaltered. As a reminder, the intent of our paper was to neutrally assess whether there is any credible and consistent evidence that switching from originator biologics to biosimilar biologics is problematic. That there may be minor disputes with the approach taken is not the most important issue here, and we caution against that becoming a distraction from the main purpose of the publication. The overall pattern remains clear and unambiguous and is what would be expected when the authors of 88 out of 90 publications reach similar conclusions about their own individual study results.

We appreciate that there are limitations to our review and therefore included a “limitations” section in our

manuscript. Even given the limitations, we believe that the available data were not over interpreted. We do not assert in absolute terms that switching from a reference medicine to a corresponding biosimilar is not problematic; rather, we conclude that there is no consistent evidence that switching is problematic and therefore there is no reason to believe that the act of switching may be inherently dangerous.

Pires et al. question the application of Cochrane methodology in our review. We appreciate the opportunity to provide further details of our methods. The effort to collate potential sources was only undertaken after clear objectives and a process to assess the qualities of each study were predefined. We utilized an independent and experienced third party to review all results and adjudications before proceeding with analyses. A key guiding principle was to be as inclusive as possible, recognizing that meeting posters and abstracts do not often provide the many details commonly provided in journal publications, but are nonetheless a key source of information. Predefined inclusiveness is neutral and does not censor for either positive or negative results.

While Pires et al. assert that the diversity in studies is too great to draw conclusions, we respectfully and emphatically disagree. The broad diversity in products studied, indications, study designs, endpoints, and analyses of individual studies is a strength of our review.

Elevated drop-out rates from individual studies are highlighted by Pires et al. as demonstrating unfavorable outcomes after switching. We acknowledge these observations, but there are many more results from these same and additional studies that showed no changes in clinical outcomes. One of the most important predefined principles

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in our review was a decision to accept the conclusions of the authors of individual publications without using individual data points to reach our own independent conclusions. It is inappropriate to select specific data points while ignoring the totality of evidence from the same study.

An examination of the citations provided by Pires et al. reveals that they were selective. One such abstract was Tweehuysen et al. [3]. A peer-reviewed article of this study was published in January 2018 [4] but was not cited by Pires et al. In the article, Tweehuysen et al. concluded that “this prospective cohort study shows that treatment with reference infliximab can be open label transitioned to a biosimilar infliximab (CT-P13) in the majority of patients in daily practice without changes in effectiveness, infliximab trough levels, anti-infliximab antibody levels, and safety.” The authors explained that the increase in drop-out rates “was mainly driven by an increase in the subjective tender joint count and the patient’s global assessment of disease activity and/or in subjective adverse events, rather than by an increase in objective signs and symptoms.” They concluded that “in our view, the reason for the substantial discontinuation rate in open-label studies is the awareness on the part of both patients and physicians of the transition to the biosimilar drug”.

And while elevated drop-out rates in Glinborg et al. [5] were also cited, it is important to note that Glinborg et al. concluded that “a nationwide non-medical switch from infliximab reference (INX) to CT-P13 in 802 patients with inflammatory arthritis, who had previously been treated with INX for > 6 years, had no apparent negative impact on disease activity. The adjusted retention rate during $\approx$ 1 year of follow-up was slightly reduced (3.4%) compared with a historic cohort.”

Continuing further, Avouac et al. [6], also cited by Pires et al., conclude that “no changes in drug trough levels or objective parameters were observed after the systematic switch to biosimilar infliximab in a real clinical practice setting. Only changes in patient-reported outcomes were observed, suggesting attribution effects rather than pharmacological differences.”

In the final article cited by Pires et al. published prior to our cut-off date as showing a disparity in drop-out rates, Fiorino et al. [7] concluded that “we have demonstrated in the evaluated time frame that the safety profile and efficacy of CT-P13 biosimilar is in line with the existing literature of infliximab. No alarming signals of immunization have been detected in patients switched from the infliximab”.

As noted by Pires et al., we suggest that results obtained by Yazici et al. [8] were chance findings. We are not suggesting that the observations from this specific data set are incorrect. We accept them as factual results obtained from the Turkish health claim database examined, but we note that the extremely high 82% drop-out rate observed

was not replicated in the > 40 additional switching studies conducted with the same biosimilar. Pires et al. cite Philips et al. [9] as also showing a very high drop-out rate. That study, however, was a replicate but smaller analysis of the same Turkish health claim database during a similar time interval. Consistent with our predefined rule of not counting individual patients twice, we did not include that abstract in our review.

There are other real-world evidence switching studies not cited by Pires et al. in which drop-out rates of reference medicine and biosimilar were similar [10–12]. We are also unaware of any randomized clinical switching trial in which there is a disparity in drop-out rates.

Pires et al. state that results from the three multiple switch studies published to date do not meet the FDA criteria of interchangeability [13] and further assert that the results from those studies are not generalizable. These comments are not relevant to our review because these studies were designed to assess the clinical impact of multiple switches and not to address a specific regulatory requirement. Contrary to Pires et al., we do not claim that the results from these studies are generalizable to all biosimilars with respect to an FDA designation of interchangeability, which is a legal issue and regulatory interpretation beyond the clinical evidence that we review. We assert that these three studies are the first multiple-switch studies and that they were large, robustly designed, and provide strong efficacy and safety data.

We are glad that Pires et al. noted the statement in the publication that due to manufacturing process changes applied over time to a specific originator biologic, patients continuously treated with these medicines have been subjected to de facto switching. Pires et al. claim that these are not regarded as switches in the literature because they comply with the ICH Q5E guidance on manufacturing comparability [14]. While it is true that the literature does not highlight these changes as switches, it is important to evaluate them in an intellectually honest and scientific manner. Many of the process changes led to changes in critical quality attributes [15, 16], including structural or functional changes [17, 18]. As a result, patients continuously treated for an extended time with a biologic medicine when major process changes occur will likely have received batches that differed in a critical quality attribute related to structure or function. To claim that this is not a switch because it complies with ICH guidelines of comparability is simply semantics. There is no doubt that under these circumstances patients were subjected to de facto switches.

When considering all the available information, the results of our review are unambiguous. It is incorrect to presume that there may be a problem with switching and that further study is necessary, or to impose a data burden

on biosimilars not applied to other biologics, especially when there is no credible basis for such a request. A total of 90 studies with 14,225 patients is larger and provides stronger evidence than any individual study could be expected to provide. We therefore stand by our original conclusion that the extensive data collected to date show that the act of switching from a reference medicine to a biosimilar is not inherently dangerous, and that patients, healthcare professionals, and the public should not assume that it is problematic.

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Compliance with Ethical Standards

Conflicts of interest HPC is an employee of Sandoz Inc. AB served as a scientific advisor and/or clinical study investigator for AbbVie, Aclaris, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Inc., Eli Lilly and Company, Genentech/Roche, GlaxoSmithKline, Janssen, Leo, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac, and as a paid speaker for Eli Lilly and Company, Janssen, Regeneron, and Sanofi Genzyme. RMR is an employee of McKesson Specialty Health/ The US Oncology Network – The Woodlands, TX, and has served on advisory boards relevant to biosimilars at Amgen, Coherus, EMD Serono (Fresenius) and Pfizer. SD served as a speaker, consultant, and/or advisory board member for AbbVie, Allergan, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Hospira, Johnson and Johnson, Janssen, EMD-Serono (Fresenius), MSD, Sandoz, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, and Vifor. SBG is an employee of Novartis Ltd. GW is an employee of Avalere Health.

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