Key Design Considerations on Comparative Clinical Efficacy Studies for Biosimilars: Adalimumab as an Example

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Abstract

The global development of a biosimilar product is a methodologically complex affair, lined with potential design pitfalls and operational missteps to be avoided. Without careful attention to experimental design and meticulous execution, a development program may fail to demonstrate equivalence, as would be anticipated for a biosimilar product, and not receive regulatory approval based on current guidance. In order to demonstrate similarity of a biosimilar product versus the originator (ie, the branded product), based on regulatory guidance, a stepwise approach is usually taken, starting with a comprehensive structural and functional characterization of the new biological moiety. Given the sequential nature of the review process, the extent and nature of the nonclinical in vivo studies and the clinical studies to be performed depend on the level of evidence obtained in these previous step(s). A clinical efficacy trial is often required to further demonstrate biosimilarity of the two products (biosimilar vs branded) in terms of comparative safety and effectiveness. Owing to the focus on demonstrating biosimilarity and not safety and efficacy de novo, designing an adequate phase III (potentially pivotal) clinical efficacy study of a biosimilar may present some unique challenges. Using adalimumab as an example, we highlight design elements that may deserve special attention.

Introduction

In order to demonstrate similarity of a biosimilar product versus the originator (ie, the branded product), based on regulatory guidance, a stepwise approach is usually taken, starting with a comprehensive structural and functional characterization. The extent and nature of the nonclinical in vivo studies and the clinical studies to be performed depend on the level of evidence obtained in these previous step(s). A phase I study in normal healthy volunteers or patients is typically used to demonstrate comparability of the biosimilar product versus the branded product in terms of pharmacokinetic (PK) characteristics. Then a clinical efficacy trial is often required to further demonstrate biosimilarity of the two products (biosimilar vs branded) in terms of comparative safety and effectiveness.[1,2]

At first approximation, the design of pivotal efficacy trials for biosimilars appears to be relatively simple and straightforward, but beneath standard objectives, there are a number of design attributes

Key Messages

What is already known about this subject?

In order to demonstrate similarity of a biosimilar product versus the originator (ie, the branded product), based on regulatory guidance, a stepwise approach is usually taken, starting with a comprehensive structural and functional characterization of the new biological moiety. A clinical efficacy trial is often required to further demonstrate biosimilarity of the two products (biosimilar versus branded) in terms of comparative safety and effectiveness.

What does this study add?

Because of the focus on demonstrating biosimilarity and not safety and efficacy de novo, designing an adequate phase III (potentially pivotal) clinical efficacy study of a biosimilar may present some unique challenges. Using adalimumab as an example, we highlight design elements that may deserve special attention, including the therapeutic indications, target patient population, background therapy, blinding, stratification, transition design (switch from originator to biosimilar product), primary dependent variable, choice of equivalence vs. noninferiority design, selection of equivalence margin, and alternative statistical considerations.

How might this impact clinical practice?

Understanding regulatory requirements for biosimilar development and design of pivotal clinical trials to demonstrate comparative efficacy and safety for biosimilars vs branded products will help clinicians with their considerations on prescribing biosimilars to patients with rheumatic/inflammatory diseases.

requiring careful consideration. As specified by regulators, the focus of these studies is not to establish the clinical effectiveness of the biosimilar product. Instead, it is to demonstrate similar clinical efficacy between the biosimilar and the branded product, predicated on an assumption that the branded product has unambiguously demonstrated evidence of efficacy and safety in a previous development program. This is generally done utilizing effect sizes which are reproducible across studies. The nature of the comparative end point study employing both a biosimilar and a branded product requires adequately powered, randomized, parallel group comparative clinical trials, preferably double blind, by using efficacy end points in either a noninferiority or equivalence design.[2]

Using adalimumab as an example, we highlight design elements that may deserve special attention, including the therapeutic indications, target patient population, background therapy, blinding, stratification, transition design (switch from the originator to the biosimilar product), primary dependent variable, choice of equivalence versus noninferiority design, selection of equivalence margin, and alternative statistical considerations. Design of phase III clinical efficacy trials in compliance with European Medicines Agency (EMA) and/or Food and Drug Administration (FDA) biosimilar guidelines for a global development program of a biosimilar product will be discussed, although it is acknowledged that different guidelines have been released in different countries of the world for the development of biosimilar products.[3]

Adalimumab (Humira) is the world's top-selling prescription drug. It is a biological tumor necrosis factor (TNF) inhibitor that has received market authorization in >87 countries for multiple inflammatory disease indications, namely rheumatoid arthritis (RA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD) and ulcerative colitis (UC).[4,5]

Since the patent for adalimumab will expire in the next few years (eg, in 2016 for the U.S. and in 2018 for most European countries), multiple drug companies are developing biosimilar versions of adalimumab. The first adalimumab biosimilar was recently granted marketing authorization in India with the brand name of Exemptia.[6] However, Exemptia is not yet approved in the U.S. or the European Union (EU). Zydus Cadila, the developer of Exemptia, has meetings scheduled with European and US regulators for 2015 seeking guidance to obtain approval in the EU and the U.S.[7]

Table 1 lists nine global phase III clinical efficacy studies for biosimilar adalimumab (data obtained from a search of Citeline's Trialtrove as of September 8, 2015, planned or local studies not included).

Key design elements of these studies as presented within the sources (eg, clinicaltrials.gov or EU clinical trial registry) vary from sponsor to sponsor, as summarized in tables 2 and 3.

Clinical Study for Regulatory Approval: What Indication?

To demonstrate biosimilarity in safety and efficacy, current FDA and EMA guidance do not mandate performing comparative clinical efficacy trials in every approved indication of the reference product, which represents a great advantage in terms of reduced cost and shortened time for biosimilar development. However, a decision should be made regarding which indication(s) to pursue in the pivotal efficacy trial(s) and in potential supportive trials. This includes what strategy to adopt in order to obtain approval for all indications of the reference product (extrapolation of indication, see also next section). Parameters used to influence this decision are multidimensional, encompassing regulatory sentiments, scientific considerations, operational demands and commercialization interests. In fact, on the basis of EMA and FDA guidance, extrapolation to other approved indications of the reference product could be acceptable, but needs to be scientifically justified.[1,2]

Remsima, the first biosimilar TNF inhibitor approved by the EMA in 2013, was granted market authorization across all indications as the originator product (Remicade), even though the pivotal clinical efficacy trial was conducted only in patients with RA with supporting efficacy, safety and PK data collected in patients with AS.[8] It is worth noting that Remsima was not granted extrapolation across all indications by all regulatory agencies (see more discussions in Extrapolation of Indications section).

Since Humira™ is also approved for multiple inflammatory disease indications, in theory it may be possible to perform the comparative clinical efficacy study in one of these patient populations and extrapolate across similar indications. As recommended by regulators, the most sensitive model in detecting clinically meaningful differences in safety (including immunogenicity) and effectiveness between the originator and the biosimilar product should be chosen.[1,2]

In terms of clinical efficacy, it has been suggested that indications with the highest placebo-adjusted response rate may be most sensitive for detecting any potential difference between the biosimilar and branded products. This is based on the principle that sensitivity for detecting small differences between agents is optimized in situations where the signal-to-noise ratio is the highest.[9] Of the five indications approved for adalimumab, the greatest placebo-adjusted response rate was found in PsO (61 to 64 percent, table 4). For RA, owing to the relatively high placebo response rate, the placebo-adjusted response rate was more modest (33 to 52 percent in combination with methotrexate (MTX) and 18 to 27 percent as monotherapy based on 20 percent improvement in the American College of Rheumatology criteria (ACR20) after either 6 months or 12 months of treatment).

In terms of immunogenicity, adalimumab is usually given as a monotherapy for psoriasis treatment and in combination with background MTX therapy for RA treatment. Immunosuppressants such as MTX are known to reduce the incidence of antidrug antibodies for TNF inhibitors, therefore most likely contributing to patients' response to therapy.[24,25] Thus, since in PsO trials the biological agent is usually not administered in combination with any immunosuppressive therapy, PsO may represent a more sensitive disease model to detect any potential difference in immunogenicity of the biosimilar versus branded adalimumab.

Out of the eight companies with ongoing global phase III biosimilar adalimumab studies, four companies appear to be conducting the pivotal phase III study only in RA, while three are conducting the pivotal study in PsO, and one in both RA and PsO (table 1). We postulate that RA may be viewed as an attractive indication since patients with RA are the largest patient population receiving anti-TNF therapies. Thus, RA may be the indication of choice for the pivotal phase III comparative clinical efficacy studies, considering the size of the patient population and RA's potential commercial impact.

Likewise, PsO is also an attractive disease model to demonstrate biosimilarity for adalimumab, due to the enhanced sensitivity for detecting a potential difference in clinical efficacy and immunogenicity in this indication, as well as the availability of the patient population. It is worth noting that in addition to the ongoing biosimilar adalimumab trials in psoriasis, biosimilar developers are also conducting pivotal phase III studies in psoriasis for other anti-TNF agents.[26,27]

Extrapolation of Indications

As discussed above, it may be possible to conduct the pivotal study in one indication to demonstrate biosimilarity in clinical efficacy and safety in order to obtain regulatory approval and request extrapolation across indications.

Regulatory agencies require sufficient scientific justification for extrapolating clinical data to support the biosimilarity for each condition in which the license is sought.[1,2] For example, the FDA specified that scientific justification should include considerations on potential differences in the mechanism of action in each indication, PK and biodistribution in different patient populations, expected toxicities in each condition and patient population (including on-target or off-target effects), and any other factors that may affect the safety or effectiveness of the product across conditions and patient populations. The FDA recommended the choice of the most sensitive model in detecting clinically meaningful difference in safety (including immunogenicity) and effectiveness and cautioned that extrapolating the safety profile across indications could be problematic due to the difference in comorbidities and concomitant medications.

Adding to the complexity of program design, different regulatory agencies have taken different approaches regarding indication extrapolation. The approval history of infliximab biosimilar Remsima/Inflectra is a good example of such different approaches. The filing dossier of Remsima included a PK study in 250 patients with AS, in addition to the pivotal study in RA. The EMA considered AS to be an appropriately sensitive model because patients with AS represent a young, otherwise healthy population not receiving concomitant immunosuppressants like MTX.

On the basis of results from the RA and AS studies, structural characterization and preclinical data demonstrating similarity of the biosimilar versus branded infliximab, and preliminary observational data in a limited number of patients with inflammatory bowel disease (IBD), the EMA granted Remsima all of the indications approved for Remicade, although Remsima was not granted extrapolation across all indications by all regulatory agencies.[8] In addition, the developer of Remsima has committed to conduct a post-authorization trial in patients with active CD.

Interestingly, Health Canada expressed a different opinion and granted approval of Remsima in RA, PsA, AS and PsO, but not in UC or CD. The extrapolation to the IBD indications was not accepted on the basis of differences in pharmaceutical attributes between the biosimilar and branded infliximab and on pathophysiological differences between rheumatic diseases and IBD that may not allow for direct extrapolation without PK/pharmacodynamic (PD) or clinical bridging studies.[28] In particular, Health Canada argued that a difference in the ability of the two products to induce antibody-dependent cell-mediated cytotoxicity (ADCC) could not be ruled out due to differences observed in the level of α-fucosylation, FCγRIIIa receptor binding and ADCC based on in vitro assays. Since ADCC may be an important mechanism of action in IBD but not in rheumatic diseases, extrapolation to IBD was not granted in the absence of clinical studies in IBD. In addition, it was not known whether the difference in quality between the two products could impact on the safety of patients with IBD, given that infliximab shows a different safety profile in IBD compared with rheumatic diseases.

Australia recently granted Inflectra market authorization for all approved Remicade indications, following the EMA opinion, while Japan granted market authorization only for RA, CD and UC (an RA study was conducted in Japan only).[29]

An application for approval for Remsima has also been filed with the FDA in 2014 as the first monoclonal antibody seeking approval through the 351(k) biosimilar pathway. It will be interesting to see what stand the FDA will take regarding the determination of biosimilarity and extrapolation of indications for Remsima.

Given the diversity of opinions expressed across major countries, a successful clinical development of a biosimilar product is predicated on early consultation with the regulatory agencies regarding the indication to pursue for the pivotal clinical efficacy trial and specific design elements of the study. It is also important to have an ongoing consultation during the course of the development program to make adjustments in the light of available preclinical and clinical data since the totality of the evidence will be used for regulatory approval.

Even if a product is approved across different indications, there may still be concerns from other stakeholders (eg, the learned societies, physicians, national healthcare systems, insurers) over the appropriateness of extrapolating indications. For example, the European Crohn's and Colitis Organisation emphasized the difficulty of extrapolation across indications for biosimilars. They recommended that direct evidence of safety and benefit from clinical trials in IBD, postmarketing pharmacovigilance, and unequivocal identification of the product as a biosimilar should be requirements before approval.[30] In addition to regulatory agency requirements, it would be beneficial to take into consideration views from additional stakeholders during the clinical development program for a biosimilar product.[31] For example, in a payer-centric market, formulary placement and patient access are strongly influenced by consideration of a value proposition that may not have been considered prior to clinical development.

Targeted Patient Population

To maximize therapeutic effects, it may be desirable to conduct a biosimilar study in patients who are naïve to biological therapies. In addition, this will allow for recruiting a more homogeneous patient population. Any imbalance between the two treatment arms that is not adequately addressed by the randomization scheme poses a risk of not achieving the objective of demonstrating equivalence or noninferiority in clinical efficacy.

There are conflicting data regarding whether prior exposure to biological therapy, and especially failure to respond to TNF therapy, will reduce the clinical efficacy of a given TNF inhibitor. For example, one study suggested that response to adalimumab therapy was lower in patients with PsO who switched to anti-TNF therapy. However, other studies suggested that the clinical efficacy of adalimumab was not significantly affected by prior biological therapy in patients

with PsO.[32,33] Regarding RA, there are indications that switching to adalimumab treatment after loss of response or intolerance to prior anti-TNF therapies is safe and effective; however, the response rate can be lower than that observed in naïve patients when adalimumab is the second TNF inhibitor.[34–37] The likelihood of response to subsequent treatment with biological agents seems to decline with the increasing number of previous treatments with TNF inhibitors.[38–40]

While requiring biologically naïve patients makes the population more homogeneous and increases the magnitude of the therapeutic effect/treatment group, it could significantly impact patient recruitment. This is especially relevant in the U.S. and Western Europe (WE), since a significant portion of patients with moderate-to-severe RA (and PsO, to a less extent) has been treated with biological agents in these regions.[41,42] The inequalities in terms of access to biological agents for RA and PsO in different countries/regions of the world present both a challenge and an opportunity. For example, while it may be challenging to recruit patients from the U.S. and WE, this may allow access to the branded and biosimilar versions of an approved biological agent as part of a biosimilar study in countries where such drugs are not affordable.[42]

Therefore, the desire for targeting biologically naïve patients may need to be balanced with the reality of patient recruitment, especially if a significant portion of the patients need to come from the U.S. and/or WE. In such cases, it may be worthwhile considering the inclusion of patients who have received one prior line of biological therapy (other than adalimumab). For example, Amgen's phase III biosimilar adalimumab trial in PsO enrolled patients who could have received up to one prior biological therapy. Amgen recently reported that the trial met its primary end point, demonstrating clinical equivalence for ABP-501 compared with Humira based on the Psoriasis Area and Severity Index (PASI) percent improvement from baseline to week 16 of treatment. Safety and immunogenicity of ABP-501 were also comparable to Humira.[43] Sandoz's phase III biosimilar adalimumab trial in PsO also permitted the enrollment of patients who have received prior biological therapies, while the study by Coherus required patients naïve to anti-TNFα agents (table 3). The same eligibility criterion permitting previous biological therapy was also used in Amgen, Boehringer Ingelheim and Fujifilm's phase III studies for an adalimumab biosimilar in patients with RA (table 2). However, Pfizer and Samsung Bioepis's phase III RA studies did not permit prior treatment of biological therapies.

If prior anti-TNF treatment is permitted, it may be worthwhile including the prior biological treatment as a factor for stratification or in post hoc analysis. In addition, it would be useful to record the reason for stopping prior treatment (eg, lack of response, intolerance, affordability, etc) as well as treatment details in terms of duration/dose/response as part of medical history during the study. All of these variables provide data points for an exploratory evaluation of factors impacting biosimilar (and reference product) use.

Background Therapy

Efficacy of adalimumab monotherapy (not with MTX or other systemic PsO therapies) was established in the phase III REVEAL study for PsO.[22] In biosimilar trials in PsO, adalimumab was administered alone without background systemic therapies for patients with moderate-to-severe psoriasis (table 3).

For RA treatment, based on the drug label for Humira, adalimumab can be used alone or in combination with MTX (or other disease-modifying antirheumatic drugs [DMARDs]),[4] although the EMA approved label specifies that use of Humira as a monotherapy should be reserved for cases of intolerance to MTX or when continuing treatment with MTX is inappropriate.[5] Clinical trials such as the PREMIER study indicated that combination therapy with adalimumab plus MTX was superior to adalimumab alone in improving signs and symptoms of RA.[44] In addition, the response rate with adalimumab versus placebo was greater when given in combination with MTX rather than as monotherapy, providing more sensitivity in demonstrating comparative efficacy.[11,12]

For the treatment of RA, adalimumab has been administered with MTX at a stable dosage of 12.5–25 mg/week in the ARMADA trial.[10] However, MTX outside of this dose range (eg, 7.5–10 mg) may also be used in clinical practice. The requirement of a MTX dosage before and during the proposed clinical study should be clearly defined as part of the inclusion criteria and concomitant medication prescription. It is worth noting that MTX dosage requirements

vary in RA clinical studies evaluating clinical efficacy of biosimilar adalimumab, from the more liberal 7.5–25 mg/week to the more restrictive 15–25 mg/week (table 3).

As discussed earlier, concomitant administration of MTX affects production of antiadalimumab antibodies (AAA), which in turn may potentially affect the response to adalimumab treatment.[24] MTX seems to be able to reduce immunogenicity in a dose-dependent manner, with a higher proportion of patients receiving MTX doses of 10 mg/week or less developing AAA compared with patients receiving doses of 12.5 mg/week or more.[25] Data from previous studies indicated comparable efficacy for MTX doses ranging from 10 to 20 mg/week in combination with adalimumab, but lower efficacy for doses below 10 mg/week.[45,46] Therefore, in order to avoid any imbalance in immunogenicity and clinical efficacy in adalimumab biosimilar trials in RA, it might be preferable to enroll patients who have been receiving stable MTX at a dose of 10–25 mg/week and can maintain the dose throughout the study.

Disease Activity

Irrespective of whatever therapeutic indication is pursued in the pivotal efficacy trial, patients should have active disease at study entry, according to standardized disease severity criteria, in order to show response to study treatment and justify treatment with a biological agent.

For PsO, a standard definition of moderate-to-severe disease, based on a combination of body surface area involvement (≥10 percent), PASI score (≥10 or 12) and Physician Global Assessment score (≥3), has been used across adalimumab biosimilar trials (table 3).

For RA, activity of disease has been defined in various ways across clinical trials, but most frequently it is defined as a combination of swollen/tender joints and elevated acute phase reactants in blood. The minimum number of swollen and tender joints required at study entry tends to vary between 4 and 6. Confirmation is usually required prior to randomization at the completion of the screening period, due to the potential variation/improvement in disease activity, for example, as a result of better compliance with concomitant treatment (MTX, steroids) or due to the natural course of the disease.

In the efficacy trials of Humira, at least nine tender joints and six swollen joints were required at study entry.[10,12] However, in recent years, more aggressive and earlier treatments have led to general improvement of disease symptoms.[47] All of the five phase III RA studies for biosimilar adalimumab listed in table 2 included a disease activity requirement of at least six swollen and six tender joints. This is in line with the eligibility criteria of reference product trials with at least six swollen joints but reduces the requirement for the number of tender joints. These observations highlight another experimental design variable, that is, changes in patterns of clinical care impacting eligibility criteria.

Acute phase reactants commonly measured in clinical practice include erythrocyte sedimentation rate (ESR) or C reactive protein (CRP). In the past, often either one of these markers had to be above a predefined threshold for the patient to qualify for enrollment, while in recent protocols, there is a preference for CRP. One of the reasons for such preference is that CRP can be evaluated by a central laboratory, while ESR must be measured locally, thus making CRP a more objective and unbiased measure with adequate clinical sensitivity.[48] In addition, compared with ESR, CRP is a simple, validated, reproducible, non-age or gender-dependent test.[49]

The cut-off level of CRP for inclusion can have a significant impact on patient recruitment. In fact, as recently pointed out by the Canadian Rheumatology Research Consortium,[50] acute phase reactants may not always be significantly elevated in the presence of active disease in many patients, particularly if patients are receiving concomitant steroid treatment. For example, ESR and CRP levels were evaluated versus swollen joint count from randomized clinical trials for golimumab enrolling >1,200 patients with RA. In this analysis, even for patients with >4 swollen and tender joints, CRP was elevated (>8 mg/L or 0.8 mg/dL as specified by the study) in only ~50 percent of the patients (11.2 percent with elevated CRP and normal ESR, and 39.7 percent with both elevated).[49] In addition, a recent publication by Kay, et al analyzed the prevalence of normal, elevated and discordant acute phase reactant levels

of 9,135 patients with active RA from a large US registry of patients with RA. These data also indicated that acute reactant levels often do not correlate with disease activity as measured by joint counts and global assessments.[51]

It is worth noting that different biosimilar adalimumab RA studies included different cut-off values for CRP (eg, >0.8 or 1 mg/dL) (table 2). Depending on the upper limit of normal (ULN) of the laboratory and the location of the study sites, it is likely that these requirements will result in 50 percent screen failure or higher for these studies. A CRP cut-off value just above the ULN for a given central laboratory can be considered to limit as much as possible the screen failure rate. Alternatively, as Kay, et al[51] proposed, clinical trials for RA may use the Clinical Disease Activity Index (CDAI), rather than elevated acute phase reactants, as a criterion for study entry, although it should be taken into account that the CDAI does not include any objective measure of disease activity.

Stratification Factors

It has been reported that efficacy of adalimumab might be affected by multiple clinical or biological factors. For example, for PsO the adalimumab phase III clinical studies indicated that treatment assignment, weight and age are the most influential factors for mean percent change in PASI score at week 16.[52] In terms of weight, it appears that efficacy is decreased mainly in patients with body weight ≥90 kg or with body mass index (BMI) ≥30 kg/m^2. The most significant decrease in efficacy occurs in patients with body weight ≥140 kg. Thus, for a biosimilar adalimumab study, it might be worthwhile to consider using weight or BMI as a stratification factor or to exclude extremely obese patients, since obesity tends to be more frequent in patients with PsO.[53]

For RA, in a post hoc multivariate regression analysis to identify characteristics that modify disease progression and therapeutic response, baseline disease activity was found to have substantial effects on the response to treatment for adalimumab.[40] Therefore, stratification based on disease activities (eg, based on baseline Disease Activity Score in 28 joints [DAS28] score) may be worth considering. In addition, as discussed previously, if prior biological treatment is permitted, it may be worthwhile to consider stratifying patients based on prior biological therapy in order to avoid imbalance between the two treatment groups.

The geographic distribution of participating sites and its impact on the characteristics of the patient population are also stratification factors to be considered. For example, it has been reported that patients from developing countries often have more active and severe RA disease and may also have a higher placebo response in placebo-controlled trials when compared with patients from more developed countries, such as the U.S. and WE.[41,48] Therefore, if the comparative clinical effectiveness study for the biosimilar adalimumab includes patients from different regions of the world (as most trials do due to the high level of competition for the same patient population and need for a large number of sites to achieve enrollment), it may be worthwhile considering stratification or post hoc analysis by region. Regulators also recommend such an approach for studies including patients from different global regions.[54]

Switching Treatment

Once a biosimilar product is approved, it might be administered to patients who have not received the branded product. However, switching a patient who is already receiving stable treatment of the branded biological drug to a biosimilar product may raise a number of concerns in terms of safety and efficacy.

The U.S. allows an "interchangeable" designation for biological medicines. According to the FDA, interchangeability is expected to produce the same clinical result in any given patient.[55] However, specific guidance from the FDA on achieving the interchangeability designation has not been released. In Europe, the EMA does not make recommendations on whether a biosimilar could be used interchangeably with its reference medicine; this is a matter for the national competent authorities.

Many biosimilar studies incorporate a transition design to test for potential changes in safety and efficacy after transitioning from the branded to the biosimilar product. Different design options can be considered in this respect.

In the most common design, patients completing the double-blind, randomized study can enter a single arm, open-label extension study, during which all patients receive the biosimilar product. This design allows for a long-term safety evaluation as well as for evaluation of the transition from the reference product to its biosimilar, but lacks any comparison with a parallel arm without the treatment switch. For example, Amgen adopted this design in the phase III RA study for their biosimilar adalimumab that was followed by a single-arm, open-label extension study.[56,57]

Other trials incorporated more complex design options, with a rerandomization after the primary end point is achieved in the blinded treatment phase. Patients from each treatment arm may be rerandomized to the reference product or its biosimilar so that part of the patients will be transitioned either from the reference to the biosimilar product or vice versa while other patients will continue on their previous treatment (eg, phase III studies for biosimilar adalimumab from Fuji Film Kyowa in RA and Sandoz in PsO).[58,59] As an alternative option, only patients initially randomized to Humira (branded product) are rerandomized to the two treatments, while the biosimilar arm will continue current treatment (eg, phase III studies for biosimilar adalimumab from Pfizer in RA and Amgen in PsO).[60,61] In this design, the only transition is from Humira to the biosimilar product.

The rerandomization phase can be either double blinded or open label, depending on how close the appearance of the biosimilar drug matches Humira. The rerandomization ratio of the reference product to the biosimilar may also vary, for example, 1:1 or 2:1. The transition design may serve different purposes: to evaluate the effects of transitioning from one product to the other, and, at the same time, to compare long-term (eg, 1 year) safety and immunogenicity of the branded versus the biosimilar product in patients who will continue their current treatment in a parallel-arm design.

Blinding and Self-injection

Blinding may represent an issue for adalimumab biosimilar (as for other biosimilars such as etanercept), because Humira is marketed in a prefilled syringe that can be very easily recognized. Proper blinding is essential when either primary-dependent or secondary-dependent variables focus on clinical symptomatology or quality of life and functionality. Therefore, either the biosimilar adalimumab is supplied in a similar syringe indistinguishable from the Humira one (the Humira label may be masked), or the study drug and adalimumab may be prepared at the site by unblinded pharmacists and administered at the study site under blinded conditions. Both options involve good planning for the drug package and supply and may require the availability of unblinded site staff. As discussed above, for a study including a rerandomization design, if the biosimilar product looks different from the Humira prefilled syringe, then it may be preferable to rerandomize both treatments arms to avoid a partial break of the blinding of the initial treatment phase. In addition, if biweekly adalimumab injections will be administered at the site (eg, rather than permitting home administration due to blinding requirements) for the duration of the double-blind treatment period, it may represent an additional burden for patients that can further discourage them from participating in a biosimilar study.

Primary End Points

Regulators do not require that studies on biosimilars use the same primary end point as the originator study, but that the chosen primary end point should be sensitive enough to detect any potential differences between the two drugs which are potentially clinically relevant.[1,2] Therefore, efficacy end points that are sensitive and best suited to show comparability are required, often selected among the primary and secondary end points used in the phase III trials of the reference product. "Hard" clinical end points recommended by guidelines for new active substances may not need to be included if the correlation between these end points and other clinical/PD end points, which are more sensitive to clinically meaningful differences, have been established for the branded product.[1,2] For example, for RA, evaluation of progression of joint damage by X-ray imaging is not usually required.

For trials in PsO, the primary end point used in the phase III pivotal studies for adalimumab is 75 percent reduction in the PASI (PASI75) at week 16 (table 3). This primary end point was also selected as the primary end point for the biosimilar adalimumab PsO studies by Sandoz and Mylan (table 3). It has been argued that the most sensitive way to compare the biosimilar with its reference product would be to show statistically equivalent clinical responses during the earlier, rapid rise phase of the time response curve rather than at the plateau.[62] It may be worthwhile considering PASI75 at week 12 instead of week 16 since it is on the rising part of the dose–response curve and may be more sensitive to detect any potential differences, as done by Coherus.[22] Furthermore, Amgen used a different primary end point for the biosimilar adalimumab phase III study in PsO. Rather than using PASI75 at week 16 (or week 12), percent improvement of PASI from baseline to week 16 of treatment was chosen as the primary end point. Indeed, percent improvement of PASI is a continuous variable and may be more sensitive to detect small differences for any given sample size than PASI75, which is a categorical variable.

For RA, ACR20 at week 24 or 52 has been employed in the pivotal phase III trials for Humira (table 4). Consistent with these studies, ACR20 at week 24 is selected as the primary end point for the majority of the RA trials for the biosimilar adalimumab (table 3). On the basis of pivotal phase III studies for Humira, the percentage of patients achieving ACR20 response increases quickly, mainly during the first 12 weeks, and largely plateaus at week 24. Therefore, a more sensitive way to detect potential differences between the biosimilar and branded adalimumab may be to compare the clinical effectiveness using ACR20 after 12 weeks, instead of after 24 weeks of treatment. Pfizer is taking this approach with their phase III RA study for biosimilar adalimumab (table 3), while Boehringer Ingelheim chose to have two coprimary end points measured at week 12 and week 24.

In addition, change in DAS28 from baseline may also represent a valuable option, because, as a continuous measure, it is more sensitive to small differences than a categorical measure such as ACR20 for any given sample size.

Equivalence or Noninferiority Designs

An equivalence design in which results observed with a biosimilar product are within a pre-established range in relation to those obtained with the reference product is recommended by both the FDA and the EMA to establish similarity in clinical efficacy for the biosimilar product versus the originator.[1,2] Both Australia (which adopted the EMA guidance) and Canada's regulatory agencies also indicated that an equivalence trial design is preferred. However, these agencies also stated that a noninferiority design may be considered if appropriately justified.

Although noninferiority trials are smaller in size than equivalence trials, these trials cannot exclude the possibility of an increased activity of the biosimilar product that may be associated with more adverse events or may suggest that the biosimilar agent should be considered as a bio-better product. Therefore, an equivalence design is more rigorous in demonstrating biosimilarity of a biosimilar versus the branded product. It is also worth noting that all nine global biosimilar adalimumab phase III studies in RA and PsO listed in table 1 use an equivalence design to demonstrate similarity in clinical efficacy.

When designing equivalence trials for biosimilars, statistical principles for designing equivalence studies as described in International Conference on Harmonisation (ICH) E9 and ICH E10 guidance documents should be followed.[63,64] One of the most challenging aspects in study design is defining the equivalence margin. It requires acceptance by regulators and can directly affect the sample size. The choice of the equivalence margin is specific to each indication, the primary end point (eg, PASI75 at week 16 for PsO or ACR20 at week 24 for RA), the placebo-adjusted response of the primary end point in historical trials, statistical considerations and clinical judgement. The lower 95 percent CI bound of the difference between the reference product and placebo usually determines the equivalence margin and hence the sample size needed for a biosimilar trial (the smaller the margin, the bigger the sample size). As discussed in section 1.11, the primary end points for biosimilar trials are derived from the primary end points or key secondary end points of the pivotal efficacy trials of the originator. The placebo-adjusted response using the chosen primary end point can therefore be obtained from a meta-analysis of these trials. On the basis of the analysis, the

equivalence range is usually selected by dividing the placebo-adjusted treatment difference by an arbitrary number (eg, 2).[62] The clinical relevance of the equivalence margin should also be considered, although it should be in context of the totality of data for the biosimilar as compared with the originator (see example below).

To date, no information is available in the public domain regarding the choice of equivalence margin for the global adalimumab biosimilar trials listed in table 1. An example is provided here using Remsima/Inflectra. In the pivotal phase III RA study for Remsima, a 15 percent equivalence margin for ACR20 at week 30 was selected.[8] This margin was agreed on by the study sponsor and the regulatory bodies (see European public assessment report [EPAR] of Remsima) and selected on the basis of a meta-analysis of historical data of Remicade, mainly on the results of the ATTRACT study that showed a treatment difference of 30 percent of ACR20 at week 30 between infliximab and placebo.[65] The equivalence margin (15 percent) was set at 50 percent of this treatment difference, thus ensuring that the response to the biosimilar product could not be ascribed to a placebo effect only. Interestingly, it was noted that "although the proposed margin of ±15 percent could be considered clinically relevant, it was accepted by the Committee for Medicinal Products for Human Use (CHMP) in the context of a biosimilarity exercise, since it is also based on physicochemical, biological, and PK comparisons" (EPAR of Remsima).[8] Therefore, in the context of designing biosimilar studies, as mandated by the EMA and FDA,[1,2] the definition and acceptance of an equivalence margin should be based on a comprehensive evaluation of the originator's clinical data, as well as on the totality of evidence of the comparability of the biosimilar product versus the originator (eg, including physicochemical, biological and PK characterization).

The same equivalence margin (15 percent) has been used also for the phase III comparative efficacy trial for Samsung Bioepis's infliximab biosimilar.[66] A similar approach and a 15 percent equivalence margin were used for the phase III study of the etanercept biosimilar SB4 developed by Samsung Bioepis.[67]

In addition to the equivalence margin, sample size estimation for these biosimilar studies is also affected by other assumptions/factors, for example, the level of α, the power and the dropout rate. The biosimilar infliximab trials discussed above used standard values to account for type I and II errors with a two-sided α level of 0.05 and 80 percent power. Both assumed a dropout rate of 20 percent.

The requirement by regulatory agencies to collect safety data from an adequate number of patients for an adequate period of time should also be taken into account when defining the overall size of the study.

As listed in table 1, the adalimumab biosimilar trials in RA with ACR20 response rate as the primary end point target approximately 500–600 patients overall for enrollment. These figures are consistent with the number of patients enrolled in the Remsima (N=606), SB2 (N=584) and SB4 (N=548) phase III RA studies. Provided that other assumptions are similar, it is likely that using ACR20 at week 24 as the primary end point, the equivalence margin of the global adalimumab biosimilar trials (table 1) is close to 15 percent. This may be reasonable considering that the placebo-adjusted response rate of adalimumab in combination with MTX is 33 to 52 percent from historical studies (table 4). Small differences in the sample size among these studies may be explained by the difference in assumptions (eg, dropout rate).

Of note, the adalimumab "biosimilar" recently approved for marketing in India (Exemptia) was evaluated in a clinical trial enrolling a total of 120 patients with RA from India who were randomized 1:1 to either Humira or investigational adalimumab (60 patients/treatment group). The primary end point was based on ACR20 response at week 12. An equivalence margin of 28.5 percent was used for statistical comparison, allowing for a much smaller sample size.[68] It remains to be seen whether regulatory agencies in other countries will request additional information (eg, a bigger study, global enrollment) before approving this biosimilar adalimumab.

A similar approach for the phase III biosimilar trial design was used for BOW015, a biosimilar infliximab approved for marketing in India. In this trial, a total of 189 patients with RA were randomized 2:1 to the biosimilar or the reference drug, respectively.[69] The equivalence margin of ACR20 response rate at week 16 was set at 23 percent. The sponsor has announced that a global clinical program of their biosimilar product will be initiated soon for the U.S. and Europe.

For biosimilar trials in psoriasis, unfortunately, published data on statistical assumptions are lacking. Looking at table 1, it is noted that the targeted enrollment for the four psoriasis trials of the adalimumab biosimilars (approximately 300–500 patients overall) tends to be lower than for the RA trials. This is consistent with the observation that the placebo-adjusted response of adalimumab is larger in psoriasis than in RA (table 4), which can support the choice of a larger equivalence margin and hence a smaller sample size.

Alternative Statistical Methods

Alternative statistical approaches may be considered for biosimilar trials that could show advantages in terms of the required sample size. For example, the sample size may vary if adaptive design features and interim analysis methods are employed, even considering issues of multiplicity which may be inherited by these design options.[70,71] A prospectively planned adaptive design based on either frequentist or Bayesian precepts allows for adaptations of trial design and/or statistical procedures after trial initiation without undermining the validity and integrity of the trial. Sample size, eligibility criteria, or even study end points may therefore be modified on the basis of interim analyses, making the study more flexible and adapted to its objectives. These more innovative, nontraditional statistical strategies might be considered but require discussion with regulators given the lack of precedents in biosimilar development and should employ extensive biostatistical simulations with the aim of improving the feasibility of the phase III biosimilar trial by reducing the study size.

Summary

Owing to the focus on demonstrating biosimilarity and not safety and efficacy de novo, a clinical study (or studies) to demonstrate therapeutic equivalence of a biosimilar versus a branded product presents peculiarities in terms of study design that deserve special attention.

Using adalimumab as an example, considerations important for designing the pivotal clinical trial of a biosimilar were provided in this report and are summarized below. These include:

- Choice of therapeutic indication and extrapolation of indication

- Study design
  - Targeted patient population (eg, disease activity, prior biological treatment)
  - Background therapy
  - Stratification factors
  - Transition design
  - Primary end point
  - Choice of equivalence versus noninferiority design
  - Defining equivalence margin

To ensure the successful clinical development of a biosimilar product, it is critically important to have early consultation with the regulatory agencies regarding the indication to pursue for the pivotal clinical efficacy trial and specific design elements for the study. It is also important to have ongoing consultation during the course of the development program to make adjustments in the light of available preclinical and clinical data, since the totality of the evidence will be used for regulatory approval.

Table 1

Summary of Global Phase III Clinical Efficacy Studies for Biosimilar Adalimumab*

Company	IMP	Indication	Study Start†	Status	Number of Patients	NCT and/or EudraCT Number
Amgen	ABP-501	PsO RA	2013 2013	Completed Completed	350 526	NCT01970488 NCT01970475
Boehringer Ingelheim	BI 695501	RA	2014	Recruiting	650	NCT02137226 2012-002945-40
Fuji Film Kyowa Kirin Biologics	FKB327	RA	2014	Recruiting	600	NCT02260791 2014-000109-11
Pfizer	PF-06410293	RA	2014	Recruiting	560	NCT02480153 2014-000352-29
Samsung Bioepis	SB5	RA	2014	Completed	490	NCT02167139 2013-005013-13
Sandoz/Novartis	GP2017	PsO	2013	Ongoing, not recruiting	448	NCT02016105 2013-000747-11
Biocon, Mylan Inc	MYL-1401A	PsO	2015	Recruiting	294	2014-003420-46
Coherus Biosciences	CHS-1420	PsO	2015	Recruiting	500	NCT02489227 2015-000632-15

*Studies included ongoing and completed global trials based on information from Citeline's Trialtrove as of 8 September 2015, and confirmed from clinicaltrials.gov (trials with the numbers starting with NCT) and/or the EU registry (trials with numbers starting with the year, eg, 2012), searched on 8 September 2015.

† If there is any difference in the start date from clinialtrials.gov versus the EU registry, the earlier date is included. EU, European Union; IMP, Investigational Medicinal Product; NCT, National Clinical Trial; PsO, plaque psoriasis; RA, rheumatoid arthritis.

Table 2

Key Study Design Elements for Adalimumab Biosimilar Studies in Rheumatoid Arthritis*

Company	Amgen	Boehringer Ingelheim	Fuji Film Kyowa Kirin Biologics	Pfizer	Samsung Bioepis
Drug	ABP-501	BI 695501	FKB327	PF-06410293	SB5
Disease activity	≥6 Swollen and ≥6 tender joints[†]. Acute reactant requirement not available	≥6 Swollen and ≥6 tender joints. Either ESR of >28 mm/h or CRP>1.0 mg/dL	≥6 Swollen and ≥6 tender joints. Either CRP ≥1.0 mg/dL	≥6 Swollen and ≥6 tender joints. hs-CRP ≥0.8 mg/dL	≥6 Swollen and ≥6 tender joints. Either ESR ≥28 mm/h or CRP ≥1.0 mg/dL
Previous biological therapy	Permitted (<2 agents)	Permitted (<2 agents)	Permitted (<2 agents)	Not permitted[‡]	Not permitted
MTX treatment	Required Stable dose of 7.5–25 mg/week	Required Stable dose of 15–25 mg/week[§]	Required Stable dose of 10–25 mg/week	Required Dose range not available	Required Stable dose of 10–25 mg/week
Transition design[¶]	At week 26, single-arm OLE with ABP-501	Transition from Humira to either Humira or BI695501 after week 24	Transition after week 24 in separate OLE with two arms, including Humira and FKB327. After week 52, all patients receive open-label FKB327	At week 26, Humira arm rerandomized to either Humira or PF-06410293. At week 52, all patients receive open-label PF-06410293**	Transition from Humira to either SB5 or Humira after week 24
Primary end point	ACR20 at week 24	Coprimary: ACR20 at week 24 and at week 12	ACR20 at week 24	ACR20 at week 12	ACR20 at week 24

* Unless specified otherwise, study design information is summarized on the basis of information from the clinicaltrial.gov or EU clinical trial registry (see table 1 for NCT or EudraCT number), searched on 8 September 2015. All studies included in table 2 have an equivalence design.

† From the 66/68 count system.

‡ No more than two doses of one biological therapy (other than adalimumab or a lymphocyte depleting therapy).

§ Dose may be as low as 10 mg per week if the patient is unable to tolerate a higher dose.

¶ Transition from the branded to the biosimilar product within the main study or in the OLE study.

** Study design information from the Peru clinical trial registry, based on a search of biosimilar adalimumab in Citeline's Trialtrove database on 8 September 2015. ACR20, 20 percent improvement in the American College of Rheumatology criteria; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; EU, European Union; hs-CRP, high-sensitivity CRP; MTX, methotrexate; OLE, open-label extension

Table 3

Key Study Design Elements for Adalimumab Biosimilar Studies in Plaque Psoriasis*

Company	Amgen	Sandoz/Novartis	Mylan	Coherus
Drug	ABP-501	BI 695501	FKB327	CHS-1420
Disease activity	PASI≥12; BSA≥10%; sPGA≥3	PASI≥12; BSA≥10%; GA≥3	PASI≥12; BSA≥10%; sPGA≥3	PASI≥12; BSA≥10%; sPGA≥3
Previous biological therapy	Permitted (<2 agents)	Permitted	Permitted[†]	Previous anti-TNFα not permitted[‡]
MTX treatment	Not permitted	Not permitted	Not permitted	Not permitted
Transition design[§]	At week 16, Humira arm rerandomized to either Humira or ABP-501	At week 16, Humira and GP2017 arms each rerandomized to Humira or GP2017	Not specified in the synopsis	At week 16, Humira arm rerandomized to either Humira or CHS-1420
Primary end point	Percent PASI improvement from baseline at week 16	PASI75 at week 16	PASI75 at week 16	PASI75 at week 12

* Study design information is summarized on the basis of information from the clinicaltrial.gov or EU clinical trial registry (see table 1 for NCT or EudraCT number), searched on 8 September 2015. All studies included in table 3 use an equivalence design.
[†] Previous adalimumab prohibited, while other biologics are not mentioned.
[‡] Previous anti-TNFα therapy is prohibited, while other biologics are not mentioned.
[§] In the main study or in the open-label extension study.

BSA, body surface area; EU, European Union; MTX, methotrexate; PASI75, 75 percent reduction in the Psoriasis Area and Severity Index score; sPGA, static physician's global assessment; TNF, tumor necrosis factor.

Table 4

Therapeutic Effects of Adalimumab in the Approved Indications in Adult Patients (FDA and EU Drug Label)

Indication	Study	Concomitant medications	Efficacy end point	Week	Adalimumab response rate (%)	Placebo response rate (%)	Placebo-adjusted response rate (%)
Rheumatoid arthritis*	Weinblett, et al[10]	MTX	ACR20	24	65	13	52
	van de Putte, et al[11]	None	ACR20 ACR20	26 24	46 63	19 30	27 33
	Keystone, et al[12]	MTX	ACR20	52	59	24	35
	Furst, et al[13]	None	ACR20	24	53	36	18
Psoriatic arthritis*	Mease, et al[13]	None	ACR20 ACR20	12 24	58 57	14 15	44 42
	Genovese, et al[15]	None	ACR20	12	39	16	23
Ankylosing spondylitis*	van der Heijde, et al[16]	None	ASAS20	12	58	21	37
Crohn's disease[†]	Hanauer, et al[17]	None	Clinical response[‡]	4	59	37	22
	Sandborn, et al[18]	None	Clinical response	4	52	34	18
	Colombel, et al[19]	None	Clinical response Clinical response	26 56	54 43	28 18	26 25
Ulcerative colitis[†§]	Reinisch, et al[20]	None	Clinical remission[¶]	8	18	9	9
	Sandborn, et al[21]	None	Clinical remission Clinical response**	8 52	17 30	9 18	8 12
Plaque psoriasis[†‡]	Menter, et al[22]	None	PASI75	16	71	7	64
	Saurat, et al[23]	None	PASI75	16	80	19	61

* Dosage of adalimumab for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: 40 mg every other week.

[†] Dosage of adalimumab for Crohn's Disease and Ulcerative Colitis: Initial dose (Day 1) is 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week.

[‡] Clinical response is defined as a decrease in the Crohn's Disease Activity Index ≥70.

[§] Ulcerative colitis is an approved indication for Humira in Europe by the EMA, but not in the U.S. by the FDA.

[¶] Clinical remission is defined as Mayo score ≤2 with no subscore >1.

** Clinical response is defined as a decrease from baseline in Mayo score ≥3 points and ≥30 percent plus a decrease in the RBS≥1 or an absolute RBS of 0 or 1.

[‡‡] Dosage of adalimumab for plaque psoriasis: initial dose is 80 mg, followed by 40 mg every other week starting one week after initial dose.

ACR20, 20 percent improvement in the American College of Rheumatology criteria; ASAS20, 20 percent improvement in the Assessments in Spondyloarthritis International Society score; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; MTX, methotrexate; PASI75, 75 percent reduction in the Psoriasis Area and Severity Index score; RBS, rectal bleeding subscore.

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