



Review

Case studies on clinical evaluation of biosimilar monoclonal antibody: Scientific considerations for regulatory approval



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ABSTRACT

The objective of this paper is to provide considerations based on comprehensive case studies important for regulatory evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) with a special emphasis on clinical aspects. Scientific principles from WHO Guidelines on SBPs were used as a basis for the exercise. Working groups consisted of regulators, manufacturers and academia. The following topics were discussed by the working groups: clinical criteria for biosimilarity, extrapolation approach and the overall regulatory decision making process.

In order to determine typical pitfalls in the design of a SBP clinical programme and evaluate the gap of knowledge, amongst different industry and regulatory stakeholders on the appraisal of the data arising from SBP clinical studies, we have presented two fictional but realistic clinical case studies. The first case consists of the fictional development programme for an infliximab SBP candidate. The second case describes clinical studies proposed for a fictional rituximab SBP candidate. In the first scenario a highly similar quality profile has been taken forward into clinical studies whereas there was an important residual difference in functional attributes for the rituximab SBP candidate.

These case studies were presented at the WHO implementation workshop for the WHO guidelines on evaluation of similar biotherapeutic products held in Seoul, Republic of Korea, in May 2014. The goal was to illustrate the interpretation of the clinical data arising from studies with SBP candidates and elicit knowledge gaps in clinical assessment. This paper reflects the outcome of the exercise and discussions held in Seoul and offers an analysis of the case studies as a learning opportunity on clinical development and evaluation of SBPs.

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1. Introduction

A demonstration of biosimilarity is based on a rigorous, comprehensive and step-wise characterization and comparison of the quality and functional attributes, safety and efficacy of a similar biotherapeutic product (SBP) and its reference biotherapeutic product (RBP). The ultimate and final stage of the comparability exercise is a clinical development programme which should be designed not only to reaffirm the conclusions on similarity but also to address residual uncertainties and differences observed

throughout quality characterization, as well as establishing the justification of potential extrapolation of the totality of the data to other indications in the label of the RBP.

Although the general framework around biosimilar clinical studies is laid out in World Health Organization (WHO), European Medicine Agency (EMA) and other guidelines, detailed discussions on the implementation of these principles in planning and execution of clinical studies have not yet been published. In order to determine typical pitfalls in the design of a SBP clinical programme and evaluate the gap of knowledge amongst different industry and regulatory stakeholders on the appraisal of the data arising from SBP clinical studies, we have presented two fictional but realistic clinical case studies.

The roadmap for development of the SBP candidate is driven by the robustness of comparative analytical studies using state-of-the-

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art orthogonal methods against its RBP. The risk-based approach is the cornerstone of a SBP development strategy. The scope, breadth and amount of nonclinical and clinical data are dictated by the extent of prior knowledge about the RBP and the magnitude of residual uncertainties and differences identified during quality development and product characterization.

At a minimum, pharmacokinetics/pharmacodynamics (PK/PD), efficacy, safety and immunogenicity data will need to be provided to support biosimilarity and extrapolation. In some circumstances, efficacy studies might be waived if sufficient evidence of the biosimilarity can be gained from PK/PD, nonclinical and quality data. However, other more extensive toxicology and/or clinical studies may be required, depending on prior knowledge or identified differences, especially in reference to the need to address residual uncertainties regarding biosimilarity.

Apart from well-known principles of selecting most homogeneous and sensitive clinical settings, numerous other factors should be accounted for in designing and executing a successful clinical development programme with a SBP candidate.

Specifically, in planning equivalence or non-inferiority studies with SBPs these factors can be grouped into several domains (Table 1).

From a scientific perspective, the presented case studies were focused around two first domains of factors and principally were determined by the degree of similarity achieved at the quality level. While the concept of the comparison at the quality level is well described in the WHO guidelines [1], the interpretation of residual uncertainties and differences observed through quality comparability and planning clinical studies with SBP candidates may pose unique challenges. To the knowledge of the authors, no detailed clinical assessment of biosimilarity including detailed interpretation of clinical development plan has been published up to now. The examples presented herein represent scenarios with a different degree of similarity established throughout structural and functional studies and resulting in different outcomes and challenges in interpretation of clinical data. In addition, WHO guidelines state “if

similarity between the SBP and the RBP has been convincingly demonstrated, and if the manufacturer can provide scientific justification for such extrapolation, the SBP may be approved for use in other clinical indications for which the RBP is used but which have not directly been tested in clinical trials”, but “how to” practically implement the principles into review or development practices of SBP might be a subject to call further assistance from WHO. These case studies were designed to focus attention on the planning of adequate clinical studies with SBP candidates and to bridge a gap in the understanding of the requirements and the assessment of clinical data as part of the multidisciplinary review of the SBP programme.

The intention was also to unravel further learning opportunities and create a training tool which is suitable for newcomers in the field. Both case studies are fictional but realistic and represent typical cases which can arise in the real life development of a SBP.

The first case consists of the fictional development programme for infliximab SBP candidate. The second case describes clinical studies proposed for a fictional rituximab SBP candidate. In the first scenario a highly similar quality profile has been taken forward into clinical studies whereas there was an important residual difference in functional attributes for a rituximab SBP candidate.

The Third WHO implementation workshop on similar bi-therapeutic products was held from 15 to 16 May 2014 in Seoul, Republic of Korea, and these two case studies were intentionally developed for the purpose of training for a better understanding of the principles laid down in the WHO guidelines. Around 65 participants from health authorities and industry organizations from 23 different countries, representative of all WHO regions joined the case study exercise. Their expertise covered the quality, nonclinical and clinical parts of the development and regulation of bi-therapeutic products. Individuals were assigned to different groups, which separately worked through the case study exercise. Subsequently, the outcome of each group was presented and discussed at the plenum with all participants.

2. Methodology

Two case studies were prepared for the WHO Implementation workshop in order to demonstrate the applicability of selected principles for clinical evaluation of SBPs outlined in WHO Guidelines [1].

For the purpose of addressing complexity of the clinical approval status, challenges in extrapolation and differences between development pathways, the examples of infliximab and rituximab SBP candidates were used. Both case studies were entirely fictional and the historical clinical data for the RBP products were extracted from EMA public assessment reports and the United States Food and Drug Administration (US FDA) review materials available on agencies websites. In addition, relevant data were extracted from the European Union (EU) and the United States of America (USA) RBP product labelling.

In order to practice the case studies through group discussions, participants were divided into eight groups with seven to eight persons per group. Distribution of the participants was arranged taking into account even distribution of WHO regions, regulators vs. manufacturers, gender ratio and expertise in quality vs. clinical study. Four questions were prepared for each case study and two questions were given to each group. This design allowed more time per question, as well as the focus of two groups on the same questions at the same time. All participants received the questions ten days before the workshop. Since groups consisted of participants with a different level of expertise for the selected topic, two facilitators per group were assigned to lead the group discussion and to present the outcomes on behalf of their group.

Table 1
Factors for consideration in planning pivotal studies with SBP products.

SBP attributes	<ul style="list-style-type: none"> - prior PK/PD target profile: linearity of dose-dependent response, expected non-target and target-mediated clearance and half-life; - results of nonclinical studies; - presence of quality and functional residual uncertainties and differences; - specific issues with extrapolation (e.g. rituximab in rheumatoid arthritis and oncology indications); - requirements for additional safety and immunogenicity surveillance.
Clinical setting attributes	<ul style="list-style-type: none"> - the dosing regimen; - route(s) of administration; - sensitivity and homogeneity; - prior historical data and experience with the RBP; - statistical considerations in sample size calculation; - statistical and clinical considerations in construction of equivalence/non-inferiority margin; - monotherapy or combination therapy and the choice of backbone regimen; - timing for primary endpoint evaluation; - current and evolving treatment paradigm.
Other factors (especially relevant to SBP industry stakeholders)	<ul style="list-style-type: none"> - operational feasibility and presence of sufficient patient pools; - attractiveness of the programme to patients and investigators; - adequacy of the programme for different regulatory authorities, ethical committees, payer and reimbursement bodies; - sustainability of the development in terms of projected market size and dynamics.

Table 2

Summary of RBP approved indications and therapeutic effect reported in pivotal registration studies.

Indication	Posology	Treatment effect
<p>Rheumatoid arthritis (RA) In combination with methotrexate (MTX), is indicated for the reduction of signs and symptoms as well as the improvement in physical function in: Adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including MTX, has been inadequate. Adult patients with severe, active and progressive disease not previously treated with MTX or other DMARDs. In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated.</p>	<p>In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.</p>	<p>ATTRACT Study: ACR20 Week 22: 20.4% MTX vs 52.3% IFX + MTX Δ31.9%; Week 30: 20% MTX vs 50% IFX + MTX Δ30%; Week 54 17% MTX vs 42% IFX + MTX Δ25%</p>
<p>Adult Crohn's disease Treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. Treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).</p>	<p>5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.</p>	<p>Induction study: Week 4 16% of placebo patients achieved a clinical response (decrease in CDAI \geq70 points) at Week 4 vs. 81% (22/27) of patients receiving 5 mg/kg REMICADE. Δ65%; 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission (CDAI<150) at Week 4. ACCENT 1 maintenance: Week 30 CDAI response: 27.3% placebo vs 51.3% in 5 mg/kg group Δ24%; Remission: 20.9% placebo vs 38.9% in 5 mg/kg group Δ18%; Week 54 CDAI response: 15.5% placebo vs 38.1% in 5 mg/kg group Δ22.6%; Remission: 13.6% placebo vs 28.3% in 5 mg/kg group Δ14.7%;</p>
<p>Ulcerative colitis Treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.</p>	<p>5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p>	<p>ACT I and ACT II studies: Week 8 Mayo response: 33.2% placebo vs 66.9% in 5 mg/kg group Δ33.7%; Remission: 10.2% placebo vs 36.4% in 5 mg/kg group Δ26.2%; Week 30 Mayo response: 27.9% placebo vs 49.6% in 5 mg/kg group Δ21.7%; Remission: 13.1% placebo vs 29.8% in 5 mg/kg group Δ16.7%</p>
<p>Ankylosing spondylitis Treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.</p>	<p>5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.</p>	<p>ASSERT study Week 2 ASAS20 response: 19% placebo vs 61% in 5 mg/kg group Δ42%; Week 24 ASAS20 response: 18% placebo vs 60% in 5 mg/kg group Δ42%;</p>
<p>Psoriatic arthritis Treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Should be administered in combination with methotrexate or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated. Remicade has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.</p>	<p>5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p>	<p>IMPACT 1 study Week 16 ACR20 response: 10% placebo vs 65% in 5 mg/kg group Δ55%; PASI scores: N/D IMPACT 2 study Week 24 ASR20 response: 16% placebo vs 54% in 5 mg/kg group Δ38%; PASI75: 1% placebo vs 60% Δ59%;</p>
<p>Psoriasis Treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.</p>	<p>5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p>	<p>EXPRESS I study Week 10 PASI75 response: 3% placebo vs 80% in 5 mg/kg group Δ77%; EXPRESS II study Week 10 PASI75 response: 2% placebo vs 70% in 3 mg/kg group Δ68%; 2% placebo vs 75% in 5 mg/kg group</p>

(continued on next page)

Table 2 (continued)

Indication	Posology	Treatment effect
<i>Paediatric Crohn's disease</i> Treatment of severe, active Crohn's disease, in children and adolescents aged 6–17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies.	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.	Δ 73%; <i>SPIRIT study</i> Week 10 PASI75 response: 6% placebo vs 72% in 3 mg/kg group Δ 66%; 6% placebo vs 88% in 5 mg/kg group Δ 82%; <i>REACH study</i> : All patients received an induction regimen of 5 mg/kg IFX. At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the Paediatric Crohn's Disease Activity Index PCDAI score of \geq 15 points and total PCDAI score of \leq 30 points), and 59% were in clinical remission (defined as PCDAI score of \leq 10 points).
<i>Paediatric ulcerative colitis</i> Treatment of severely active ulcerative colitis, in children and adolescents aged 6–17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.	All patients received an induction regimen of 5 mg/kg IFX. The proportion of patients in clinical response at week 8 was 73.3% and clinical remission at week 8 was 33.3% as measured by the Paediatric Ulcerative Colitis Activity Index (PUCAI) score (defined as a decrease from baseline in the PUCAI score by \geq 15 points for response and reduction of the total PUCAI score to \leq 10 points for remission)

Abbreviations: ACR20 – American College of Rheumatology definition of a 20% improvement; AS – ankylosing spondylitis; CDAI – Crohn's Disease Activity Index; 6-MP – mercaptopurine; MTX – methotrexate; PCDAI – Paediatric Crohn's Disease Activity Index; PASI – Psoriasis Area Severity Index; PUCAI – Paediatric Ulcerative Colitis Activity Index; PUVA – photochemotherapy with 8-methoxypsoralen in conjunction with high-intensity long-wave ultraviolet light; RA – rheumatoid arthritis; Δ – treatment effect difference.

3. Case study description

3.1. *Infliximab SBP case*

3.1.1. *Background information on the RBP*

The RBP infliximab (Remicade[®], Janssen Biologics B.V.) is approved in the USA, the EU and numerous global markets in several adult and paediatric indications and varying posologies [2]. The product has shown consistent effectiveness and considerable safety experience since its launch in 1999 [3]. Infliximab neutralizes the biological activity of TNF- α by binding with high affinity to the soluble and transmembrane forms of TNF- α , and inhibits or prevents the effective binding of TNF- α with its receptors.

3.1.2. *Background information on SBP*

Manufacturer A (Mfg A) is developing an infliximab SBP in accordance with a target product profile of the RBP of Remicade[®].

Mfg A has successfully completed all quality development steps and demonstrated indistinguishable target product profile across more than 50 different molecule and product attributes. The features of all Fab- and all Fc-related functional activities appeared to be highly similar with those of RBP, with almost no residual uncertainties found at the transition into clinical phase. It is also assumed, that a single-dose three-group parallel designed, randomized, double-blinded pharmacokinetic (PK) study in healthy volunteers has been completed with the 5 mg/kg dose. The study was aimed to determine PK equivalence between SBP and RBP approved in territories A and B. Several PK parameters such as the area under the curve: $AUC_{(0-t)}$; $AUC_{(0-\infty)}$ and C_{max} were shown to be equivalent in terms of 90% confidence intervals (CI) for all parameters being confined to 80–125% boundaries for all three-way comparisons. The PK of the SBP product appeared to be linear exactly as with the RBP. The proportions of human anti-chimeric antibodies (HACA)-positive subjects, adverse events (AEs), treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) across all three groups were balanced.

Mfg A is now preparing to enter the pivotal clinical phase and try to select the most optimal, sensitive and homogeneous

indication(s), patient population, dose and the study duration in order to demonstrate biosimilarity. It is desired that, based on a highly similar target product profile (TTP) of the SBP, an extrapolation approach will be applied from the main comparability setting. Table 2 briefly summarized the indications and posology and the treatment effect observed in clinical studies as referenced in the EMA EPAR and US FDA review summaries [4,5].

3.1.3. *Case scenario: part 1*

After an extensive review of the available prior clinical data on the efficacy and safety of the RBP and related products that work through the same or a similar mechanism, Mfg A decided to conduct a pivotal study in the rheumatoid arthritis (RA) indication at a dose of 3 mg/kg every 8 weeks following an initial loading period (0, 2 and 6 weeks). The proposed study will be carried out in patients with active RA who failed or are intolerant to prior DMARD therapies. The main reason for the choice of indication was a lowest approved dose of 3 mg/kg in RA patients and it was deemed more sensitive for the purpose of clinical comparability (not only from an efficacy, but also an immunogenicity viewpoint).

The primary endpoint for the study is equivalence of ACR20 with a 15% margin at week 24 (as per historical data and Δ 31.9%). Mfg A has also conducted a meta-analysis of historical data with RBP, in particular the ATTRACT trial, and showed that an equivalence margin of 15% will ensure superiority over placebo. No radiographic assessment of joint progression was carried out as advised by one of the key regulatory agencies, which recommended that demonstration of therapeutic equivalence will substitute the need for radiographic data.

A number of secondary efficacy endpoints (e.g. Disease activity score in 28 joints (DAS28), ACRn, ACR50, ACR70, quality of life (QoL)), PK (measurement of AUC_{ss} , C_{maxSS} ; C_{minSS} in a subset of patients) and pharmacodynamics (PD) markers (C-reactive protein (CRP), anti-cyclic citrullinated peptide antibodies (CCP), erythrocyte sedimentation rate (ESR), Rheumatoid factor (RF)), comprehensive evaluation of safety and immunogenicity were integrated into the protocol.

Based on the proposed margin and a power of 80%, the sample size was projected to be approximately 500 patients. This global study will involve recruitment of patients from all regions of the world. During this part of the scenario, participants were requested to discuss the primary indication for comparability and comment on the choice of the studied doses, indication, construction of the margin, power of the study, the choice of primary and secondary efficacy objectives and overall appropriateness of the study from efficacy and safety perspectives.

3.1.4. Case scenario: part 2

In the second part, there is a hypothetical situation that Mfg A has concluded the proposed pivotal RA study and the outline of the results has been shown. Demographic and other baseline characteristics were well balanced between treatment groups. Minimal discontinuations and protocol violations occurred and the conduct has complied with Good Clinical Practice (GCP). Top-line results were summarized in Table 3.

Participants were requested to discuss the results of the RA study summarized in Table 3 and provide an opinion on whether these data along with comprehensive CMC, nonclinical data and PK study in healthy volunteers will be sufficient to address regulatory requirements for SBP product approval. Further, questions were asked: (a) whether the RA indication will be sufficient for extrapolation of the entire RBP label given the highly similar TTP of the SBP infliximab candidate and (b) if RA data is insufficient to obtain full label approval, which indication(s) should be added into the clinical development plan and why. If participants wished to recommend an additional study, they were requested to elaborate on the study design and endpoints.

3.2. Rituximab SBP case

3.2.1. Background information on RBP

Rituximab was developed by Biogen Idec and is co-marketed by Genentech, Inc. and Biogen Idec in the United States as Rituxan[®], while in the EU, Roche markets rituximab as MabThera[®].

In the EU, RBP under the name of MabThera[®] it is currently approved for treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis (RA) and most recently new indications of active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA). Different posology has been recommended for different indications. Furthermore, a new subcutaneous formulation of MabThera[®] was approved in the NHL indication in 2014 (this formulation is not available in the USA). The dose regimen for different indications is considerably different, but the range of the approved indications and dose regimens for rituximab in the EU and USA are broadly similar [6–8].

3.2.2. Background information on the mode of action of RBP

Rituximab is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 145 kDa. Rituximab binds

specifically with high affinity to the CD20 surface antigen that is expressed selectively on B lymphocytes. Following binding to the CD20, rituximab is believed to exert its therapeutic effect by promoting B cell lysis. This proposed mechanism of rituximab action, supported by *in vitro* data, is based on the following three major immunological and cellular effects, which in combination result in the elimination of B cells, including malignant B cells [9–11]:

- complement-dependent cytotoxicity (CDC) through binding of C1qA;
- antibody-dependent cellular cytotoxicity (ADCC) through binding of FcγIII receptor-bearing effector cells to the Fc portion of rituximab;
- apoptosis and direct growth arrest postulated through CD20 clustering and migration to lipid rafts and/or cross-linking, resulting in intracellular signalling.

In the normal immune system, B cells are responsible for maintenance of cellular and humoral memory. The therapeutic benefits of selective destruction of malignant B cells in oncological indications are self-evident, however, as the various functions and attributes of B cells have been elucidated, so too has their role in RA: B cells form complexes with and become activated by, rheumatoid factors (RF) and in RA, disease activity generally correlates with increased numbers of RF-secreting cells [12]. Despite many remaining uncertainties, it is evident that RBP has a favourable therapeutic effect in both RA and NHL related indications.

3.2.3. Background information on the SBP

Manufacturer B (Mfg B) is developing a rituximab SBP in accordance with a target product profile of the RBP of MabThera/Rituxan[®] (Roche-Genentech).

It is hypothesized that Mfg B has successfully completed all CMC development steps and demonstrated indistinguishable target product profile across more than 50 different molecule and product attributes. The features of all Fab-related functional activities appeared to be highly similar with those of RBP, with almost no residual uncertainties found.

3.2.4. Case scenario

Whilst most of the functional attributes appeared to be comparable or in range with RBP derived from the EU and USA (accounting for time-related and regional RBP drifts) [13], one residual uncertainty has been identified throughout an iterative cycle of development. The proportion of variants with afucosylated Fc-region appeared to be 15–20% greater in the SBP compared to the RBP and this was linked to a proportional increase in ADCC activity. Mfg B believed that this difference is not of clinical relevance and decided to initiate the clinical development phase.

The proposed plan includes two studies: a therapeutic equivalence study in RA patients with primary endpoint for equivalence of ACR20 and one smaller PK/PD study in NHL patients on the

Table 3

Summary of the efficacy, safety and immunogenicity results from the pivotal RA study with the infliximab SBP candidate.

Endpoint	SBP	RBP
ACR20	55% SBP and 57% for RBP: Estimate of treatment difference: -0.02 ; 95%CI $(-0.10; 0.05)$	
ACR50	39%	41%
PK: AUC _{ss} , C _{maxSS} , C _{minSS}	All 90%CI contained within 80–125%	
PD: CRP, RF, anti-CCP; ESR	Comparable using descriptive statistics	
Safety	Comparable in terms of descriptive statistics for incidence of AEs, TEAEs, SAEs and events of special interest	
Immunogenicity	25% (including 90% of patients developing neutralizing HACA)	29% (including 88% of patients developing neutralizing HACA)

Table 4
A simplified outline of RA and NHL studies with rituximab SBP.

Study	Design	Patient population	Primary endpoint	Secondary endpoint	Margin/acceptable range	Sample size
RA	Double-blind randomized controlled therapeutic equivalence study. Dosing with 1000 mg IV infusion on Day 0 and Day 14, respectively. Second course is offered to eligible patients in safety long-term cohort.	Active RA patients DMARD and anti-TNF failures, excluded patients at risk of infections and congestive heart failure.	Equivalence of ACR20 at 24 weeks	Compare DAS28, ACR50, ACR70 Immunogeni-city, safety. In a subset of patients: PK equivalence for AUC_{0-t} , C_{maxSS} Time to B cell depletion, AUC for B cell depletion, time to recover of B cells Safety and immunogeni-city.	15% based on $\Delta = 33\%$ for 18% and 51% ACR20 response at week 24 in REFLEX trial [12].	Target population of approximately 500.
NHL	Double-blind RCT, PK/PD equivalence. Dosing with 375 mg/m ² body surface area per cycle (3 weekly), for up to 8 cycles (24 weeks).	Previously untreated and relapsed advanced follicular lymphoma on background of CHOP.	Equivalence of $AUC_{T(4)}$; C_{maxSS} at Cycle 4	AUC_{0-t} $C_{troughSS}$ AUC_{0-t} for B cell depletion Time to B cell recovery ORR at week 24 Safety and immunogeni-city.	Range of 70–133% as justified by high CV = 50%	Approximately 150 patients.

background of CHOP chemotherapy. The summary of study particulars is provided in Table 4.

Participants were requested to review proposed RA and NHL studies, identify some deficiencies and discuss whether these studies will be able to address residual uncertainties identified throughout the initial steps of rituximab SBP candidate development. Furthermore, their opinions were invited on whether the results from these two studies along with a comprehensive CMC and nonclinical data will be sufficient to satisfy regulatory requirements for SBP rituximab product approval and achieve extrapolation of the entire RBP label. Whether alternative studies are recommended and if this is the case, the participants were asked to elaborate on the design, patient population, duration and rationale of such studies.

4. Evaluation of the case studies and key discussion points

4.1. Infliximab SBP case

Various aspects of the clinical development programme including the design of the pivotal equivalence study in a RA patient population, selected endpoints, dose and immunogenicity were discussed.

4.1.1. Patient population and proposed doses

The fact that the initial clinical study in healthy volunteers was commenced with a single dose of 5 mg/kg in a three-way parallel group, randomized, double-blind PK study in healthy volunteers to compare SBP with RBP triggered, a number of questions regarding sensitivity to detect potential differences. Given that the RBP was studied and approved across several indications in three dose regimens (i.e., 3, 5 and 10 mg/kg) and at two schedules (every 6 weeks or every 8 weeks), in order to support a full label approval of SBP candidate, it was questioned whether the lowest dose of 3 mg/kg every 8 weeks following the loading dose was the most appropriate option. In particular, a dose of 5 mg/kg was considered as an alternative and potentially more representative dose regimen that would potentially allow extrapolation to other indications. Overall, the choice of RA indication and selecting the patients who failed or are intolerant to DMARD was considered appropriate from a homogeneity and sensitivity perspective and justified by the magnitude of the ACR20 difference observed in historical studies with the RBP. A single dose in healthy volunteers of 5 mg/kg was considered

useful but not sufficiently sensitive to address all concerns for extrapolation and an additional multiple-dose patient study in a separate indication was desired, despite that an undistinguishable CMC target product profile has been demonstrated through the structural and analytical comparability exercise. An alternative indication was suggested in patients with psoriasis or psoriatic arthritis due to the highest historically observed treatment difference and consequential assay sensitivity, whilst the inflammatory bowel disease (IBD) indications were regarded as highly heterogeneous and less sensitive to reliably detect differences in immunogenicity and safety due to the use of background immunomodulatory therapies. It was noted that the use of methotrexate in dermatological indications is less common but other immunosuppressive therapies such as cyclosporine and steroids are commonly employed and therefore, it is cannot be concluded that psoriasis or psoriatic arthritis could be the most sensitive from an immunogenicity perspective. Furthermore, the planning of studies in earlier monotherapy settings in psoriasis and psoriatic arthritis might be problematic from feasibility and standards of care perspectives as infliximab and other biological DMARDs are approved in patients with moderately to severe disease which is refractory to prior non-biological DMARDs. Therefore, from an immunogenicity perspective, there are limitations in all approved indications of the RBP.

4.1.2. Study endpoints

It was found that the endpoints were typical for the RA indication. The primary endpoint was found appropriate but an extensive range of secondary endpoints raised some questions regarding the evaluation of descriptive endpoints. It was found that the interpretation of the results for descriptive endpoints might be quite challenging, especially if not all secondary endpoints display consistent pattern.

4.1.3. Sample size and the choice of the margin

At least one group stated that the construction of the pre-specified equivalence margin is expected to be supported by a meta-analysis, carried out using well-controlled randomized historical clinical studies. The group also mentioned that the size of specified 15% margin should be supported not only using a statistical approach but also on grounds of clinical relevance and preserving at least 50% of the effect observed with the reference product. It was noted that 80% is the minimum power required for

the majority of clinical trials but a higher power is a preferred option which would allow minimizing the probability of a type II error. A higher power of the pivotal equivalence study closer to 90% rather than the proposed 80% was desired by some groups, provided it was feasible to conduct such a study.

4.1.4. Interpretation of clinical findings

Although most participants were reassured by the comparative efficacy, safety and immunogenicity data from the global pivotal RA study, concerns were raised regarding the interpretation of the immunogenicity and safety data from different regions in which the use of methotrexate is not universally employed. One of the comments from the group was related to difficulties in interpretation of the immunogenicity data from the RA study and clinical relevance of the numerical difference in proportions of HACA-positive and proportions of patients with neutralizing antibodies between SBP and RBP treatments. In addition, at least one group suggested that granting a therapeutic claim for delay in structural progression of RA would not be possible in the absence of relevant radiographic data from the pivotal study.

4.2. Rituximab SBP candidate

All participating groups expressed concerns and reservations about the adequacy of the proposed clinical development programme for the rituximab SBP candidate from the perspective of planned studies to address a residual uncertainty. Specific guidance was given that the residual uncertainty was of potentially clinically relevant impact and it should be further examined in the following two potential scenarios:

- (1) The clinical development plan could be amended in order to revise the proposed RA therapeutic equivalence study and position this study as a PK/PD equivalence study. The supportive PK equivalence study in advanced follicular lymphoma should be re-designed into a larger efficacy study exploring an impact of ADCC difference on clinically relevant outcomes.
- (2) The clinical development plan should be amended with a view to maintain an existing RA therapeutic equivalence study, whilst a supportive PK/PD equivalence study in the NHL indication should be carried out in patients who carry specific genetic polymorphism of Fc γ R [14]. The latter study was deemed to be a much more sensitive model in evaluating the effect of ADCC on PD and clinical response.

4.2.1. Patient population and proposed doses

All participants stated that a potential increase in ADCC consequential to a 15–20% increase in the proportion of afucosylated variants of 15–20% in SBP candidate may have an impact on efficacy and safety features. The prior experience with the recently approved anti-CD20 monoclonal antibody obinutuzumab with an Fc-region that has been enriched in bisected afucosylated variants allowed achieving an enhanced ADCC [15]. Clinically this has translated into a higher response rate, and an extended progression free survival in patients with chronic lymphocytic leukaemia. Whilst there were theoretical safety concerns, there was no apparent increase in risk of infections. Toxicities of obinutuzumab were similar to those of other anti-CD20 antibodies, although infusion-related reactions and neutropenia appeared to be more common. In the case of the development of another glyco-engineered anti-CD20 monoclonal antibody, ocrelizumab, the clinical development in RA patients was halted due to an elevated risk of serious infections potentially attributed to increased ADCC

[16,17] therefore, participants anonymously concluded that the pivotal RA will not be sufficiently sensitive to adequately resolve the impact of increased ADCC on efficacy, whilst further data in the NHL or CLL indication might be needed to address the effect on efficacy. On another hand, all groups noted that the RA indication is a more sensitive model for evaluation of immunogenicity, infusion related reactions and safety, whilst the study in lymphoma patients is unlikely to provide reliable discrimination of potential differences between the SBP candidate and RBP on the background of immunosuppressive CHOP chemotherapy. Therefore, the study in RA patients would serve as a more reliable source of comparative immunogenicity and safety data. Participants recommended conducting the study in NHL in monotherapy settings rather than with CHOP backbone regimen in order to increase the sensitivity of the study in detecting potential differences between the SBP candidate and the RBP.

4.2.2. Study endpoints

The groups recommended a step-wise clinical evaluation approach with careful and systematic evaluation of PK/PD, safety and immunogenicity data from ideally either an initial part of a cohort of RA study or through adequately planned interim analysis of the data. To increase the sensitivity of the PK comparison, AUC_{2nd-∞} was recommended as one of the co-primary PK endpoints. Some participants questioned the choice of ACR20 as a primary endpoint because it is a dichotomous categorical endpoint which may not be appropriate for the comparison. Instead, the use of DAS28 was recommended as a continuous and potentially more robust and sensitive endpoint than ACR20, provided that there is sufficient historical data to support the construction of the equivalence margin.

4.2.3. Sample size and the choice of the margin

The size of the proposed 15% equivalence margin was questioned in view of the observed residual uncertainty and the revised margin was suggested to be in line with respective changes in the overall programme, e.g. consideration of DAS28 as an alternative primary endpoint. Sample size in both studies would be subject to changes in line with the aforementioned alternative scenarios of clinical development proposed by the groups.

5. Lessons learnt during the case studies

Following on the introduction into each case study, the workshop participants were asked to review case study data with the focus on the following questions/issues:

- appropriateness of the overall clinical development programme and specifically pivotal efficacy study from a clinical bio-similarity perspective and for evaluating efficacy, immunogenicity and safety as well as suitability of specific points such as the choice of the study population, dosing regimen, construction of the equivalence/non-inferiority margin, sample size, primary and secondary objectives proposed by manufacturers A and B for development of fictional infliximab and rituximab SBP candidates, respectively;
- evaluation of the results of the infliximab SBP programme from perspectives whether the totality of the CMC, nonclinical data and results from two clinical studies satisfies the regulatory requirements for SBP licensure;
- review of the proposed clinical development plan for the rituximab SBP candidate in context of residual uncertainty identified throughout the CMC comparability phase and assessment of its adequacy in terms of WHO similarity requirements;

- in both case studies evaluate whether extrapolation of the entire RBP label on the basis available or proposed data will be both scientifically appropriate and feasible;
- if the extrapolation of the entire RBP label is not appropriate or possible, what additional study(ies) should be planned and what is their rationale? Participants were asked to propose a suitable study design (e.g., non-inferiority/equivalence) and elaborate on the study population, endpoints, tentative non-inferiority/equivalence margin and timing for the primary endpoint evaluation.

The application of the following principles from WHO guidelines on SBP [1] to the specific cases was the main theme of the discussion. A number of points discussed in that context are systematically described below.

Previous WHO implementation workshops revealed that the concept of a comparability exercise is not well understood in a number of developing countries [18,19]. Therefore, the starting point in the case study was recognition of the fact that “the comparability exercise is designed to show that the SBP has quality attributes that are highly similar to those of the RBP. To provide an integrated and comprehensive set of comparative data however, it must also include the nonclinical and clinical studies.” Discussion on that aspect was based on the assumption that the results of the quality assessment and nonclinical studies were in line with the expectations for demonstrated biosimilarity. One of the key lessons from the workshop was that the evaluation of biosimilarity requires a multi-disciplinary approach and the interpretation of clinical comparative data should be done in conjunction with comprehensive CMC and *in vitro* functional data. This emphasized the criticality of the finger-printing structural and functional comparability data in the overall assessment of residual uncertainties and their impact on the scope of proposed clinical studies. In given clinical scenarios the focus was made on the clinical particulars of proposed development programmes with two complex RBP products. The complexity of infliximab RBP is driven by the presence of multiple approved autoimmune indications associated with different dose regimens and different degree of therapeutic response. In relation to rituximab RBP, apart from complex posology, there are some potential differences between the mechanisms of action in RA and lymphoma-related indications that pose challenges to extrapolation.

In accordance with WHO guidelines and amongst considerations for the choice of RBP, there are several aspects of particular importance for the case studies discussed: (1) similarity of the RBP and the SBP at the quality level; (2) sameness of the dosage form and route of administration of the SBP as that of the RBP (although this does not require for all approved dose regimens to be studied in the SBP programme); (3) clinical studies should be designed to demonstrate comparable safety and efficacy of the SBP and the RBP and need to employ testing strategies that are sensitive enough to detect any relevant differences between the products; (4) selection of the margin should be justified both statistically and clinically and adequate evidence on magnitude of the effect size of the RBP derived from historical trials and the variability of the effect in terms both of the end-point chosen and of the population to be studied; (5) statistical analysis for both equivalence and non-inferiority designs is generally based on the use of two-sided confidence intervals (typically at the 95% level) for the difference between treatments; (6) scientific considerations for extrapolation approach (including relevance of efficacy, safety and immunogenicity findings); (7) focus on pre-authorization investigation of immunogenicity with particular care taken to ensure that immunogenicity is investigated in the patient population that carries the highest risk of an immune response and immune-related adverse events.

In line with the WHO guidelines and throughout the workshop several lessons were learned that identified knowledge gaps and the need for future training of national regulatory agencies (NRAs).

In the first case study, despite a seemingly undistinguishable analytical comparability profile between infliximab SBP candidate and RBP, the reservation of participants was primarily confined to the extent of clinical data and challenges in accepting a single study in overall sensitive and homogeneous RA patient population for the purpose of extrapolation towards the entire range of approved indications. This clearly illustrates that the decision making process around extrapolation can be influenced by background level of expertise and level of prior knowledge, amount of information available to NRAs, and overall risk- and uncertainty-averse regulatory approach. With some division of the opinions between groups, it was concluded that with some limitations clinical data with infliximab SBP candidate could be potentially sufficient to obtain an approval with full extrapolation. One group noted that a structural progression claim should not be granted in the absence of relevant radiographic data in a RA study. In opposite, the current line of recommendation from some major regulatory agencies is that such data are no longer required in scenarios when a therapeutic equivalence has been established and impact on structural progression can be then readily extrapolated from respective data with the RBP.

In addition, comments related to study power were made in disconnect with margin construction as these are two independent statistical issues. The study can be powered at 80% or greater power with the same pre-specified margin at 95% confidence intervals. The power of 80% is commonly employed by SBP and innovator developers at their own risk and certainly may increase the probability of trial failure or reduce the potential to address in satisfactory fashion the comparison of some secondary efficacy endpoints [20]. Invariably, the sample size of the pivotal study is also inherently linked to the size of the safety and immunogenicity database.

One of the comments from the group was related to difficulties in interpretation of the immunogenicity data from the RA study and the clinical relevance of the numerical difference in proportions of HACA-positive and proportions of patients with neutralizing antibodies between SBP and RBP treatments. It should be noted that the evaluation of immunogenicity is typically done in a descriptive manner and there is an expectation for some numerical differences and their clinical relevance needs to be assessed in terms of potential impact on efficacy and safety.

Since immunogenicity and safety considerations are crucial in the evaluation of SBP candidates [1] it is reasonable to expect that SBP developers should consider the needs for the extent of clinical evaluation, overall probability of trial success, as well as ethical, operational, cost and feasibility-related factors. Given limited pre-approval safety data, developers should establish a good pharmacovigilance system and risk management plan to continue safety monitoring of SBPs.

The difference in proportion of afucosylated forms in the rituximab SBP candidate was escalated as a feature that could potentially preclude the conclusion on similarity due to theoretically anticipated impact of increased ADCC on clinical efficacy and safety. Therefore, substantially larger clinical studies (e.g. efficacy study in lymphoma) or studies in more sensitive settings (e.g. lymphoma patients with specific genetic polymorphisms of FcγR) might be required. These revisions pose considerable challenges to SBP developer Mfg B in terms of operational, recruitment and cost burden and may as well translate into development delays. Crucially, there is a high probability that during planned studies clinically relevant efficacy and safety findings may preclude the candidate product to be considered as a SBP. In accordance with

WHO guidelines [1], in such a case, a stand-alone development rather than the SBP pathway will be more appropriate. The case illustrated that with complex scenarios such as rituximab, when an extrapolation approach is already challenging due to pathophysiological and clinical differences between B-cell depletion in a RA, CLL and NHL clinical settings, a prudent step-wise approach and highly similar target product profile established during CMC comparability exercise is desired in order to overcome potential development difficulties and minimize additional development and risk burden throughout clinical studies.

An intriguing hypothetical situation may arise if revised clinical studies in RA and NHL patients will not show any clinical differences in terms of PK, B-cell depletion, efficacy and safety. Such a scenario could illustrate on how clinical studies might be imperfect in terms of biosimilarity and/or that there is a degree of variability in ADCC which may not necessarily translate into obvious clinical findings. It should be noted that there are currently no published data on the degree of quantitative correlation between specific glyco-engineering manipulations of Fc-region and the level of ADCC and the magnitude of ADCC enhancement, following glyco-engineering manipulation in newly developed stand-alone products may considerably exceed the levels detected in the fictional candidate product described in the case study.

6. Conclusions and next steps

6.1. Conclusions

As illustrated in the previous workshop [21], a careful and step-wise development approach with SBP candidates is essential in undertaking a continuous assessment of risks and residual uncertainties arising from structural and functional comparability studies and resolving these uncertainties prior to making the “Go” decision for clinical studies. Since clinical comparability studies are inherently limited and imperfect in detecting the impact of even minor structural or functional differences, an effort should be made in increasing the study sensitivity and homogeneity in order to determine the extent of their clinical relevance.

During the latest workshop the participants were given an opportunity to learn that, apart from quality-related uncertainties, numerous other factors should be considered in designing clinical studies with SBP. Productive discussion in the groups and good will to understand different perspectives and viewpoints can assist with the constructive dialogue and decision making process. Both regulators and manufacturers contributed well to the discussion by raising some critical questions, sharing different opinions and making some proposals for improving the evaluation of the data with SBP monoclonal antibodies. The case studies provided a very good opportunity for translating divergent opinions into a consensus on the proposed regulatory decision driven by review of the clinical data with SBP. It was also apparent that there is a considerable gap in expertise in clinical evaluation of bi-therapeutic products including biosimilars at some NRAs and this led to a proposal for organizing regular training programmes for regulatory reviewers with case studies based on real data scenarios.

6.2. Proposals for the next steps

Presented case studies were simplified in comparison to real-world biosimilarity data packages with SBP candidates. Challenges identified in the interpretation of the clinical data with SBPs emphasize the need and importance of further training in evaluating SBP dossiers. Discussions have revealed a need for preparing a series of case studies for different levels of expertise, starting with a relatively simple scenario for addressing some basic principles and

then providing an advanced training programme for those who already have a good understanding of the basic principles and its application to various cases. In particular, better understanding of the critical elements from a clinical perspective, benefit-risk appraisal as well as statistical considerations in the context of clinical evaluation was identified as one of the greatest needs of regulators in developing countries. Future workshops would benefit from being strengthened with sufficient representation of experts with clinical and statistical expertise who may balance the groups and improve an overall learning experience.

Based on these outcomes and lessons, for future workshops, further plans were made to dedicate more time to case studies, appoint more facilitators from developing countries, divide participants based on clinical and quality expertise and provide sufficient background on relevant principles laid out in the guidelines. With respect to the contents of case studies, quality and clinical assessment of the SBP were practiced separately however, in reality, these two categories should be linked and the decision should be made on the totality of evidence. It would therefore, be more beneficial for a number of NRA's if in future workshops WHO could develop similar case studies spanning quality, nonclinical and clinical studies and mimicking real-life scenarios in evaluating SBP products.

7. Disclaimer

The information and data in these case studies are fictitious and do not represent products approved or under development. The scenarios of case studies are intended to outline evaluation principles in clinical study with biosimilar products. This article contains the views of the authors and does not necessarily represent the decisions or the stated policy of the World Health Organization.

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