Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1298-1304 | ISSN:2251-6727

Tofidence Biosimilar: A Promising Frontier

Kaveri G. Bhosale[1*],Chetan S. Nerkar[1*] Shruti S. sangamnere[2],Ruchika V.Ambekar[3],Rohit B. Lomate[1], Dimple D. Marathe[4]

[1]M Pharm, Department of Regulatory Affairs, Sanjivani College of Pharmaceutical Education and Research Kopargoan, Maharashtra, India 423601.

[2]M Pharm, Department of Pharmaceutics, MVG s College Panchavati Nashik, Maharashtra, India-422003.

[3]M Pharm, Department Pharmaceutical Quality Assurance at PRES's College of Pharmacy (for women) Chincholi, Nashik, Maharashtra, India- 422103

[4]Professor, Department of Drug Regulatory Affairs, Sanjivani College of Pharmaceutical Education and Research Kopargoan, Maharashtra, India-423601.

(Received: 07 January 2024 Revised: 12 February 2024 Accepted: 06 March 2024)

KEYWORDS

Rheumatoid arthritis, Tofidence, Tocilizumab, Regulatory Overview

ABSTRACT:

Tofidence, a biosimilar of Actemra (Tocilizumab), has been approved for use in the United States, offering new hope for individuals suffering from autoimmune disorders. The significance of Tofidence in addressing autoimmune diseases including rheumatoid arthritis. Tofidence is seen as a positive step toward enhancing access to advanced therapies for chronic autoimmune disorders, benefiting both patients and healthcare systems. Biogen's involvement in commercialization and licensing arrangements for Tofidence has been highlighted, further underlining the importance of biosimilars in expanding treatment options and improving affordability for patients with autoimmune diseases. Along with providing a review of regulations, this article also highlights the difficulties in developing biosimilars. The first biosimilar for the RA, the biosimilarity of bioequivalence and bioavailability research requirements are addressed by regulation. The successful adoption of biologics has the potential to reduce costs, which will benefit both patients and healthcare providers. We go over the available biologics, those that are being developed, and the difficulties that biosimilar producers are facing in this article.

Introduction: Rheumatoid arthritis (RA) is an autoimmune illness that affects 0.5–1% of people worldwide. It is the second most frequent kind of arthritis, after osteoarthritis [1]. This translates to about 400,000 individuals in the United Kingdom and 78 million people worldwide. Nearly 30% of patients still have untreated disease despite the wide range of medications available; this means that 23–25 million people are searching for alternative therapies. acknowledge this, hence there's a rivalry to take market share from biologics that are losing their Patents [2]. As the primary cause of work impairment, RA accounts for two-thirds of lost workdays yearly for its patients, costing the UK economy £1.8 billion in lost output [3]. Patients in the US are estimated to pay between $1300 and $3000 for every treatment, adding up to a total of $30,000 per year. The average yearly cost of RA treatment is significant. In the United Kingdom, the National Health Service (NHS) is anticipated to spend £560 million annually on RA [4]. A recent analysis estimates that the annual expenses of Medicare and privatised healthcare in the US will be $600 million and $306 million, respectively. Thus, RA indicates a substantial load on global healthcare systems [5]. Since pharmaceutical companies are aware of this, a race has arisen to capture market share from biologics that are no longer covered by patents. The number of potential biosimilars and biobetters for a variety of biologics available on the market.

1. Introduction

RA:

When anti-citrulinated protein antibodies and/or rheumatoid factor immune complexes are found in the synovium, they cause an inflammatory response by allowing leukocytes to infiltrate the synovial compartments. The production of chemokines by the synovial cells or the expression of adhesion molecules (such as selectins, integrins, and other microglobulins) in the synovial tiny vessels starts this process. These complexes either activate macrophage-like synovial cells through surface receptors or antigen-presenting cells via phagocytosis. Like synoviocytes, fibroblasts cause T-cells to release interleukins, TNFa, and other cytokines. This causes macrophages to become more stimulated, which sets off a chain reaction that results in an uncontrollable autoimmune response. Beyond presenting antigens, B-cells also play a part in the

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1298-1304 | ISSN:2251-6727

synthesis of antibodies (autoantibodies in rheumatoid arthritis) and the production of cytokines. B-cells also express cell surface proteins such as development markers (CD20 and CD22) and immunoglobulins. Larger immune complexes made of B-cell-produced autoantibodies further stimulate the Fc receptor and complement system, which in turn triggers the release of cytokines. More T, B, and macrophage activation results from elevated cytokine production. Because they generate a variety of significant cytokines, including interleukins (IL) and tumour necrosis factor (TNFa), macrophages have a role in osteoclastogenesis [6]. Because of its low cost, ease of administration, safety, and effectiveness, methotrexate, a csDMARD, is advised as the initial drug for patients diagnosed with rheumatoid arthritis (132 M. S. AKRAM ET AL). Most patients continue to be intolerant to methotrexate or stay resistant to it. The initial line of treatment in the scenario might be leflunomide or sulfasalazine. When initiating therapy, csDMARDS may be coupled with glucocorticoids; however, they should be reduced as soon as it is clinically appropriate[7].

2. Tocilizumab

Recombinant humanised IgG1 monoclonal antibody tocilizumab binds to membrane-bound (mIL-6Rs) and soluble (sIL-6) receptors (mIL-6Rs), blocking IL-6-mediated signalling via these receptors. IL-6 is a pleiotropic proinflammatory cytokine that is produced by different kinds of cells, namely T cells, B cells, monocytes, lymphocytes, & fibroblasts. In inflammatory joints, as those with rheumatoid arthritis, mucosal and vascular cells likewise primarily produce IL-6[8]. The initial two to three years of the course of the disease are often marked by an elevated risk of impairment in rheumatoid arthritis patients. According to Zeng et al. (2008), joint degeneration can escalate to 70% in three years for individuals who do not obtain prompt therapy. Tocilizumab and other comparable pharmaceutical therapies are therefore desperately needed. Furthermore, biosimilars must become readily available immediately in order to lower the cost of the medication for patients [9]. Inhibiting IL-6-mediated signal transduction via these receptors is how tocilizumab attaches to free and bound to membranes interleukin (IL)-6 receptors. Multipotent pro-inflammatory cytokine IL-6 is secreted by a range of cell types, including lymphocytes, monocytes, fibroblasts, and T and B cells. Inflammation in the joints, such as rheumatoid arthritis, is triggered by IL-6, which is also developed by cartilage cells and endothelial cells. Multi-joint juvenile idiopathic arthritis, giant cell arteritis, and rheumatoid arthritis can all be effectively treated with tocilizumab. Tocilizumab did not increase the survival rate of hospitalised COVID-19 pneumonia patients in a prior study, although it did lower the chance that they would move to the composite endpoint of ventilatory support or death. Although there have been conflicting preliminary data, tocilizumab is presently being studied as a possible COVID-19 therapy [10].

3. Tofidence :

Actemra (tocilizumab)'s biosimilar drug is called Tofidence. A healthcare professional may utilise tofidence (tocilizumab-bavi), an interleukin-6 (IL-6) receptor blocker, as an intravenous infusion to treat individuals who meet specific criteria for rheumatoid arthritis or polyarticular or systemic juvenile arthritis with idiopathic characteristics. A biosimilar is a biologic medication that shares similarities with the reference biologic (Actemra in this case) and for whose safety, purity, and efficacy have not changed in a clinically significant way. Since biosimilars are expensive to produce and are naturally variable due to their synthesis from live cells instead of chemicals, they are not categorised as "generic." Generic medications are less costly to produce and have the same active ingredients as their reference counterparts [11]. Why People with fairly to extremely severe rheumatoid arthritis in adulthood who have not responded well to one or more disease-modifying treatments may benefit from using Tofidence-Adjusting DMARDs, or anti-rheumatic drugs. Those with polyarticular juvenile idiopathic arthritis who are active and at least two years of age. Individuals with systemic juvenile idiopathic arthritis who are active and at least 24 months of age. A tocilizumab biosimilar called Tofidence was licenced for use in the US initially. According to clinical data, Tofidence is very similar to Actemra, as there aren't any clinically notable distinctions among the biosimilar and reference products. This information was used by the FDA to approve Tofidence. Tofidence is a biosimilar to Actemra but is not classified as interchangeable. Not every indication for which Actemra is approved also applies to Confidence. Actemra is licenced for identical conditions as Tofidence, as well as for the management of hospitalised adult COVID-19 patients, giant cell arteritis, cytokine release condition, and interstitial lung disease linked to systemic sclerosis. There is a Packaged Notice on the Tofidence product label about the higher risk of fatal infections. Tofidence is given intravenously over an hour. For polyarticular juvenile idiopathic arthritis and rheumatoid arthritis, every four weeks, and every 2 weeks for systemic juvenile idiopathic arthritis. Severe illnesses, GI (gut) perforations, hepatotoxicity, unexpected lab results, and hypersensitivity responses are among the risks and warnings linked with Tofidence. It is best to stay away from live vaccinations. the dose causes side effects like respiratory infection, headache, high blood pressure and elevated ALT [12]. Tofidence is a new biosimilar tocilizumab that has been authorised in the US. Biosimilars are biologic medicines with the potential to save costs and support more widespread and long-term access to medications. They are proven to have comparable safety and efficacy to the approved reference product. Over the last ten years, there has been a steady annual increase in spending of 10% to 25% on treatments for autoimmune diseases1. Since biosimilars were introduced into the US market, more patients have embraced these medications, accounting for over fifteen billion days of individual treatments. The U.S. clearance of Tofidence "marks another

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1298-1304 | ISSN:2251-6727

positive step towards enabling more individuals who suffer from chronic autoimmune disorders to obtain access to cutting-edge therapies," stated Ian Henshaw, Biogen's global head of biosimilars. We anticipate more sustainability and cost savings for healthcare systems, as well as greater patient and physician choice and access to biologics, as the number of approved biosimilars rises. A commercialization and licencing deal for Tofidence (BAT1806/BIIB800) was signed in April 2021 by Biogen and Bio-Thera. Biogen will market Tofidence in the US after it was developed by Bio-Thera. As per the agreement, Biogen holds the only rights to regulate, manufacture, and market Tofidence in every nation outside China, which includes Hong Kong, Macau, and Taiwan. Tofidence's potential launch schedule is being considered by Biogen in the US [13].Based on an extensive analytical, non-clinical, and clinical data package that Biogen provided to the FDA in September 2022, the FDA approved Tofidence. A comprehensive analytical assessment of Tofidence's physicochemical, biological, and structural characteristics was carried out, confirming its biosimilarity to the reference product. Furthermore, in a randomised double-blind, single-dose, three-arm, parallel phase I study, Tofidence's pharmacokinetics, safety, and immunogenicity were compared with both the EU and US reference tocilizumab in healthy volunteers. In a randomised double-blind, multi-dose, three-arm parallel phase III study, Tofidence was compared with tocilizumab to determine equivalent efficacy and comparable pharmacokinetic, safety, and immunogenicity profiles in participants with rheumatoid arthritis that was not adequately managed with methotrexate. The body of evidence proved that Tofidence is a biosimilar to the original biologic [14].

Study design: Phase 1 study:

In phase 1, the medicine is administered at varying dosages to about fifteen to thirty healthy human volunteers to ascertain the drug's risk profile. Phase 2 enrols no fewer than 200 participants for the optimal dose, and Phase 3 enrols up to 3,000 patients to increase medication efficacy and safety**.** The primary requirements for inclusion: 1) Men in good health, aged between 18 and 55; 2) BMI of 18.0–28.0 kg/m2; 3) a total mass of 55–85 kg; 4) Normal or clinically insignificant outcomes for routine blood and urine tests, along with hepatic and kidney function tests conducted at the time of registration; a total neutrophil number of ≥1.8 × 109 /L and several platelets of ≥125 × 109 /L. The research protocol has received approval from the ethical committee of the hospital. Local regulatory requirements were met, and the International Conference on Harmonization's Good Clinical Practice Guidelines and the Declaration of Helsinki were adhered to. Every research subject provided written informed permission. This three-arm, randomised, double-blind, single-dose, parallel trial examined the bioequivalency of the suggested biosimilar, BAT1806 (4 mg/kg), concerning Actemra-US and its reference products, which are sold in the US, in healthy Chinese men. Pharmacokinetics (PK), immunogenicity, and tolerance of the biosimilar and reference medicines were examined**.**

The following were the primary criteria for exclusion: 1) Having other clinically indicated conditions, such as digestive, renal, liver, neurological, haematological, hormonal, cancer, pulmonary, immunological, psychological, or cardiovascular disorders, or clinically noteworthy laboratory findings as described above; Patients with a history of 2) blood donation or participation in previous clinical trials within the last three months, and 3) positive results in the T-SPOT® tuberculosis (TB) interferon-γ-release assay, being near a TB patient, and/or presenting with suspected TB symptoms or signs during the same time frame[15].About 138 volunteers were randomly selected in a 1:1 ratio to receive a single Iv drip of BAT1806 and Actemra -US resp. with an interval of 5kg body weight randomization was used to assign each member of the predetermined weight interval evenly to one of the three treatment groups. All participants received a single intravenous infusion of the IP at the same dose (4 mg/kg) for 60 min (±6 min): BAT1806 (BioThera Solutions, Ltd.; [Roche (United States) and Actemra-US [Roche(United States) The screening was performed 7 days before the drug dosing date. The screened participants were admitted to the clinical research unit a day before the biosimilars were administered. The participants fasted for at least 8 h before the biosimilars were administered and were randomized into either the test drug (BAT1806) or the reference drug Actemra-US[16].

4. Statistical Analysis:

Descriptive statistics for the PK factors and demographics were estimated; the chi-square test for categorical variables, the t-test for normally distributed data, and the Wilcoxon rank test for data with unknown distribution were used for data analysis; all statistical analyses were conducted with SAS 9.4 (SAS Institute Inc., Cary, NC, USA). A p-value of <0.05 was considered significant. A PK evaluation set was used to perform PK analysis in the study population. The assessment of variance (ANOVA) model additionally included mass as a fixed factor to adjust for its effect on biological equivalents. The safety analysis set included participants who were administered the study drug[17].

Result:

Out of the 138 people who participated and were accounted for in the risk analysis, 129 received the assigned medicines. There were 46 people in the BAT1806 group in all. Six participants from the Actemra-US group and one participant from the BAT1806 group were removed from the trial before the drug's administration for various reasons, including hypertension, fast pulse, polycardia, or family issues or emergencies, which were deemed unrelated to the study drug**.** As soon as the infusion stopped, there was a swift drop in serum concentration, followed by a gradual phase of elimination and a little faster phase at lower concentrations. This pattern was shown in the typical sera concentration-time graphs for tocilizumab versus

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1298-1304 | ISSN:2251-6727

its biosimilar. The non-compartmental analytical model demonstrated lower Vz values, extended t1/2, and sluggish elimination for tocilizumab and its biosimilars. The three groups' median Tmax ratios were comparable two hours following intravenous administration. A range of 72.57 to 89.81 hours was seen in the estimated average geometric t1/2 values for tocilizumab across all treatments. Similarities existed between the three groups' Vz levels and total clearance rate (CL). Within a mere 10% difference, the three groups' projected AUC values were comparable. The inter-CVs and the mean concentration-time curve mean Cmax, AUC0–t, and AUC0–∞ estimations were comparable, with relatively low CV values (range: 14.5%–21.5%). n(18)The groups' PK characteristics were similar; the ratios of Cmax, AUC0–t, and AUC0–∞ for BAT1806 compared to Actemra-US were 90% Confidence Intervals (CIs) of 91.70–106.15%, indicating biosimilarity[18].There were no recorded deaths, serious adverse events (SAEs), or AE-related discontinuations. 93 participants (72.1%) reported treatment-related adverse events (TEAEs); of these, 27 (60.0%) and 32 (76.2%) were from the Actemra-US and BAT1806 groups, respectively. BAT1806 had less impact on "neutrophil count decreased" than reference products. Overall, one person reported taking an Actemra-US group medicine temporarily concurrently. Cefixime, fenofibrate, roxithromycin capsules, and acetaminophen pills were the medications used. This study found no connection between TEAEs and the development of ADA. Following IP delivery, none of the subjects experienced an injection-site reaction, anaphylaxis, or hypersensitivity that was clinically severe or serious. The IRB of The First Hospital of Jilin University received reports of every drug-induced adverse event. ADA-positive and -negative subjects' plasma concentration-time curves for BAT1806 and Actemra-US were comparable. The conclusions regarding the PK were comparable since the results for ADA-related sensitivities and the possible impact of ADA on PK analyses agreed with the results from the previously mentioned bioequivalence analysis set. This investigation was unable to confirm the immunogenic reactions to tocilizumab PK. The results above showed that tocilizumab and its biosimilar's PK were unaffected by ADA. We propose a more thorough investigation of the immunogenicity and efficiency of BAT1806 and Actemra in a subsequent phase III research with a bigger population, more doses, and a longer duration of treatment, even though there were no verified immune-stimulating effects of tocilizumab on medication safety and PK in this and previous investigations [19]. When given as an intravenous infusion at a dose of 4 mg/kg, this single-dose phase I trial proved to be bioequivalent to RoActemra-EU (and Actemra-US). The natural log-transformed data for each comparison fell within the predefined bioequivalence range of 80–125%, as revealed by an ANOVA compared of the Cmax as well as AUC values across all three treatment groups. The 90% CIs of the GMRs for each of these PK parameters were in the range of 86.90–106.15 percent. All treatment groups exhibited similarity in other PK metrics, including Tmax and t½. The safety and immunogenicity characteristics of BAT1806, RoActemra-EU, and Actemra-US were shown to be comparable. There were no SAEs, and all TEAEs associated to the treatment had mild to moderate severity. There were no local responses either. The three medications were tolerated well in this group of healthy volunteers, according to all these characteristics.

Phase 3 studies:

A biosimilar to tocilizumab (TCZ) is called BAT1806/BIIB800. A biosimilar development process included a Phase III randomised, double-blind, active-controlled clinical trial.
The study aimed to compare the safety, pharmacokinetics (PK), immunogenicity, and efficacy of BAT1806/BIIB800 with TCZ supplied from EU in individuals suffering from mild to serious rheumatoid arthritis who did not respond well to methotrexate (MTX).

Methodology:

The research was carried out from June 2018 to January 2021 at 55 locations in China and Europe. A 211:1 randomization process was used to place eligible patients in one of three treatment groups: (1) BAT1806/BIIB800 up to Week 48; (2) TCZ up to Week 48; or (3) TCZ up to Week 24, followed by BAT1806/BIIB800 from Week 24 to Week 48, which was given intravenously every four weeks at a dose of 8ng/kg. The percentage of participants who met the standards of various regulatory agencies (EMA, Week 12; FDA, Week 24) by achieving an ACR20 reaction at predetermined time points was the main outcome. Equivalence margins were pre-specified as follows: +/-14.5% for EMA (95% confidence interval (CI); -12.0%,15% for FDA (90% CI); and +/-13.6% for NMPA (95% CI) when applied to variations in ACR20 reaction rates in the BAT1806/BIIB800 and TCZ treatment categories. Pharmacokinetics, safety, and immunogenicity were examples of secondary outcomes. For the ACR20 evaluation, the ICH E9(R1) estimands framework was used, which includes intercurrent events that are either connected to or unrelated to COVID-19. Equivalency for the primary endpoint was evaluated using a logistic regression model that included "region" (China and Europe) and "previous biologic or targeted synthetic DMARD use" as stratification factors recorded in the Interactive Web Response System. For the primary endpoint, equivalency was evaluated by estimating the variance in response rates and deriving associated confidence ranges. Scores up to Week 24.

Result:

A total of 621 participants were randomly assigned to receive TCZ (N=155), BAT1806/BIIB800 (N=312), or TCZ after receiving BAT1806/BIIB800 (N=154). Age, gender, disease activity, and length of illness were among the initial demography and disease characteristics that were similar

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1298-1304 | ISSN:2251-6727

among the groups. In the BAT1806/BIIB800 versus the TCZ groups, the estimated percentages of individuals reaching an ACR20 response were 68.97% vs. 64.82% at Week 12 and 69.89% vs. 67.94% at Week 24. The predicted variation in ACR response rates was 1.94% (90% CI-4.04, 7.92; 95% CI-5.18, 9.07) at Week 24 and 4.15% (95% CI-3.63, 11.93) at Week 12. The pre-established equivalency margins encompassed the confidence intervals (CIs) for the estimated variations among the treatment groups. Serum trough levels, TEAE incidence, and ADA/NAb positive were similar throughout the therapy groups [20].

Conclusion:

Comparable tocilizumab in terms of effectiveness at Weeks 12 and 24, as well as PK, safety, and immunogenicity profiles, have been shown for BAT1806/BIIB800 up to Week 24. The first FDA-approved medication for Bio-Thera in the US is TOFIDENCE (BAT1806 / BIIB800), which is also the first biosimilar created and produced by a Chinese pharmaceutical company to be approved in the US. Multipurpose autoimmune inflammatory diseases such as rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis are treated with tocilizumab-bavi, a monoclonal antibody that binds to interlukin-6 receptors. The first biosimilar created and produced by a Chinese pharmaceutical business to receive FDA approval in the US is called TOFIDENCE (BAT1806 / BIIB800), which is also the first product from Bio-Thera to receive this approval. The monoclonal antibody tocilizumab-bavi binds to interlukin-6 receptors and is used to treat a variety of inflammatory autoimmune diseases, such as systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, and rheumatoid arthritis.

Regulatory overview on Biosimilars development:

The development of biosimilars has been urged to follow a phased approach by the US Food and Drug Administration (FDA), the European Medicines Agency, and the National Medical Products Administration (Agency, 2014). To compare similarities between biological functions, we start there. Following this, an assessment is conducted on the PK and PD features. Lastly, the same approved doses and methods as the reference product are used to evaluate clinical similarities, including effectiveness, safety, and immunogenicity.

The expense of cutting-edge medical treatments including genetic therapy, regenerative medicine (RM), and monoclonal antibodies (mAbs) is a challenge for healthcare systems around the globe. Though this hasn't happened yet, the biosimilar industry is expected to expand as the most well-known monoclonal antibodies in the world approach their patent expiration. The idea is to lower the cost of treating autoimmune diseases and cancer by using biosimilars. Because of greater manufacturing costs and therapeutic equivalency testing, the development expenses of biosimilars are far higher than those of their generic counterparts.

Since proteins have intricate structures that might cause variations in batch quality even in the original molecules, producing biosimilars faces several challenges. The primary one is this. Biologics Price Competition and the Innovation Act of 2009 acknowledge this fact, stating that a "biosimilar" product is one that is "highly similar" to the reference product, despite slight variations in clinically inactive components, and for which "there have no clinically significant distinctions among the biological product and the reference product with respect of the safety, purity, and effectiveness of the product." The FDA states that it "will probably evaluate petitions that attempt to demonstrate that biosimilar biologics are Diagram 3. The development pathways of originators and biosimilars are compared. (A) New originator molecules' development route. This is also probably the route that the biobetters will take. (B) The biosimilars' shortened route was taken. (C) Physicochemical properties that, in some cases, are crucial quality qualities and need to be monitored and characterised. (D) Eliminate process-related contaminants that must be eliminated from the finished batches. (E) Additional variables to take into account that could result in minor variances are crucial to take into account when assessing similarity[21]. Biosimilar to a biological product that is authorised as a "reference." Initially, 'analytic' evidence demonstrating the similarity between [company] substances and an innovator version approved by the FDA will be reviewed. Furthermore, the regulatory body will decide the amount of animal and clinical information needed for approval on a case-by-case basis.Similar to other novel chemicals or molecular entities (NCE/NME) development, the originators' work is centred on conducting clinical trials to assess safety and efficacy. On the other hand, since the therapeutic value of biosimilars has already been determined, thorough biologic characterisation and comparative analysis serve as a focal point [22]. Because the biosimilar depends on the original product's prior clinical studies, it is therefore exempt from the need to fully reevaluate its therapeutic benefit when it is highly comparable [23]. Because there would be no more information about the drug beyond what is already known about the original, it is therefore

appropriate to shorten the clinical path for biosimilars and skip phase II. In terms of both, this is a substantial savings [24]. Due to the intricate architectures of biomolecules, which can cause batch-to-batch differences even in the original molecules, the

primary problem facing producers of biosimilars is their intrinsic nature. A truth that the Innovation Act of 2009 and the Biologics Price Competition acknowledge is as follows: If the process of production results in any unfavourable modifications, the analytical techniques may need to be adjusted to account for the change. The producer should be capable of verifying that the methods and tests used to quantify and eliminate contaminants are still appropriate, for instance, if modifications result in an unusual contaminant profile of the

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1298-1304 | ISSN:2251-6727

host-cell proteins. An analysis of the pre-and post-change products' side-by-side analytical profiles that show consistency with respect to the chosen characterisation test and important quality parameters should be a part of the comparability exercise [25]. All contaminants associated with the process are managed in compliance with ICHQ6B. The ICH guidelines, in particular, Q2A Q2B and Q5C for stability testing, should be followed in the validation of these tests and methods.

Summary:

Biosimilars are biologic medicines designed to be highly similar to reference products with no clinically significant differences in safety, purity, and effectiveness. The development of biosimilars follows a phased approach, including analytical, pharmacokinetic, pharmacodynamic, and clinical assessments. The regulatory requirements for biosimilars aim to ensure patient safety and efficacy while reducing the cost of treatment. Overall, the development and approval of biosimilars like Tofidence offer a promising opportunity to provide effective treatments for autoimmune diseases like RA at a more affordable cost, potentially relieving the economic burden on healthcare systems and improving patient access to advanced therapies.

Table 1: Summary Table

Pk study	Tolerance study	Immunogenicity study	Sample size
A total of 2581 samples were tested 1. About 544 samples are below the limit of quantitation 2. 130 samples on day 0 3. 414 samples at other time points. Pk parameters were determined by using a non-compartmental analysis model. and internally validated software like Phoenix WinNonLIn v8.0	Evaluations, including physical examination, vital sign verification, electrocardiogram, and common laboratory investigations such as urinalysis and chemistry, were performed to monitor adverse events (AEs). The AEs were recorded and graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE; V.4.03)	Blood samples collected at 1 h before and on 15, 43, and 57 days after drug administration were analyzed for the presence of antidrug antibodies (ADAs) using an electrochemiluminescence immunoassay (ECLIA). ADA-positive samples were further examined for the presence of neutralizing antibodies	According to recent FDA guidelines, the ratio of the geometric mean (GMR) of Cmax and AUC for the test drug against the reference drug was set at 95% to obtain 92.8% power (1−β) at the significance level (two-sided α 5%). The inter-CV was represented by the coefficient of variation (CV). The NQuery 8.3.0.0 (Boston, USA) software was used to determine the sample size. The final sample size was 138 (46 participants/group) allowing for a 10% dropout rate

References:

1. Farid SS, Baron M, Stamatis C, Nie W, Coffman J. Benchmarking biopharmaceutical process development and manufacturing cost contributions to R&D. InMAbs Taylor & Francis 2020 Jan 1 (Vol. 12, No. 1, p. 1754999). Taylor & Francis.
2. Dan N, Setua S, Kashyap VK, Khan S, Jaggi M, Yallapu MM, Chauhan SC. Antibody-drug conjugates for cancer therapy: chemistry to clinical implications. Pharmaceuticals. 2018 Apr 9;11(2):32.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1298-1304 | ISSN:2251-6727

3. Neubauer S, Cifaldi M, Mittendorf T, Ganguli A, Wolff M, Zeidler J. Biologic TNF inhibiting agents for the treatment of rheumatoid arthritis: persistence and dosing patterns in Germany. Health Economics Review. 2014 Dec;4:1-1.
4. Pesu M, Laurence A, Kishore N, Zwillich SH, Chan G, O'Shea JJ. Therapeutic targeting of Janus kinases. Immunological reviews. 2008 Jun;223(1):132-42.
5. Zhang W, Anis AH. The economic burden of rheumatoid arthritis: beyond health care costs. Clinical rheumatology. 2011 Mar;30:25-32.
6. Landré-Beauvais AJ. The first description of rheumatoid arthritis. Unabridged text of the doctoral dissertation presented in 1800. Joint bone spine. 2001 Mar 1;68(2):130-43.
7. Jimenez-Boj E, Redlich K, Turk B, Hanslik-Schnabel B, Wanivenhaus A, Chott A, et al. Interaction between synovial inflammatory tissue and bone marrow in rheumatoid arthritis. The Journal of Immunology. 2005 Aug 15;175(4):2579-88.
8. Zhang H, Li X, Liu J, Li C, Wu M, Zhu X, et al. A randomized phase-I pharmacokinetic trial comparing the potential biosimilar tocilizumab (QX003S) with the reference product (Actemra®) in Chinese healthy subjects. Annals of Medicine. 2021 Jan 1;53(1):375-83.
9. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. New England Journal of Medicine. 2021 Jan 7;384(1):20-30.
10. Biggioggero M, Crotti C, Becciolini A, Favalli EG. Tocilizumab in the treatment of rheumatoid arthritis: an evidence-based review and patient selection. Drug design, development, and therapy. 2018 Dec 19:57-70.
11. Tofidence dosage use and warning,2oct 2023 https://www.drugs.com/tofidence.html
12. Tofidence (Tocilizumab-bavi)FDA approval History,2Oct 2023 https://www.drugs.com/history/tofidence.html
13. Association for Accessible Medicines. The U.S. Generic & Biosimilars Medicines Savings Report, September 2022. https://accessiblemeds.org/sites/default/files/2022-09/AAM-2022-Generic-Biosimilar-Medicines-Savings-Report.pdf Accessed August 2023
14. FDA clears Actemera Biosimilar Tofidence 9oct 2023https://www.drugs.com/newdrugs/fda-approves-tofidence-tocilizumab-bavi-biosimilar-actemra-6103.html
15. Schropp J, Khot A, Shah DK, Koch G. Target-mediated drug disposition model for bispecific antibodies: properties, approximation, and optimal dosing strategy. CPT: pharmacometrics & systems pharmacology. 2019 Mar;8(3):177-87.
16. Chinese Clinical Trial Registry, Registration No. CTR20180039; http://www.chinadrugtrials.org.cn/index. html; ClinicalTrials.gov, Registration No. NCT03606876; https://clinicaltrials.gov
17. Zhang H, Wang H, Wei H, Chen H, Liu J, Li C, et al. A phase I clinical study comparing the tolerance, immunogenicity, and pharmacokinetics of proposed biosimilar BAT1806 and reference tocilizumab in healthy Chinese men. Frontiers in Pharmacology. 2021 Jan 25;11:609522.
18. Zhang X, Georgy A, Rowell L. Pharmacokinetics and pharmacodynamics of tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, following single-dose administration by subcutaneous and intravenous routes to healthy subjects. International journal of clinical pharmacology and therapeutics. 2013 Jun 1;51(6):443-55.
19. Boyce EG, Rogan EL, Vyas D, Prasad N, Mai Y. Sarilumab: review of a second IL-6 receptor antagonist indicated for the treatment of rheumatoid arthritis. Annals of Pharmacotherapy. 2018 Aug;52(8):780-91.
20. Leng X, Leszczynski P, Jeka S, Liu S, Liu H, Miakisz M, et al. Pos0287 A Phase Iii, Randomised, Double-Blind, Active-Controlled Clinical Trial To Compare Bat1806/Biib800, A Proposed Tocilizumab Biosimilar, With Tocilizumab Reference Product In Subjects With Moderate To Severe Rheumatoid Arthritis With An Inadequate Response To Methotrexate Therapy.
21. Kogan LA. The US Biologics Price Competition and Innovation Act of 2009 triggers public debates, regulatory/policy risks, and international trade concerns. Global Trade and Customs Journal. 2011 Nov 1;6(11/12).
22. Alten R, Cronstein BN. Clinical trial development for biosimilars. In Seminars in Arthritis and Rheumatism 2015 Jun 1 (Vol. 44, No. 6, pp. S2-S8). WB Saunders.
23. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Narayanan G, et al. Biosimilars—why terminology matters. Nature biotechnology. 2011 Aug;29(8):690-3.
24. Akram MS, Pery N, Butler L, Shafiq MI, Batool N, Rehman MF, et al. Challenges for biosimilars: focus on rheumatoid arthritis. Critical reviews in biotechnology. 2021 Jan 2;41(1):121-53.
25. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. Jama. 2020 Mar 3;323(9):844-53.