



# Understanding the Role of Comparative Clinical Studies in the Development of Oncology Biosimilars

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Biosimilars have the potential to broaden patient access to biologics and provide cost savings for health care systems. During the development of a biosimilar, data that directly compare the proposed biosimilar with the reference product are required. Such comparative data are generated in a stepwise hierarchical process that begins with extensive laboratory-based structural analyses and functional assays. This initial analytical phase serves as the foundation for the demonstration of biosimilarity and is followed by nonclinical in vivo testing (if required) and then clinical evaluation, including a comparative pharmacokinetics/pharmacodynamics study that is usually conducted in healthy volunteers. The development program typically culminates with a comparative clinical efficacy study. The aim of this study is to confirm clinical equivalence of the potential biosimilar and reference product on the basis of prespecified margins, using a study population and efficacy end point that are sufficiently sensitive for detecting potential product-related differences. Such studies also include detailed analyses of safety as well as evaluation of immunogenicity. As biosimilars become more widely available in oncology, especially with recent regulatory approvals of rituximab, trastuzumab, and bevacizumab biosimilars, it is critically important that clinicians understand how the comparative clinical study differs from a traditional phase III efficacy and safety study in the development of a novel biologic originator product. Here, we review the role of comparative clinical studies in biosimilar development, with a focus on trials conducted to support approved trastuzumab biosimilars. We discuss the study populations and end points used, extrapolation of indications, and the confirmatory nature of these studies within the totality of evidence supporting biosimilarity.

**J Clin Oncol 38:1070-1080. © 2020 by American Society of Clinical Oncology**

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## INTRODUCTION

Biologic products (biologics) contain an active substance from a biologic source and are manufactured by complex processes using living systems.<sup>1</sup> They have a significant role in the clinical management of a range of medical conditions, including cancer. At a time when there is an increasing need to address the sustainability of cancer care, biosimilars have the potential to widen patient access to biologics and provide cost savings for health care systems,<sup>2-4</sup> and detailed regulatory guidance has been created to guide their development. From a regulatory perspective, a biosimilar is a biologic that has been shown to be highly similar to an approved reference biologic product in terms of structure, biologic activity, safety, and efficacy.<sup>1,5,6</sup> To gain regulatory approval in the United States, for example, it must be demonstrated that a proposed biosimilar is “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the [biosimilar] and the reference product in terms [of] safety, purity, and potency.”<sup>6(p3)</sup> The term biosimilar reflects the fact that

because of the inherent degree of natural minor variability exhibited by all biologic products, it is not possible to create a structurally identical copy of a reference product.<sup>1,6</sup> In practice, however, biosimilars approved through a robust regulatory pathway may be considered clinically equivalent to the relevant reference product. Reflecting this, in regions such as the European Union (EU) and United States, biosimilar product labeling is aligned closely with that of the reference product.<sup>1,7</sup> Furthermore, patient materials recently issued by the US Food and Drug Administration (FDA) describe biosimilars as having the same expected benefits and risks as their respective reference products.<sup>8</sup>

During the development of a biosimilar, an array of data that directly compare the candidate biosimilar with the reference product is required.<sup>5,6,9</sup> This is generated in a stepwise hierarchical process, which begins with extensive characterization of the proposed biosimilar and the reference product, using a range of laboratory-based comparative structural analyses and functional assays, such as assessment of antibody-dependent cellular cytotoxicity (ADCC).<sup>5,6,10</sup> This initial

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on January 21, 2020 and published at [ascopubs.org/journal/jco](https://ascopubs.org/journal/jco) on February 14, 2020; DOI <https://doi.org/10.1200/JCO.19.02953>

step serves as the foundation for a demonstration of biosimilarity, and the more rigorous this assessment in showing similar structure and function, the greater the justification for a selective, tailored program of nonclinical in vivo testing (if required) and clinical studies.<sup>6</sup> The determination of biosimilarity is based on the totality of the evidence from all stages of development.<sup>5,6,9,10</sup>

With respect to the underlying scientific principles, regulatory requirements for demonstrating biosimilarity are generally consistent among stringently regulated regions, such as Australia, Canada, the EU, Japan, and the United States.<sup>11</sup> Although biosimilar supportive care agents have been available for use in oncology for a number of years in several of these regions,<sup>12,13</sup> it is only more recently that biosimilar monoclonal antibodies (mAbs) for the treatment of cancer, including rituximab, trastuzumab, and bevacizumab biosimilars, have received regulatory approval.<sup>14-17</sup> Indeed, in the United States, the first bevacizumab and trastuzumab biosimilars became available for commercial sale in July 2019.<sup>18</sup> While representing a new development in oncology, biosimilar mAbs have been used successfully for several years in the treatment of chronic inflammatory diseases,<sup>4</sup> including conditions that were not initially studied in comparative trials as part of the biosimilarity assessment. Although oncologists may be accepting of biosimilar supportive care agents, it has been suggested that they could be less comfortable with anticancer biosimilars.<sup>19</sup> A recent survey of US community oncologists identified educational gaps with respect to the regulatory approval framework for biosimilars, with some respondents reporting that they were uncomfortable or unfamiliar with the current process.<sup>20</sup> A separate survey by the European Society for Medical Oncology among oncology prescribers identified gaps in knowledge related to biosimilar development, clinical trial design, and selection of end points.<sup>21</sup> To maximize the potential of biosimilars, such knowledge gaps must be addressed.<sup>22</sup> With the introduction of biosimilar mAbs into clinical practice, it is critically important that oncologists understand how the comparative clinical efficacy and safety study, which typically serves as the final step in the biosimilarity exercise, differs from the traditional phase III study in the development of a novel biologic originator product. In this review, we consider the role of comparative clinical studies in biosimilar development, with reference to approved trastuzumab biosimilars as an illustrative example.

## COMPARATIVE CLINICAL STUDIES IN THE DEVELOPMENT OF BIOSIMILARS

The main aim of a biosimilar clinical development program is to confirm that any differences between a potential biosimilar and the reference product are not clinically meaningful.<sup>1,5,6,10</sup> Thus, the number and scope of clinical studies performed for a potential biosimilar depend on the degree of residual uncertainty with regard to biosimilarity

following the earlier analytical assessment (and nonclinical in vivo testing, if performed).<sup>6</sup> The clinical program includes a comparative pharmacokinetics (PK) study (with a pharmacodynamics [PD] comparison where suitable biomarkers exist), which is commonly conducted in healthy volunteers.<sup>6,23,24</sup> This is typically followed by a comparative clinical study that assesses efficacy and safety in at least one relevant indication.<sup>6,23</sup>

The aim of the comparative clinical efficacy study is not to demonstrate clinical benefit, as this has already been established independently for the reference product.<sup>23,25</sup> Rather, the aim is to confirm clinical equivalence of the potential biosimilar and reference product on the basis of prespecified margins, using a study population and efficacy end point that are sufficiently sensitive for detecting potential product-related differences while at the same time minimizing the influence of patient- or disease-related factors.<sup>23,25</sup> A sensitive study population would typically be one for which the treatment effect of the reference product has been shown to be robust in prior trials, which thus enhances the ability to detect small differences in efficacy.<sup>26</sup> Factors such as prior lines of therapy and the effect of concomitant medications are also relevant to sensitivity.<sup>10</sup> Ideally, a first-line study conducted in a homogeneous patient population (eg, in terms of disease severity) with a short-term clinical efficacy end point that measures pharmacologic activity would be recommended.<sup>1,10,25</sup> These studies should also include a detailed analysis of safety as well as an evaluation of immunogenicity. The end point chosen may differ from that used to demonstrate the efficacy of the reference product in pivotal studies. For example, although disease-free survival (DFS), progression-free survival (PFS), or overall survival (OS) end points are often required for demonstrating clinical benefit in registration trials of novel anticancer therapeutics, short-term surrogate end points, such as overall response rate (ORR) measured at a certain time point or pathologic complete response (pCR), are considered both adequate and more appropriate for detecting potential product-related differences in a comparative clinical study of a potential anticancer biosimilar.<sup>25</sup>

To statistically test whether a biosimilar is inferior or superior to the reference product in terms of the primary efficacy end point, an equivalence study design is preferred.<sup>6,23</sup> Equivalence is established if the CI for the selected parameter for treatment effect (eg, the difference or ratio between treatments) is completely contained within upper and lower equivalence margins; this is tantamount to performing two one-sided tests, simultaneously testing the null hypotheses of inferiority and superiority.<sup>10,27</sup> Such margins are derived specifically for the indication and end point studied and are based on historical data that concern the efficacy of the reference product as well as on clinical judgment.<sup>1</sup> In contrast to equivalence studies, noninferiority studies are one-sided and, hence, do not exclude the possibility that

a potential biosimilar may be superior in efficacy to the reference product.<sup>10</sup> If such superiority was considered clinically relevant, this might contradict the principle of similarity.<sup>9</sup> Guidelines from the European Medicines Agency (EMA), FDA, and WHO state that a noninferiority design for comparative clinical studies may be appropriate and acceptable in certain circumstances,<sup>6,9,23</sup> although a strong scientific rationale would be required.<sup>23</sup>

If biosimilarity has been successfully demonstrated on the basis of a comparative development program that includes data derived from a clinical study in one therapeutic indication, regulatory guidelines allow for the possibility of the biosimilar being approved for additional indications held by the reference product without conducting additional clinical studies (termed extrapolation).<sup>6,23,28</sup> From scientific, cost, and ethical perspectives, biosimilar studies should not seek to replicate the efficacy and safety data of the reference product across all indications.<sup>28</sup> However, extrapolation must be scientifically justified and considered within the context of the totality of the analytical, nonclinical, and clinical evidence supporting biosimilarity.<sup>6,23</sup> For example, extrapolation may be challenging if the mechanism of action (MOA) of the active substance involves several receptors or binding sites, the contribution of which may vary between the tested and extrapolated indications.<sup>29</sup>

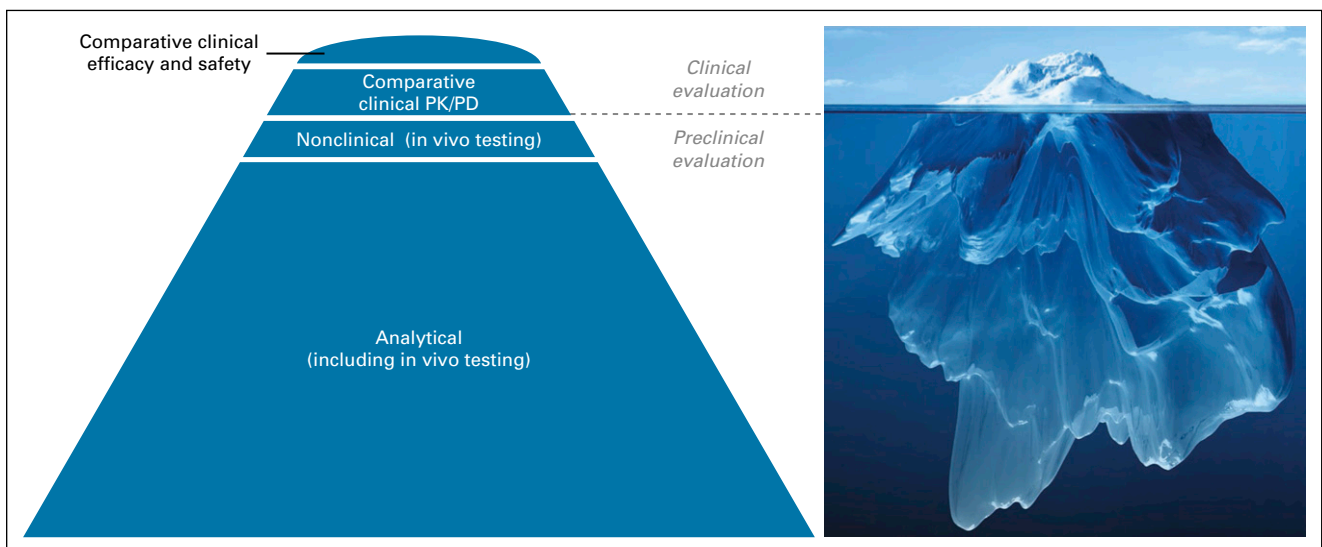
Because prescribers and clinicians are familiar with evaluating novel drugs on the basis of clinical studies, it is important that they appreciate the distinct role of comparative clinical studies in the biosimilar development paradigm.<sup>30</sup> Although the paradigm for the development and approval of a novel biologic is that the positive benefit-risk profile is established mainly on the basis of controlled

studies that demonstrate efficacy and safety in each indication approved, this is not the case for a biosimilar.<sup>1</sup> For biosimilars, the positive benefit-risk profile is established on the basis of the totality of the evidence that demonstrates biosimilarity to the reference product, with comparative clinical efficacy trials serving a confirmatory function, and highly sensitive analytical methods providing the foundation for the data<sup>1,5,6,23</sup> (Fig 1). Such analytical methods are generally much more sensitive than clinical studies for detecting potential differences.<sup>1,30</sup> Furthermore, significant differences observed in quality attributes cannot be justified using clinical data.<sup>5</sup>

## COMPARATIVE CLINICAL STUDIES OF TRASTUZUMAB BIOSIMILARS IN BREAST CANCER

### Which Study Settings and End Points Have Been Used?

Several of the points highlighted in the previous section can be illustrated by considering the example of recently approved biosimilars in reference to trastuzumab (Herceptin; Genentech, South San Francisco, CA; Roche Registration GmbH, Grenzach-Wyhlen, Germany). As of December 2019, five trastuzumab biosimilars have been approved in the EU and United States for intravenous use<sup>31-40</sup> (Table 1). During their respective clinical development programs, all five molecules were assessed in single-dose comparative PK similarity studies in healthy male volunteers,<sup>41-45</sup> and in comparative clinical efficacy and safety studies in women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer.<sup>46-50</sup> There were differences in the designs of the comparative clinical efficacy studies that support biosimilarity, with the study setting (ie, patient population) representing one point of variation, although all



**FIG 1.** Totality of the evidence that supports biosimilarity. Extensive analytical characterization of a proposed biosimilar and the reference product, using an array of comparative structural analyses and functional assays, provides the foundation for a demonstration of biosimilarity. Data from comparative clinical efficacy and safety studies are confirmatory and are represented as the tip of the iceberg. PD, pharmacodynamics; PK, pharmacokinetics. Iceberg image copyright © Adike/Shutterstock.com.

studies used combinations with taxane-based chemotherapy<sup>46-50</sup> (see Table 2 for an overview of the studies, including primary results). For example, the approvals of ABP 980, CT-P6, and SB3 were supported by studies that compared each biosimilar with reference trastuzumab in the neoadjuvant and adjuvant treatment of early breast cancer (EBC).<sup>46,47,50</sup> In contrast, MYL-14010 and PF-05280014 were compared with reference trastuzumab in the first-line treatment of metastatic breast cancer (MBC).<sup>48,49</sup> In addition, PF-05280014 was compared with reference trastuzumab in a comparative PK noninferiority study in the neoadjuvant treatment of EBC.<sup>51</sup>

Study end points also differed across the development programs (Table 2). For example, although the EBC studies of ABP 980, CT-P6, and SB3 used a pCR primary end point, the definition of pCR varied. The studies of ABP 980 and CT-P6 assessed pCR defined as the absence of invasive tumor cells in the breast and axillary lymph nodes regardless of ductal carcinoma in situ (ie, ypT0/is ypN0, hereafter referred to as total pCR [tpCR]).<sup>46,47</sup> In contrast, the SB3 study used the primary end point of breast pCR (bpCR) defined as the absence of invasive tumor cells in the breast regardless of ductal carcinoma in situ (ie, ypT0/is).<sup>50,52</sup> Some experts have recommended standardizing the use of tpCR as the primary end point for evaluating neoadjuvant treatments (including biosimilars) on the grounds that tpCR is a stronger prognostic marker than bpCR.<sup>53</sup> Indeed, both the FDA and the EMA include absence of nodal involvement in their recommended definitions of pCR as an end point in neoadjuvant studies.<sup>54,55</sup> The investigators of the SB3 study stated that they selected bpCR to eliminate potential confounding factors related to tpCR determination that are not attributable to product-related differences, such as the extent of axillary dissection (tpCR was assessed as a secondary end point, however).<sup>50</sup> Longer-term survival-related end points included EFS and OS in the ABP 980 and SB3 studies and DFS, PFS, and OS in the CT-P6 study; planned follow-up durations differed across the trials<sup>46,47,50,56-61</sup> (see Table 2 for selected results available at the time of writing). The first-line MBC studies for MYL-14010 and PF-05280014 each used the primary end point of ORR on the basis of complete or partial responses achieved by week 24 and week 25, respectively.<sup>48,49</sup> In both MBC studies, secondary efficacy end points included assessment of PFS and OS.<sup>48,49</sup> The neoadjuvant study of PF-05280014 was a noninferiority trial that was considered supportive to the main MBC study and included a PK primary end point (the percentage of patients with trough plasma concentrations of the biosimilar or reference product > 20 µg/mL after five cycles of treatment).<sup>51</sup> Secondary end points included tpCR and ORR.<sup>51,62</sup>

Some experts have argued that a comparative study in the neoadjuvant EBC setting using a pCR end point could offer the greatest level of homogeneity and sensitivity for detecting potential differences between a potential trastuzumab

biosimilar and the reference product because patients have received the same prior treatments, have lower disease burden, and may be less likely to be immunologically impaired, for example.<sup>63,64</sup> In addition, at the individual patient level, achieving pCR has been associated with longer EFS and OS compared with not achieving pCR.<sup>65</sup> However, the MBC setting is also appropriate for an assessment of biosimilarity, provided that effort is made to control and minimize heterogeneity sufficiently.<sup>62</sup> Indeed, biosimilar clinical trials conducted with MYL-14010 and PF-05280014 in the first-line MBC setting included relatively homogeneous populations. The MYL-14010 study excluded patients with prior exposure to chemotherapy or reference trastuzumab in the metastatic setting and required at least 1 year since adjuvant therapy with reference trastuzumab.<sup>48</sup> Similarly, the PF-05280014 study excluded patients with prior systemic therapy for MBC (except endocrine therapy) along with those who had relapsed within 1 year of the last dose of adjuvant or neoadjuvant treatment (again, except endocrine therapy).<sup>49</sup> In both studies, a low proportion of patients had prior exposure to reference trastuzumab (MYL-14010 study, 8%; PF-05280014 study, 10%).<sup>48,49</sup> Eligibility criteria for both studies also ensured proper identification of HER2-positive patients.<sup>48,49</sup> More generally, it is worth noting that potential heterogeneity in patient populations can be addressed by stratifying for important covariates during randomization, carefully selecting the prespecified equivalence margin, and/or increasing sample size, for example. With regard to their results, both first-line MBC studies robustly demonstrated similarity in ORR between the biosimilar and reference product<sup>48,49</sup> (Table 2). In both the MYL-14010 and the PF-05280014 studies, no clinically meaningful differences in PFS or OS were observed compared with reference trastuzumab<sup>48,49,66,67</sup> (selected results are listed in Table 2). An analysis of data from the MYL-14010 study also provided support for the use of ORR as a primary end point by showing a correlation between the responder/non-responder category at week 24 and the probability of PFS (biserial correlation coefficient across all patients, 0.752).<sup>68</sup> An additional consideration with regard to study setting is that while neoadjuvant/adjuvant therapy is given for 1 year in an EBC study, patients in a first-line MBC trial continue trastuzumab until disease progression (or unacceptable toxicity); therefore, studies in the metastatic setting offer the possibility of assessing safety and immunogenicity outcomes associated with long-term treatment.<sup>69</sup>

From a regulatory perspective, there is no requirement for potential trastuzumab biosimilars to be assessed in a comparative clinical efficacy study in the neoadjuvant setting, and with the approval of MYL-14010 and PF-05280014, the EMA and FDA clearly consider the first-line MBC setting as acceptable and sufficiently sensitive for assessing similarity. In short, both neoadjuvant EBC and first-line MBC settings provide the data needed for confirming a lack of



**TABLE 1.** Trastuzumab Biosimilars Approved in the EU and United States

| Biosimilar    | EU Approval                       | US Approval                  | Approved for Same Indications as Reference Trastuzumab (Herceptin)? <sup>a</sup> |
|---------------|-----------------------------------|------------------------------|--|
| ABP 980       |                                   |                              | Yes  |
| Name          | Kanjinti (trastuzumab)            | Kanjinti (trastuzumab-anns)  |  |
| Company       | Amgen Europe B.V.                 | Amgen Inc                    |  |
| Approval date | May 16, 2018                      | June 13, 2019                |  |
| CT-P6         |                                   |                              | Yes  |
| Name          | Herzuma (trastuzumab)             | Herzuma (trastuzumab-pkrb)   |  |
| Company       | Celltrion Healthcare Hungary Kft. | Celltrion Inc                |  |
| Approval date | February 8, 2018                  | December 14, 2018            |  |
| MYL-14010     |                                   |                              | Yes  |
| Name          | Ogivri (trastuzumab)              | Ogivri (trastuzumab-dkst)    |  |
| Company       | Mylan S.A.S.                      | Mylan GmbH                   |  |
| Approval date | December 12, 2018                 | December 1, 2017             |  |
| PF-05280014   |                                   |                              | Yes  |
| Name          | Trazimera (trastuzumab)           | Trazimera (trastuzumab-qyyp) |  |
| Company       | Pfizer Europe MA EEIG             | Pfizer Inc                   |  |
| Approval date | July 26, 2018                     | March 11, 2019               |  |
| SB3           |                                   |                              | Yes  |
| Name          | Ontruzant (trastuzumab)           | Ontruzant (trastuzumab-dttb) |  |
| Company       | Samsung Bioepis NL B.V.           | Samsung Bioepis Co., Ltd.    |  |
| Approval date | November 15, 2017                 | January 18, 2019             |  |

NOTE. Includes trastuzumab biosimilars approved in the EU and United States as of December 2019. Information in columns 2 and 3 was retrieved from web sites of the European Medicines Agency ([www.ema.europa.eu/en/medicines](http://www.ema.europa.eu/en/medicines)) and US Food and Drug Administration ([www.accessdata.fda.gov/scripts/cder/daf/index.cfm](http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm)), respectively. Information in column 4 is based on EU summaries of product characteristics<sup>31-35,70</sup> and US prescribing information.<sup>36-40,71</sup>

Abbreviation: EU, European Union.

<sup>a</sup>The trastuzumab (Herceptin; Genentech) biosimilars included are for intravenous use only. Column refers to the indications of the intravenous formulation of reference trastuzumab.

clinically meaningful differences between a trastuzumab biosimilar and the reference product, and each has its own advantages and disadvantages.<sup>69</sup> All five trastuzumab biosimilars discussed here have been approved for the same indications as the intravenous formulation of reference trastuzumab (ie, HER2-positive EBC, MBC, and metastatic gastric cancer in the EU and HER2-positive adjuvant breast cancer, MBC, and metastatic gastric cancer in the United States).<sup>31-40,70,71</sup> Thus, both EBC and MBC have been considered as sufficiently sensitive settings to support extrapolation. For trastuzumab biosimilars, the scientific justification for extrapolation includes the fact that the MOA of trastuzumab is the same across indications, and the target receptor involved (HER2) is the same in each case.<sup>57,72-78</sup> Furthermore, on the basis of data available for the reference product, there are no significant differences in expected toxicities between patient populations or indications.<sup>72,75</sup>

### How Have Regulatory Authorities Interpreted Comparative Clinical Study Data Within the Context of the Totality of the Evidence?

As described earlier, biosimilarity is determined on the basis of the totality of evidence. To illustrate how regulators

interpret data from comparative clinical efficacy studies within the overall assessment of biosimilarity, it is helpful to consider the evaluation of SB3 and ABP 980 by the EMA's Committee for Medicinal Products for Human Use (CHMP) as described in European Public Assessment Reports (EPARs) and the subsequent EU approval of these biosimilars.<sup>46,50,57,73</sup>

In the SB3 study in EBC, equivalence was assessed on the basis of an analysis of the 95% CIs of both the ratio of bpCR rates and the difference in bpCR rates between arms.<sup>50</sup> The 95% CI for the adjusted ratio of bpCR rates was contained within the predefined equivalence margin, demonstrating equivalence (Table 2). In contrast, the upper limit of the 95% CI for the adjusted difference in bpCR rates was outside the predefined equivalence margin,<sup>50</sup> meaning that while noninferiority of SB3 was demonstrated, nonsuperiority was not. The CHMP primarily considered the difference in bpCR rates in its assessment of SB3.<sup>73</sup> Structural and functional analyses conducted by the sponsor of numerous lots of reference trastuzumab identified that certain lots exhibited a marked downward drift in glycosylation levels, FcγRIIIa binding, and ADCC.<sup>50,79</sup> ADCC is a known component of the trastuzumab MOA, and some of the affected

**TABLE 2.** Comparative Clinical Studies of Trastuzumab Biosimilars in Patients With HER2-Positive Breast Cancer

| Biosimilar  | Study Setting (No. of patients)                                | Treatment Regimen  | Primary End Point                         | Primary End Point Result (BS v RP), % | Primary End Point Treatment Comparison, %          |                                |   | Selected Survival-Related End Point Data*  |
|---|--|--|---|---------------------------------------|--|--------------------------------|---|--|
|   |  |  |   |                                       | Comparison   | Equivalence Margin             | Equivalence Shown?                                |  |
| ABP 980   | Neoadjuvant and adjuvant HER2-positive EBC (725) <sup>46</sup> | Neoadjuvant phase: EC → trastuzumab + P<br>Adjuvant phase: trastuzumab (until 1 year from first dose of neoadjuvant trastuzumab; during adjuvant phase, patients either continued BS IBS/BSI, continued RP [RP/RP], or switched from RP to BS [RP/BS]) | tpCR (local assessment <sup>†</sup> )     | 48 v 41                               | Difference, 7.3 (90% CI, 1.2 to 13.4)              | -13-13                         | No (upper CI limit exceeded margin <sup>†</sup> ) | Study did not include long-term follow-up after adjuvant phase. As of final database lock, HR for on-study EFS was 0.9969 (90% CI, 0.5340 to 1.8612) for patients receiving BS/BS v RP/RP and 0.5414 (90% CI, 0.2207 to 1.3282) for RP/BS v RP/RP. <sup>56,57</sup> No HR for OS was identified. |
| CT-P6 <sup>c</sup>                                | Neoadjuvant and adjuvant HER2-positive EBC (549) <sup>47</sup> | Neoadjuvant phase: trastuzumab + D → trastuzumab + FEC<br>Adjuvant phase: trastuzumab (until 1 year of neoadjuvant and adjuvant treatment)   | tpCR (local assessment <sup>†</sup> )     | 46.8 v 50.4                           | Difference, -0.04 (95% CI, -0.12 to 0.05)          | -0.15-0.15                     | Yes   | At median follow-up of 39 months, HR for DFS was 1.23 (95% CI, 0.78 to 1.94; P = .3808), and HR for OS was 0.87 (95% CI, 0.42 to 1.82; P = .7181). <sup>61</sup> No HR for PFS was identified.   |
| MYL-14010   | First-line HER2-positive MBC (500) <sup>48</sup>               | Trastuzumab (until disease progression) + taxane (D or P)  | ORR (week 24; blinded central assessment) | 69.6 v 64.0                           | Ratio, 1.09 (90% CI, 0.974 to 1.211)               | 0.81-1.24                      | Yes   | Cumulative through 36 months from last patient in the study; HR for PFS was 0.98 (95% CI, 0.78 to 1.24), and HR for OS was 0.90 (95% CI, 0.69 to 1.17). <sup>66</sup>  |
| PF-05280014                                       | First-line HER2-positive MBC (707) <sup>49</sup>               | Trastuzumab (until disease progression) + P  | ORR (week 25; blinded central assessment) | 62.5 v 66.5                           | Ratio, <sup>5</sup> 0.940 (95% CI, 0.842 to 1.049) | 0.80-1.25                      | Yes   | Using data up to 378 days post-random assignment, HR for PFS was 1.00 (95% CI, 0.80 to 1.26; P = .505). <sup>49</sup> Cumulative through 5 years from first patient screened, HR for OS was 0.888 (95% CI, 0.624 to 1.264; P = .254). <sup>67</sup>  |
| Neoadjuvant HER2-positive EBC (226) <sup>51</sup> | Trastuzumab + DC   | Percentage of patients with cycle 5 C <sub>trough</sub> > 20 µg/mL   |   | 92.1 v 93.3                           | Difference, -0.76 (95% CI, -8.02 to 6.49)          | -12.5; (noninferiority margin) | Noninferiority shown (equivalence not assessed)   | Not applicable (secondary efficacy end points included ORR and tpCR). <sup>51,62</sup>   |

(continued on following page)

**TABLE 2.** Comparative Clinical Studies of Trastuzumab Biosimilars in Patients With HER2-Positive Breast Cancer (continued)

| Biosimilar | Study Setting<br>(No. of patients)                             | Treatment Regimen  | Primary End Point       | Primary End Point Result (BS v RP), % | Primary End Point Treatment Comparison, % |                    |                    |  |
|------------|--|--|-------------------------|---------------------------------------|---|--------------------|--------------------|--|
|            |  |  |                         |                                       | Comparison                                | Equivalence Margin | Equivalence Shown? |  |
| SB3        | Neoadjuvant and adjuvant HER2-positive EBC (875) <sup>50</sup> | Neoadjuvant phase: trastuzumab + D → trastuzumab + FEC<br>Adjuvant phase: trastuzumab (until 1 year of neoadjuvant and adjuvant treatment) | bpCR (local assessment) | 51.7 v 42.0                           | Ratio, 1.259 (95% CI, 1.085 to 1.460)     | 0.785-1.546        | Yes                | Selected Survival-Related End Point Data <sup>a</sup><br>At median follow-up of 437 days (BS) and 438 days (RP), HR for EFS was 0.94 (95% CI, 0.59 to 1.51), and HR for OS was 0.23 (95% CI, 0.03 to 1.97). <sup>59</sup> In an extension study that enrolled a subset of 367 patients, at median follow-up of 40.8 months (BS) and 40.5 months (RP) from enrollment in the main study, HR for EFS was 0.47 (95% CI, 0.26 to 0.87), and HR for OS was 0.37 (95% CI, 0.13 to 1.04). <sup>60</sup> |

NOTE. Includes trastuzumab BSs approved in the European Union and United States as of December 2019. Studies included are those with primary publications available from PubMed. Comparative studies in healthy volunteers not included. Information in columns 1-8 is based on primary publications. In column 3, trastuzumab denotes either the BS or the trastuzumab RP. Consult cited references for information on dosing and treatment cycles and for additional details of the presented analyses (eg, analysis populations, statistical methods).

Abbreviations: bpCR, breast pathologic complete response; BS, biosimilar; C<sub>trough</sub>, trough plasma concentration; D, docetaxel; DC, docetaxel and carboplatin; EBC, early breast cancer; EC, epirubicin and cyclophosphamide; EFS, event-free survival; FEC, fluorouracil, epirubicin, and cyclophosphamide; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; P, paclitaxel; pCR, pathologic complete response; RP, reference product; tpCR, total pathologic complete response.

<sup>a</sup>Column reports HRs for treatment group comparisons (where available) for longest follow-up data identified for each study/end point as of December 2019. Consult cited references for additional results (eg, median values, event rates at specific time points).

<sup>b</sup>In sensitivity analyses that were based on central review of tumor samples, 90% CIs for the risk difference and risk ratio were contained within the predefined equivalence margins.<sup>46</sup>

<sup>c</sup>CT-P6 was also assessed in MBC<sup>89</sup>; however, these data were not part of submissions to regulators in the United States and European Union.<sup>74,75</sup>

<sup>d</sup>Histopathology reports were assessed centrally by a blinded reviewer.

<sup>e</sup>As noted in the European Medicines Agency assessment report for PF-05280014, equivalence was also assessed on the basis of ORR risk difference (-3.979%; 95% CI, -11.005 to 3.080). The 95% CI was contained within the equivalence margin of -13% to 13%.<sup>62</sup>

<sup>f</sup>For quality control, all bpCRs were reviewed by a study pathologist board

lots were used in the clinical study.<sup>50,73</sup> It was considered by the CHMP that this apparent shift in ADCC activity could have added variability to the estimation of the treatment difference, thereby contributing to the upper limit of the CI exceeding the margin.<sup>73</sup> As noted in the EPAR for SB3, “the magnitude of the differences observed can be in part attributed to other factors and the true difference is considered likely to fall within the equivalence margins and [be] of no clinical relevance.”<sup>73(p68)</sup>

In the study of ABP 980 in EBC, equivalence was evaluated using the 90% CIs of both the risk difference and the risk ratio of locally assessed tpCR, using a sequential testing method.<sup>46</sup> In analyses that were based on both the risk difference and the risk ratio, the upper boundaries of the 90% CIs exceeded the predefined equivalence margins (Table 2). Thus, nonsuperiority of ABP 980 was not demonstrated. In a sensitivity analysis that was based on central review of tumor samples, 90% CIs of the risk difference and risk ratio were contained within the margins, however.<sup>46</sup> According to the EPAR for ABP 980, the CHMP seems to have considered 95% CIs (rather than 90% CIs) of the tpCR risk difference and risk ratio on the basis of local laboratory review.<sup>57</sup> Again, the upper limits of both 95% CIs exceeded the prespecified margins.<sup>57</sup> As with SB3, it was acknowledged in the EPAR for ABP 980 that the apparent difference between the groups was considered to be at least partly confounded by a shift in ADCC activity observed for certain lots of the trastuzumab reference product used in the study, which may have contributed to a more extreme location of the upper CI limit.<sup>57</sup> The CHMP noted that the observed difference in efficacy results was not considered clinically relevant.<sup>57</sup>

For both SB3 and ABP 980, considering the similarity data from across all stages of the respective comparison exercises, the CHMP determined that biosimilarity to reference trastuzumab had been sufficiently shown.<sup>57,73</sup> These examples help to illustrate that it is the totality of the evidence, with comprehensive and robust analytical data as the foundation, that is of crucial importance in a regulatory determination of biosimilarity. Data from comparative clinical studies, while clearly important, serve a confirmatory rather than a central function. As shown by the regulatory assessment of SB3 and ABP 980 in the EU, in certain circumstances, small apparent differences between a proposed biosimilar and reference product when using a sensitive clinical end point may be considered unlikely to be clinically meaningful and in view of the totality of data, may not preclude a determination of biosimilarity.

### WHAT IS THE ROLE FOR COMPARATIVE CLINICAL STUDIES IN THE FUTURE DEVELOPMENT OF BIOSIMILARS?

Recently, some experts have argued that from a scientific, economic, and ethical perspective, comparative clinical efficacy studies may be unnecessary in the development of most biosimilars.<sup>80-82</sup> A recent opinion article proposed that

the current approach to biosimilar development should be replaced with a more efficient paradigm that “emphasizes analytical likeness between a biosimilar and its reference but does not generally require...in vivo nonclinical studies or clinical equivalence studies.”<sup>82(p604)</sup> The authors of the article based their proposal on the observation that

no biosimilar that has been found to be highly similar to its reference by both analytical and human pharmacokinetic studies has ever failed to be approved because it was found not to be clinically equivalent to its reference in a powered [efficacy] study.<sup>82(p604)</sup>

It should be noted that current regulatory guidelines do not mandate comparative clinical efficacy studies in all circumstances.<sup>5,6</sup> FDA guidance, for instance, states that a comparative clinical study will be necessary “if there is residual uncertainty about whether there are clinically meaningful differences between the proposed [biosimilar] product and the reference product based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.”<sup>6(p18)</sup> Factors that affect the type and extent of clinical data required include the complexity of the reference product, the magnitude of differences observed in comparative structural and functional assessment, the degree to which the MOA is understood, and the availability of a PD end point that correlates with efficacy.<sup>1,6</sup> In the EU, regulatory requirements with regard to clinical data have evolved since the biosimilar framework was first introduced, and although comparative PK/PD studies remain essential, the strict requirement for comparative efficacy studies has been waived (or is proposed to be waived) for certain product categories, along with comparative safety/immunogenicity studies in specific circumstances.<sup>5,83,84</sup> For granulocyte colony-stimulating factor, for example, structure, physicochemical characteristics, and biologic activity can be well characterized, and clinically relevant PD parameters are available.<sup>85</sup> Whereas the original version of the EMA guidance concerning biosimilar granulocyte colony-stimulating factor (published in 2006)<sup>86</sup> includes significant emphasis on comparative clinical efficacy and safety trials, a draft revision to the guideline (released in 2018 for consultation) stated that a dedicated comparative efficacy trial is “not considered necessary.”<sup>84(p7)</sup> For many biosimilar mAbs, however, the absence of robust PD efficacy measures, as well as their importance to clinical outcome, means that comparative clinical trials will likely remain necessary.<sup>87,88</sup> In our view, the requirement for such studies is also particularly likely for oncology mAbs, where biosimilars may be used with curative intent, and prescribers will want to appraise comparative clinical data.

In summary, the paradigm for the development and approval of biosimilars differs markedly from that for novel biologics. For biosimilars, the positive benefit-risk profile is



based on the totality of the evidence that demonstrates biosimilarity to the reference product rather than on efficacy and safety studies in each approved indication. In biosimilar development, the comparative clinical efficacy study aims to confirm clinical equivalence between a proposed biosimilar and its reference product on the basis of prespecified margins, along with comparable safety and immunogenicity. Such studies do not aim to establish de novo efficacy and safety. Reflecting this difference, comparative clinical studies should be performed in a sensitive population using appropriate end points to allow detection

of any clinically meaningful differences between the treatments, should they exist. As is evident from experience with recently approved trastuzumab biosimilars, for certain reference products, there may be more than one appropriate design for such studies in terms of the population studied and end point used. Furthermore, there may be more than one acceptable study setting to support extrapolation. As biosimilars become more widely available in oncology, it is important that clinicians appreciate the distinct confirmatory role of comparative clinical studies in the biosimilar paradigm.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.02953>.

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## ACKNOWLEDGMENT

Medical writing support was provided by Paul Shepherd of Engage Scientific Solutions and was funded by Pfizer.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

### Understanding the Role of Comparative Clinical Studies in the Development of Oncology Biosimilars

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

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**Patents, Royalties, Other Intellectual Property:** Four patents on nanotechnology  
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**Travel, Accommodations, Expenses:** Pfizer, Puma Biotechnology, Mylan, Amgen, AstraZeneca, MacroGenics, Daiichi Sankyo, Merck, Novartis, OBI Pharma

No other potential conflicts of interest were reported.