

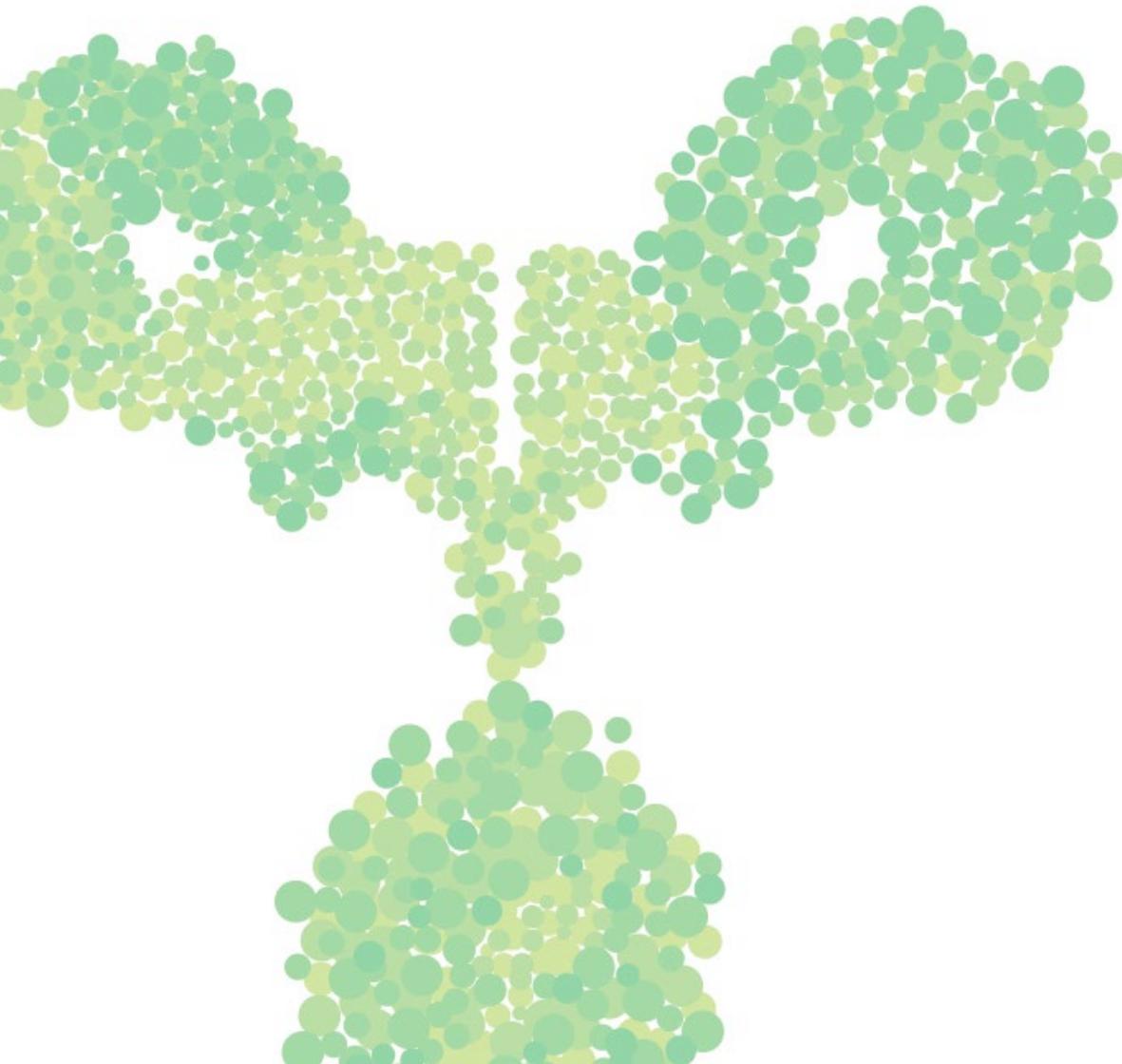


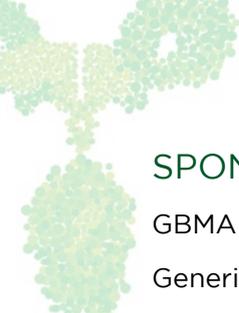
School of
Pharmacy and
Medical Sciences

International Biosimilar Medicines

Review of the Literature: Quarterly Update

April 2019 – June 2019





SPONSOR

GBMA Education

Generic and Biosimilar Medicines Association

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INTRODUCTION

This report provides an update to the comprehensive literature search previously conducted on behalf of the Department of Health. To inform activities related to GBMA Education's Biosimilar Education Grant, these reviews examine all international and Australian clinical, academic and policy journals in relation to biosimilar medicines.

The reviews are conducted with an emphasis on ensuring that the evidence is up-to-date in the following key topic areas:

- Comparability of biosimilar medicines to reference biological medicine, specifically in reference to substitution (including single switch and multiple switch scenarios), and extrapolation of indication
- Biosimilar medicine uptake related to prescribing and dispensing trends, particularly evidence relating to policies on biosimilar medicine use
- Health outcomes and adverse events of biological and biosimilar medicines from a pharmacovigilance perspective, and
- Current perceptions of biosimilar medicines (qualitative and quantitative evidence) relating to awareness, confidence, attitudes and acceptance.

The broad objectives for the review relate to four stages that influence biosimilar use; that is, the national and international regulatory environment that is the foundational determinant of biosimilar availability and associated switching and substitution; the subsequent uptake of biosimilar medicines by prescribers, pharmacists and participants; outcomes resulting from the use of biosimilar medicines outside of the clinical development pathway; and finally the stakeholder perceptions that influence uptake, including the factors that modify these perceptions such as advocacy and associated programmes. In reflection of this, the following central themes have been identified.

Determining Access and Subsidisation

This theme is based on the clinical development pathway of biosimilar medicines, including phase I studies through to the design and conduct of phase III clinical trials to provide evidence of similarity in clinical safety and efficacy in specific patient populations.

As a strong determinant informing policy relating to biosimilar access and use, this theme also examines the economic impact of the introduction of biosimilar medicines.

Biosimilar Medicine Uptake

This theme examines uptake, switching and substitution of biosimilar medicines, including the international status and a specific focus on policy changes involving prescribers, pharmacists and patients.

Health Outcomes and Adverse Events

This theme captures evidence related to pharmacovigilance activities required to detect adverse events and health outcomes with biosimilar medicines, specifically to determine the impact of substitution, switching and extrapolation of indication.

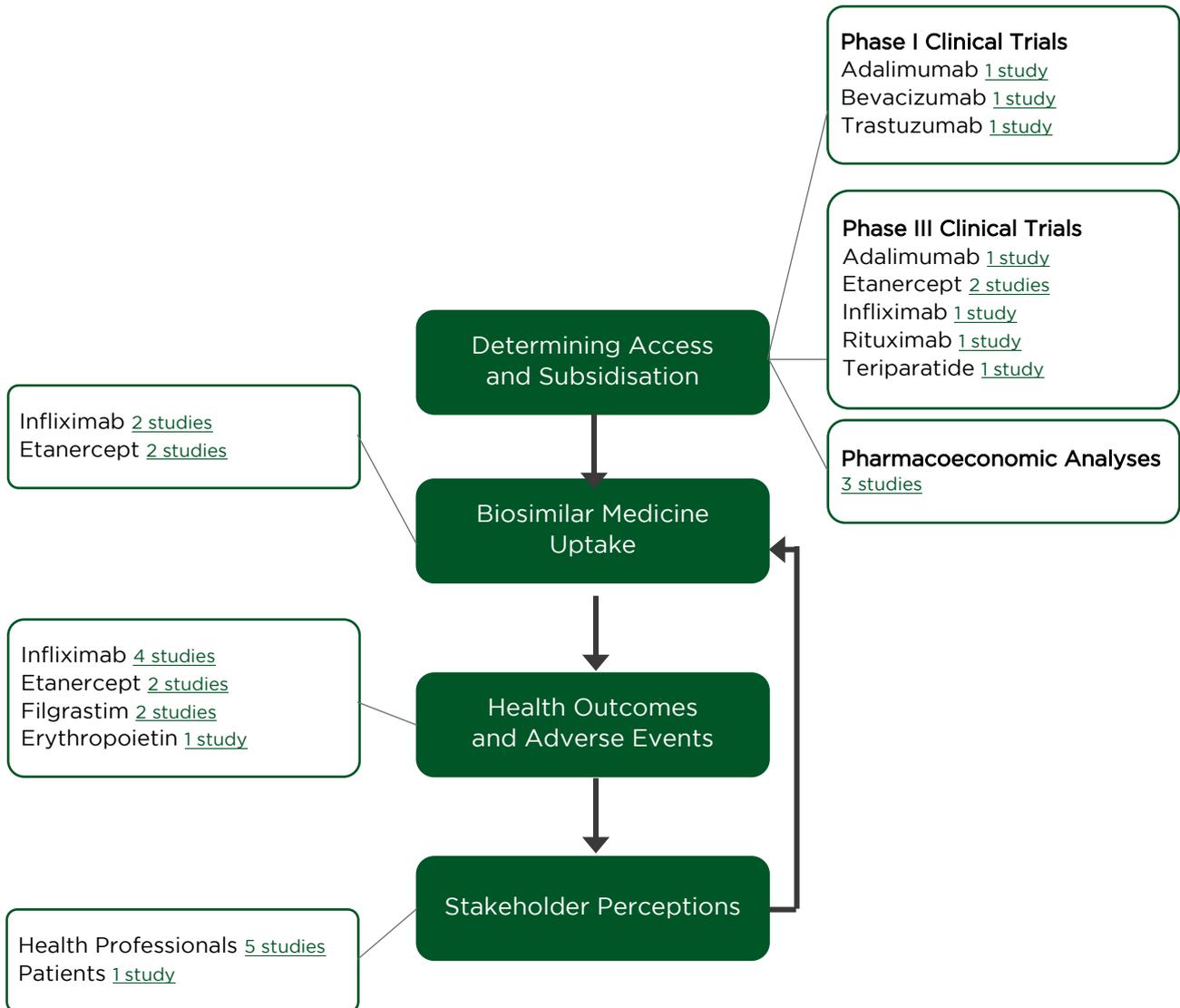
Stakeholder Perceptions

This theme encompasses the literature pertaining to evaluating and improving the awareness, confidence, attitudes and acceptance of biosimilar medicines by stakeholders, including literature that describes or evaluates any existing programs that aim to increase stakeholder understanding and confidence in biosimilar medicines.

OVERVIEW OF THE LITERATURE

This report includes literature published between 1 April 2019 and 30 June 2019.

The following figure summarises the literature reviewed in this update period (follow hyperlinks within diagram to corresponding study summaries).



Appendix 1: Educational/Review Articles
[44 manuscripts](#)

Appendix 2: Technical
[9 manuscripts](#)

DETERMINING ACCESS AND SUBSIDISATION

Phase I Clinical Trials

In the development and regulatory evaluation process of potential biosimilar medicines, compounds that demonstrate appropriate results in the extensive physicochemical and pharmacological characterisation are then subjected to clinical evaluation in phase I studies to compare their pharmacokinetic (PK) characteristics with those of the reference product. As these studies are specifically designed to assess pharmacokinetic endpoints these studies are typically conducted in healthy volunteers but may be conducted in participants depending upon a range of factors such as the potential risks associated with the use of the agent.

During the current update period, there were three papers that reported phase I pharmacokinetic studies comparing a potential biosimilar medicine with a reference product. In each of the trials reported, the potential biosimilar met the pre-specified acceptance criteria for the relevant pharmacokinetic/pharmacodynamic parameter endpoints. A summary of the results of these studies are presented in Table 1.

TABLE 1: Summary of phase I pharmacokinetic studies of potential biosimilar medicines

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
ADALIMUMAB						
GP2017 Study GP17-103	None	Inter-study comparison of GP2017 data between:	Healthy adult males (GP17-103 n=90; GP17-104 n=107)	90% CI of the ratio of geometric least square means for AUC _{0-last} , AUC ₀₋₃₆₀ , AUC _{0-inf} and C _{max}	The proportion of subjects who received GP2017 and tested positive for ADA was higher in study GP17-103 compared to study GP17-104 at each of the measured time points.	von Richter et al ¹
versus GP2017 Study GP17-104		GP17-103: Randomised, double-blind, two-arm, parallel, single-dose study GP17-104: Randomised, double-blind, three-arm, parallel, single-dose study		extended below the pre-defined equivalence interval of 80-125% for the comparisons of GP2017 administered in study GP17-103 or GP17-104.		
(NOTE: same batch of GP2017 used in two studies)						

REVIEWER COMMENTARY: It is important to note that the same batch of GP2017 was administered to subjects in the two studies, as such the differences observed are reflective of undefined inter-study variability, rather than biosimilar-related variability.

ADALIMUMAB

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
BEVACIZUMAB						
BAT1706	EU Avastin and US Avastin	Randomised, double-blind, three-arm, parallel, single-dose study	Healthy adult males (n=128, randomised 1:1:1)	90% CI of the ratio of geometric least square means for AUC _{0-last} , AUC _{0-inf} and C _{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of BAT1706 with either EU Avastin or US Avastin, and between EU Avastin and US Avastin.	No ADAs were detected at all time-points during the study.	Wu et al ²

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
TRASTUZUMAB						
PF-05280014 (combination with paclitaxel)	Herceptin (combination with paclitaxel)	Randomised, double-blind, two-arm, parallel, multiple-dose study	Patients with HER2-positive metastatic breast cancer (n=707, randomised 1:1)	Undertaking a population pharmacokinetic approach, similar estimated pharmacokinetic parameters, and parameter variability were obtained for PF-05280014 and Herceptin (CL 0.0104L/hr vs 0.00948L/HR; V _c 3.15L vs 3.10L; V _p 5.55L vs 5.66L, respectively).	Not reported.	Chen et al ³

Phase III Clinical Trials

Potential biosimilar medicines that demonstrate appropriate pharmacokinetic parameters in phase I studies are then subject to phase III clinical trials to evaluate efficacy and safety outcomes in comparison with the reference product. Within the update period there were six reports of phase III trials of potential biosimilars or additional reports related to biosimilars that have been approved in at least one jurisdiction. A number of manuscripts extend upon previous reports, including reporting on extension studies that incorporate switching.

ADALIMUMAB

Hercogová et al: AURIEL-PsO: A randomised, double-blind phase III equivalence trial to demonstrate the clinical similarity of the proposed biosimilar MSB110222 to reference adalimumab in patients with moderate-to-severe chronic plaque-type psoriasis⁴

SPONSOR: Merck, Fresenius Kabi

REFERENCE PRODUCT: Humira® (EU)

OBJECTIVE(S): To compare the efficacy, safety and immunogenicity of a proposed adalimumab biosimilar (MSB110222) with reference adalimumab in participants with moderate-to-severe chronic plaque-type psoriasis, including the impact of a single switch from reference product to biosimilar at week 16.

DESIGN: Multicentre, randomised, double-blind parallel group trial. At week 16 participants who achieved a 50% improvement in Psoriasis Area and Severity Index from baseline (PASI 50) were eligible to enter the extension period. Participants in the reference product arm were re-randomised to either continue reference product or switch to biosimilar adalimumab.

SAMPLE SIZE: 443 patients randomised at study commencement: MSB110222 = 222, reference adalimumab = 221; at Week 16, 214 participants (96.4%) continued MSB110222, 101 participants continued reference product and 101 switched from reference product to MSB110222.

PATIENT CHARACTERISTICS: Mean PASI at baseline = 20.6 (MSB110222) vs 21.2 (reference adalimumab), percent body surface area affected at baseline = 28.6% (MSB110222) vs 29.9% (reference adalimumab), previous non-adalimumab anti-TNF alpha biologic = 24 (MSB110222) vs 25 (reference adalimumab).

EQUIVALENCE CRITERIA: Containment of 95% confidence interval for the difference in Psoriasis Area and Severity Index (PASI) 75 response rates at Week 16 within the pre-specified equivalence interval of $\pm 18\%$.

RESULTS: The PASI 75 response rate at Week 16 was 89.7% in the MSB110222 group as compared with 91.6% in the reference product group equating to a difference of -1.9% with a 95%CI of -7.82% to 4.07% which was within the pre-specified equivalence criteria of $\pm 18\%$. Prior to week 16, 88.1% of participants in the MSB110222 group had at least one positive result for anti-drug antibodies as compared with 88.4% of participants in the reference adalimumab group. The PASI 50, 75 and 90 rates at weeks 24 and 52 were comparable between the groups that continued MSB110222, continued reference adalimumab and those that switched from reference adalimumab to MSB110222. From baseline through to week 52, anti-drug antibodies were detected at least once in 93.2% of participants that continued MSB110222 as compared with 92.1% of participants that continued reference adalimumab and 94.1% of participants that switched from reference adalimumab to MSB110222. There was no impact of anti-drug antibody status on PASI 75 response rate at Weeks 16, 24 and 52.

REVIEWER COMMENTARY: The reported high incidence (>90%) of participants in this study that were positive for anti-drug antibodies across all treatment groups is likely due to technological developments in anti-drug antibody assays that have increased sensitivity and reduced the interference of adalimumab present in samples.

ETANERCEPT

Jaworski et al: Switch from reference etanercept to SDZ ETN, an etanercept biosimilar, does not impact efficacy, safety, and immunogenicity of etanercept in patients with moderate-to-severe rheumatoid arthritis: 48-week results from the phase III, randomized, double-blind EQUIRA study⁵

SPONSOR: Hexal AG

REFERENCE PRODUCT: Enbrel® (EU)

OBJECTIVE(S): To describe the efficacy, safety and immunogenicity of continued long-term use of biosimilar etanercept (Erelzi®/GP2015) and of switching from reference product to Erelzi®/GP2015 in participants with moderate-to-severe, active rheumatoid arthritis.

This manuscript extends the previous report of the first 24-week double blind treatment period (TP1) comparing Erelzi®/GP2015 with reference product.*

DESIGN: Randomised, double-blind, two treatment period study. At week 24 participants receiving biosimilar etanercept (TP1) who achieved at least a moderate EULAR response, continued receiving biosimilar for a further 48 weeks (TP2). Participants receiving reference product who achieved at least a moderate EULAR response at week 24 (TP1) were switched to biosimilar etanercept (TP2).

SAMPLE SIZE: Of the 376 participants enrolled in the study, 341 entered TP2. Of these, 175 participants continued biosimilar etanercept and 166 switched from reference product to biosimilar etanercept.

PATIENT CHARACTERISTICS: At baseline of TP2 there were no clinically significant differences in swollen joint count, tender joint count, C-reactive protein, DAS28-CRP or HAQ-DI, consistent with primary end-point at the end of TP1 meeting the pre-specified equivalence criteria.

RESULTS: The least squares mean (SE) change in DAS28-CRP from baseline to week 48 in the group that continued biosimilar etanercept was – 2.90 (0.12) as compared with – 2.78 (0.130) in the group that switched from reference product to biosimilar. At week 48, ACR20, ACR50, and ACR70 response rates were 89.1%, 63.3%, and 36.7%, respectively, in the group that continued biosimilar as compared with 82.4%, 65.6%, and 42.0% in the group that switched from reference product to biosimilar. The ACR50 and ACR70 response rates were numerically higher at all TP2 time points in the group that switched from reference product to biosimilar, but these differences were not considered to be clinically significant. During TP2, none of the participants in the group that switched from reference product to biosimilar developed anti-drug antibodies as compared with four participants in the group that continued biosimilar, all of whom experienced a single event of very low titre, non-neutralizing anti-drug antibody detection. During TP2, injection site reactions occurred in six participants in the group that switched from reference product to biosimilar and in no participants in the group that continued biosimilar.

* Matucci-Cerinic M, Allanore Y, Kavanaugh A et al. Efficacy, safety and immunogenicity of GP2015, an etanercept biosimilar, compared with the reference etanercept in patients with moderate-to-severe rheumatoid arthritis: 24-week results from the comparative phase III, randomised, double-blind EQUIRA study. RMD Open 2018; 4: e000757.

Park et al: Long-term efficacy, safety and immunogenicity in patients with rheumatoid arthritis continuing on an etanercept biosimilar (LBEC0101) or switching from reference etanercept to LBEC0101: an open-label extension of a phase III multicentre, randomised, double-blind, parallel-group study⁵

SPONSOR: LG Chem, Mochida Pharmaceutical Co. and Korea Health Industry Development Institute

REFERENCE PRODUCT: Enbrel®

OBJECTIVE(S): To describe the long-term efficacy, safety and immunogenicity of treatment with biosimilar etanercept (LBEC0101) in patients with rheumatoid arthritis who continued therapy with biosimilar etanercept or were switched from the reference product to biosimilar following 52 weeks of treatment in the double-blind treatment period.[†]

DESIGN: A multicentre, single-arm, open-label extension study of a phase III multicentre, randomised, double-blind, parallel-group study. The open label extension study was only available to Korean participants.

SAMPLE SIZE: Of the 156 Korean participants that completed the randomised double-blind part of the study, 148 participated in the extension study with 69 participants continuing biosimilar etanercept in the open-label period and 78 switching from reference product to biosimilar etanercept. One patient in the maintenance group failed to complete the post-week 52 DAS28-ESR.

PATIENT CHARACTERISTICS: At baseline of open label treatment there were no clinically significant differences in swollen joint count, tender joint count, C-reactive protein, DAS28-ESR, HAQ-DI, consistent with the attainment of the pre-specified equivalence criteria of the double-blind treatment period.

RESULTS: Least squares mean change in the DAS28-ESR from week 52 (baseline of the open label period) to week 100 was – 0.052 (95% CI: – 0.314 to 0.210) in the group that continued biosimilar etanercept as compared with – 0.149 (95%CI: - 0.417 to 0.119) in the group that switched from reference product to biosimilar, equating to a difference between the groups of – 0.097 (95%CI: – 0.200 to 0.393). There were no statistically significant differences in ACR20, ACR50 and ACR70 response rates between the group that continued biosimilar etanercept and the group that switched from reference product to biosimilar. During the open label period, 10 injection site reactions occurred in five participants in the group that switched from reference product to biosimilar as compared with a single reaction in one participant in the group that continued biosimilar and one participant in each group had a new positive anti-drug antibody result.

[†] Matsuno H, Tomomitsu M, Hagino A et al. Phase III, multicentre, double-blind, randomised, parallel-group study to evaluate the similarities between LBEC0101 and etanercept reference product in terms of efficacy and safety in patients with active rheumatoid arthritis inadequately responding to methotrexate. *Ann Rheum Dis* 2018; 77: 488-94.

INFLIXIMAB

Alten et al: Randomised, double-blind, phase III study comparing the infliximab biosimilar, PF-06438179/GP1111, with reference infliximab: efficacy, safety and immunogenicity from week 30 to week 54[‡]

SPONSOR: Sandoz and Pfizer

REFERENCE PRODUCT: Remicade®(EU)

OBJECTIVE(S): To describe the efficacy, safety and immunogenicity of continued long-term use of biosimilar infliximab (PF-06438179/GP1111) and of switching from reference product to PF-06438179/GP1111 in participants with moderate-to-severe, active rheumatoid arthritis.

This manuscript extends the previous report of the first 30-week double blind treatment period (TP1) comparing PF-06438179/GP1111 with reference product.[‡]

DESIGN: Randomised, double-blind, parallel-group, three treatment period study. At week 30 participants receiving biosimilar infliximab in TP1 continued to receive biosimilar infliximab in treatment period 2 (TP2) whilst those receiving reference product in TP1 were re-randomised (1:1) to biosimilar infliximab or reference product for a further 24 weeks for TP2.

SAMPLE SIZE: Of the 650 participants enrolled in the study 566 completed TP1 and entered TP2. Of these, 280 participants continued biosimilar infliximab and 286 participants were re-randomized to either continue reference product (n=143) or to switch from reference product to biosimilar infliximab (n=143).

PATIENT CHARACTERISTICS: At baseline of TP2 there were no clinically significant differences in swollen joint count, tender joint count, C-reactive protein, DAS28-CRP, HAQ-DI or concomitant methotrexate dose.

RESULTS: At week 54, the mean DAS28-CRP values were 3.4 in the group that continued biosimilar infliximab as compared with 3.6 in the group that continued reference product and 3.6 in the group that switched from reference product to biosimilar. The ACR20/50/70 response rates remained comparable between the three treatment groups at all time points in TP2. Anti-drug antibodies were detected in 52.1% of participants that continued biosimilar infliximab as compared with 60.1% of participants in the group that continued reference product and 58.0% of those that switched from reference product to biosimilar. A total of 45 participants who were negative for anti-drug antibodies at the end of TP1 developed anti-drug antibodies during TP2, of whom one participant in the group that continued reference product in TP2 experienced an infusion related reaction after testing positive for anti-drug antibodies. The retention rate in TP2 was 89.4%, as compared with 87.2% in TP1, and was “*comparable across treatment groups in TP2*”.

[‡] Cohen SB, Alten R, Kameda H et al. A randomized controlled trial comparing PF-06438179/GP1111 (an infliximab biosimilar) and infliximab reference product for treatment of moderate to severe active rheumatoid arthritis despite methotrexate therapy. *Arthritis Res Ther* 2018; 20: 155.

RITUXIMAB

Shim et al: Efficacy and safety of switching from rituximab to biosimilar CT-P10 in rheumatoid arthritis: 72-week data from a randomized Phase 3 trial⁷

SPONSOR: Celltrion Inc.

REFERENCE PRODUCT: Mabthera® (EU), Rituxan® (US)

OBJECTIVE(S): To investigate long-term clinical outcomes in participants with rheumatoid arthritis (RA) of extended treatment for up to 72 weeks with biosimilar rituximab (CT-P10) as compared with reference product, including a single switch from reference product to biosimilar.

DESIGN: Randomized, double-blind, active-controlled, parallel-group phase III study.

SAMPLE SIZE: Prior to the extension phase reported in this manuscript a second treatment course was administered to 140 participants in the CT-P10 arm, 134 participants in the US-reference product arm and 56 participants in the EU-reference product arm.[§] Of these participants, 122 continued treatment with CT-P10, 64 participants continued US-reference product, 62 participants switched from US-reference product to CT-P10 and 47 switched from EU-reference product to CT-P10.

PATIENT CHARACTERISTICS: There were no significant differences in measures such as DAS-28ESR, DAS28-CRP and HAQ-DI at the baseline of the extension period (week 48). Anti-drug antibodies were detected prior to the switch in 15 (12.3%) participants in the group that continued CT-P10, 9 (14.1%) participants in the group that continued US-reference product, 13 (21.0%) participants in the group that switched from US-reference product to CT-P10 and 10 (21.3%) participant in the group that switched from EU-reference to CT-P10.

RESULTS: At week 72, the mean change in DAS28-CRP from baseline was -3.0 in the group that continued CTP-10 as compared with -3.0 in the group that continued US-reference product, -2.9 in the group that switched from US-reference product to CT-P10 and -3.0 in the group that switched from EU-reference product to CT-P10. Disease worsening occurred in five (4.2%) participants in the group that continued CT-P10, two (3.1%) participants in the group that continued US-reference product, two (3.3%) participants in the group that switched from US-reference product to CT-P10 and in one (2.1%) participant in the group that switched from EU-reference to CT-P10. At week 72, anti-drug antibodies were detected in five (4.1%) participants in the group that continued CT-P10, two (3.1%) participants in the group that continued US-reference product, eight (12.9%) participants in the group that switched from US-reference product to CT-P10 and three (6.4%) participant in the group that switched from EU-reference to CT-P10. Of these, two participants had new positive anti-drug antibodies results during the extension phase; one participant that continued US-reference product and one participant that switched from US-reference product to CT-P10.

[§] Suh CH, Yoo DH, Berrocal Kasay A et al. Long-Term Efficacy and Safety of Biosimilar CT-P10 Versus Innovator Rituximab in Rheumatoid Arthritis: 48-Week Results from a Randomized Phase III Trial. *BioDrugs* 2019; 33: 79-91.

TERIPARATIDE

Hagino et al: A multicenter, randomized, rater-blinded, parallel-group, phase 3 study to compare the efficacy, safety, and immunogenicity of biosimilar RGB-10 and reference once-daily teriparatide in patients with osteoporosis⁸

SPONSOR: Mochida Pharmaceutical Co., Ltd

REFERENCE PRODUCT: Forteo®

OBJECTIVE(S): To evaluate equivalence in efficacy and compare safety between a proposed biosimilar teriparatide (RGB-10) and reference teriparatide over 52-weeks of treatment in participants with osteoporosis at high risk of fracture.

DESIGN: Multicentre, randomized, active comparator-controlled, rater-blinded, parallel-group.

SAMPLE SIZE: 250 participants randomised 1:1; 219 participants completed 52-week treatment period: RGB-10 = 107, reference product = 112.

PATIENT CHARACTERISTICS: Participants mean age = 70.5 years (RGB-10) vs 70.3 years (reference teriparatide), all participants were Japanese, percent with prior bisphosphonate treatment: 4.8% (RGB-10) vs 4% (reference teriparatide); baseline lumbar spine (L2-L4) bone mineral density (g/cm²) = 0.6276 (RGB-10) vs 0.6273 (reference teriparatide); percent with no prevalent vertebral fracture at baseline = 61.6% (RGB-10) vs 70.4% (reference teriparatide).

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval (CI) for the least squares mean difference between groups in the percent change in lumbar spine (L2-L4) bone mineral density from baseline to 52 weeks.

RESULTS: The mean percent change in lumbar spine (L2-L4) bone mineral density from baseline to 52 weeks was 8.94% (\pm 6.19%) in the RGB-10 group as compared with 9.65% (\pm 6.22%) in the reference product group equating to a difference of - 0.65% with 95%CI of - 2.17% to 0.87% which was within the pre-specified equivalence criteria of \pm 2.8%. The incidence of new vertebral fractures was 0.9% (1/117 patients) in the RGB-10 group as compared with 0.8% (1/124) in the reference product group whilst non-vertebral fractures occurred in 2.4% (3/125) and 1.6% (2/125) of patients, respectively. Hypercalcaemia occurred in a single participant in the RGB-10 group and in no participants in the reference product group. A single participant in the reference product group and none in the RGB-10 group developed anti-drug antibodies.

REVIEWER COMMENTARY: Due to differences in the appearance of the injection device between the RGB-10 and reference product, participants were not blinded to the treatment group. However, the name of the injection device was masked, and participants were not specifically informed of which group they had been allocated to. Assessment of response, including L2-L4 bone mineral density, was undertaken by a central blinded facility.

Pharmacoeconomic Analyses

Once biosimilarity of potential biosimilars against the reference product has been established through phase I and III trials, it is the national and international regulatory environment that is the foundational determinant of use. Within this quarterly update period, three publications were identified that examined the economic impact of the introduction of biosimilars

Lee et al: Budget impact of switching to biosimilar trastuzumab (CT-P6) for the treatment of breast cancer and gastric cancer in 28 European countries⁹

SPONSOR: Celltrion Healthcare Co., Ltd (partial funding)

LOCATION(S): European Union

DATES: Based on 2018 drug cost

DESIGN: A budget impact model was developed to estimate changes in drug costs associated with switching from originator to biosimilar trastuzumab over a 5-year period. The model assumed the cost of the originator to be the country-specific price in 2018, and the biosimilar to be 70% of originator in 26 EU countries, and 85% and 52% of the cost of the originator in the Czech Republic and Austria respectively. The switching rate was assumed to be 20% in the first year, with an annual growth in the switching rate of 5%. The number of patients treated were explored using two methods, based on epidemiological data and sales volume data.

OBJECTIVE(S): To determine savings made following introduction of a biosimilar trastuzumab in the treatment of EBC, MBC, and MGC in 28 European countries and to calculate the number of additional patients who may be treated using the resulting savings.

RESULTS: With a 20% switching rate and 5% annual switching growth rate, budget impacts from the base-case analyses were €68 million (epidemiological data) and €58 million (sales volume data) in the first year (2018). Budgets were reduced by 3.0% and could thereby allow an additional 3503 (epidemiological data) or 3538 (sales volume data) patients to receive trastuzumab therapy.

Xue et al: A cost-effectiveness evaluation of the originator follitropin alfa compared to the biosimilars for assisted reproduction in Germany¹⁰

SPONSOR: Merck KGaA

LOCATION(S): Germany

DATES: Drug prices as at August 2017

DESIGN: The costs for assisted reproductive therapy were extracted from the relevant national data sources and publications. Live birth rates were obtained from phase III clinical trials** demonstrating biosimilarity between Bemfola® & originator GONAL-f® (32.1% vs 40.7% respectively) and Ovaleap® & originator GONAL-f® (26.8% and 32.2% respectively).

OBJECTIVE(S): To compare the overall costs to achieve live birth using originator follitropin alfa (GONAL-f®) with two biosimilar follitropin alfa treatments (Bemfola® and Ovaleap®) in Germany.

RESULTS: Based on the reported live birth rates in the phase III clinical trials, the estimated average cost per live birth for women treated with the originator are lower than those treated with biosimilars: GONAL-f® versus Bemfola® (€10,510 vs €12,192); GONAL-f versus Ovaleap® (€12,590 vs €13,606). The originator was associated with an ICER of €4,168 and €7,540 versus Bemfola® and Ovaleap® respectively.

REVIEWER COMMENTARY: The cost per live birth analysis assumes a difference in live birth rates between originator (40.7%) and Bemfola® biosimilar follitropin (32.1%), and originator (32.2%) and Ovaleap® biosimilar follitropin (26.8%). These values were obtained from the respective phase III clinical trials. However, in the phase III studies the live birth rates between biosimilar and originator were not statistically significantly different (odds ratio of 0.78 (95% CI: 0.47-1.29, p=0.335) for Ovaleap® vs originator; data not reported for Bemfola®). As noted by Xue et al, this cost-effective analysis was limited as the phase III studies “*were not designed or powered to assess live birth rates*”.

** Rettenbacher M, Andersen AN, Garcia-Velasco JA, et al. A multi-centre phase 3 study comparing efficacy and safety of Bemfola versus Gonalf in women undergoing ovarian stimulation for IVF. *Reprod Biomed Online* 2015; 30(5): 504-513.

Strowitzki T, Kuczynski W, Mueller A, et al. Randomized, active controlled, comparative phase 3 efficacy and safety equivalence trial of Ovaleap (recombinant human follicle-stimulating hormone) in infertile women using assisted reproduction technology (ART). *Reprod Biol Endocrinol* 2016; 14: 1

Patel et al: Cost-effectiveness of early treatment with originator biologics or their biosimilars after methotrexate failure in patients with established rheumatoid arthritis¹¹

SPONSOR: Pfizer Inc.

LOCATION(S): UK

DATES: Not specified

DESIGN: A Markov model was developed to estimate lifetime costs and utilities for patients with rheumatoid arthritis who do not respond to methotrexate monotherapy, comparing a standard intervention pathway (initiation of an anti-TNF alpha agent at 12 months) with two early intervention pathways (either addition of an originator anti-TNF alpha agent or addition of a biosimilar anti-TNF alpha agent at 6 months). The costs of originator anti-TNF alpha agents were based on UK National Health Service list prices and biosimilar agents' costs were based on a single local contract agreement.

OBJECTIVE(S): To estimate the cost-effectiveness of early initiation of anti-TNF alpha agent treatment (originator or biosimilar) in patients with rheumatoid arthritis who have an inadequate response to methotrexate monotherapy.

RESULTS: Early initiation of an anti-TNF alpha agent was associated with a gain of 0.10 QALYs per patient. The increased total lifetime costs of early initiation of originator was £1692 as compared with £70 for biosimilar, resulting in ICERs of £17,335/QALY and £713/QALY, respectively.

REVIEWER COMMENTARY: The intention of the study was to examine the early introduction of biologic treatment, rather than a formal cost-effectiveness analysis of originator versus biosimilar. Whilst the analysis has made significant cost assumptions around the cost difference between originator and biosimilars, it does highlight that as the price of these therapies reduces, opportunities arise to examine earlier introduction of biologic treatment.

BIOSIMILAR MEDICINE UPTAKE

This theme encompasses papers examining the current practice of prescribers, pharmacists and patients, and the policy informing such. During the update period, there were three papers published examining this theme.

INFLIXIMAB

INFLIXIMAB

Moorkens et al: Different policy measures and practices between Swedish counties influence market dynamics: Part 1 - biosimilar and originator infliximab in the hospital setting¹²

SPONSOR: Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL)

LOCATION(S): Sweden

DESIGN: Literature review of biosimilar policies across Swedish counties, comparison of biosimilar infliximab market share (market data provided by IQVIA™) at the county level with local biosimilar policy, discussion of findings with key experts from 3 counties.

DATES: 2015 – 2017. Face to face interviews March 2018.

OBJECTIVE(S): Quantitative and qualitative analysis of the influence of policy measures and practices on infliximab biosimilar market share in Sweden.

RESULTS: Market share of biosimilar infliximab in the final quarter of 2017 varied across Swedish counties (range 18% - 96%). Rate of uptake also varied between 2015 and 2017. Simple linear regression demonstrated that a positive linear relationship was observable between price difference (discount in DDD) between originator and biosimilar market share across the counties. Overall across Sweden the volume of infliximab prescribed increased by 54% between 2012 and 2017, with a more rapid escalation observed in 2015 after the market entry of the first biosimilar infliximab. During the interviews experts explained that the difference in uptake rate of biosimilars was likely to be due to counties being locked into contracts of differing durations. Gainsharing was identified as a major driver for biosimilar uptake whereby half of the savings from switching to biosimilars were returned to the hospital departments to access other products and services.

REVIEWER COMMENTARY: This study is Part 1 of 2 investigating the impact of biosimilar policy on uptake.

ETANERCEPT

Moorkens et al: Different policy measures and practices between Swedish counties influence market dynamics: Part 2 - biosimilar and originator etanercept in the outpatient setting¹³

SPONSOR: Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL)

LOCATION(S): Sweden

DESIGN: Literature review of biosimilar policies across Swedish counties, comparison of biosimilar etanercept market share (market data provided by IQVIA™) at the county level with local biosimilar policy, discussion of findings with key experts from 3 counties.

DATES: 2015 – 2017. Face to face interviews March 2018.

OBJECTIVE(S): Quantitative and qualitative analysis of the influence of policy measures and practices on etanercept biosimilar market share in Sweden.

RESULTS: Market share of biosimilar etanercept in 2017 varied across Swedish counties (range 40% - 82%). Rate of uptake also varied between 2015 and 2017 although the rate was quicker than that observed with infliximab. The authors suggested that this was due to the experience gained with the prior entry of infliximab. The relationship between price difference and market share was less well defined for etanercept than was observed for infliximab in the sister study. The authors suggested that rebates offered by managed etanercept market entry were not appropriately captured by the IQVIA database and hence “*only a limited analysis of etanercept prices, based on publicly available information, could be performed.*” An overall increase in etanercept volume was observed (56%) between 2012 and 2017. However, the relationship between increasing etanercept usage and etanercept biosimilar market share was not linear. The authors explained that “*in contrast to the infliximab market..., prices of etanercept are the same across Sweden*” and that “*differences between rebated prices might not be as substantial as for infliximab*”. It was noted that in the latest managed entry agreement, the originator product (Enbrel®) was the least expensive product.

REVIEWER COMMENTARY: This study is Part 2 of 2 investigating the impact of biosimilar policy on uptake. The etanercept pricing used in this arm of the study was determined using a simulation.

INFLIXIMAB & ETANERCEPT

Reuber and Kostev: Prevalence of switching from two anti-TNF biosimilars back to biologic reference products in Germany¹⁴

SPONSOR: None

LOCATION(S): Germany

DESIGN: Retrospective cohort study utilising IQVIA™ market data

DATES: February 2016 – December 2017 (Etanercept) and February 2015 – December 2017 (Infliximab)

OBJECTIVE(S): Investigate the rate of switching from two biosimilars back to originator products in Germany.

RESULTS: 49,068 patients were being prescribed etanercept or infliximab of which 2956 were switched to a biosimilar product during the study period. 14.7% of patients included were reported to switch back to originator within 3 months, with 30.3% switching back within 12 months. There was no relationship between sex, co-therapy (used as a crude measure of co-morbidity) or medical specialty and the rate of switching.

REVIEWER COMMENTARY: This study did not capture the reasons for switching, which may have been clinical, due to local policy change or changes in cost. The data does not include the individual patient's biologic history, such as duration of biologic treatment, previous (or subsequent) switching behaviour or severity of disease. The data does not include prescribing in the hospital sector. The authors acknowledge that this study *"should not be interpreted as a drug safety study"*.

HEALTH OUTCOMES AND ADVERSE EVENTS

Within the period encompassed by this update, there have been nine papers that have examined pharmacovigilance of biosimilar medicines, specifically the impact of substitution, switching and extrapolation of indication.

INFLIXIMAB

Meyer et al: The effectiveness and safety of infliximab compared with biosimilar CT-P13, in 3112 patients with ulcerative colitis in real-life¹⁵

SPONSOR: None

LOCATION(S): France, nationwide

DESIGN: Comparative equivalence cohort study using the Système National des Données de Santé health administrative database

DATES: 1 January 2015 to 31 May 2017; patients censored at study end (30 June 2017).

OBJECTIVE(S): To compare the effectiveness and safety of biosimilar infliximab (CT-P13) and the originator infliximab in patients with ulcerative colitis who were infliximab-naïve.

PATIENT CHARACTERISTICS: A total of 3112 patients; 1434 received originator infliximab, 1678 received biosimilar infliximab; median duration of follow-up: originator infliximab = 423 days (IQR 189-757) vs biosimilar infliximab = 286 days (IQR 168-466); prior ulcerative colitis hospitalisations = 43.2% (originator) vs 49.6% (biosimilar); biologic therapy in the prior 12 months = 31.5% (originator) vs 35.3% (biosimilar).

OUTCOME(S): The primary outcome was the composite endpoint of death, ulcerative colitis-related surgery, all-cause hospitalisation and reimbursement for other biologics. Equivalence was defined as containment of the 95% confidence interval of the hazard ratio (HR) of the primary outcome of biosimilar infliximab versus originator between 0.80 and 1.25.

RESULTS: The cumulative incidence rates of the primary outcome at 12 months in the originator group was 43.0% (95% CI: 40.5 to 45.6) as compared with 45.1% (95% CI: 42.7 to 47.5) in the biosimilar group and at 24 months 57.5% (95% CI: 54.9 to 60.0) as compared with 59.8% (95% CI: 57.5 to 62.1), respectively. The corresponding hazard ratio was 1.04 with a 95%CI of 0.94 to 1.15 which was within the pre-defined equivalence criteria of 0.80 to 1.25. During follow-up, 208 (14.5%) patients discontinued originator infliximab as compared with 187 (11.1%) patients in the biosimilar infliximab group. Switching from originator to biosimilar occurred in 163 (11.4%) patients and from biosimilar to originator in 171 (10.2%). There were fewer serious infections, defined as infection requiring hospitalisation, in the biosimilar group as compared to the originator group (HR 0.65; 95% CI: 0.48 to 0.88) including fewer skin and subcutaneous tissue infections (6.6 vs 12.3/1000 patient years), fewer lung infections (7.3 vs 9.5/1000 patient years) and fewer urinary tract infections (4.6 vs 7.3/1000 patient years).

REVIEWER COMMENTARY: The authors report a reduced risk of infection with biosimilar infliximab. It should be noted that the number of infections is small (e.g. 7 urinary tract infections in the biosimilar group as compared with 13 in the originator group). The authors state that on the basis of the infection result "*A true biological effect between these two drugs (e.g. a more profound immunosuppression with reference product) cannot be excluded.*" However, the authors also note that "*...this result can also be explained by a residual confounding or even by chance alone.*" The potential impact of the shorter duration of follow-up in the biosimilar group (median 286 days vs 343 days) and the timing of severe infections is not discussed. However, examination of the supplementary material indicates that the risk of infection is very similar up until 12 months and starts to deviate after that time, but this is in the context of small numbers of patients in the biosimilar group at those longer time points.

Viola et al: Outcome in ulcerative colitis after switch from adalimumab/golimumab to infliximab: A multicenter retrospective study¹⁶

SPONSOR: None

LOCATION(S): Italy, eight centres

DESIGN: Multicentre, retrospective study

DATES: Not specified

OBJECTIVE(S): To investigate disease outcome in patients with ulcerative colitis who changed therapy from adalimumab or golimumab to infliximab, including biosimilar infliximab (CTP-13), as result of primary failure, secondary loss of response or medication intolerance.

PATIENT CHARACTERISTICS: 76 patients, mean age 46 years (± 16); reason for discontinuation of adalimumab or golimumab: primary failure=60 (79%), loss of response=14 (18%), adverse events=2(3%).

OUTCOME(S): Rates of clinical remission (defined as partial Mayo score ≤ 1 without additional steroids and normalized CRP) and clinical response (defined as a decrease in the Mayo score of 3 or more points from baseline, along with a reduction of the rectal bleeding sub-score of at least 1 point).

RESULTS: Of the 76 patients identified, 20 changed to originator infliximab and 56 to biosimilar infliximab (CTP-13). At 3 months after commencing infliximab an overall clinical response was achieved in 24/76 (32%) patients and clinical remission in 29/76 (38%). At 6 months, 10 patients had stopped infliximab due to treatment failure, a single patient stopped due to an infusion reaction and three patients were lost to follow-up.

REVIEWER COMMENTARY: The authors do not provide an analysis of outcome according to whether patients received originator or biosimilar infliximab. Analysis is restricted to the impact of whether patients were changed to infliximab as a result of primary failure or loss of response to prior therapy, perhaps suggesting that the authors consider that this is a more important factor in determining a patient's outcome than whether the patient received the originator or biosimilar product.

Guerra Veloz et al: Long-term follow up after switching from original infliximab to an infliximab biosimilar: real-world data¹⁷

SPONSOR: Kern Pharma (medical writing support)

LOCATION(S): Virgen Macarena University Hospital, Seville, Spain

DESIGN: Prospective single-centre observational study

DATES: 24 months follow-up post switching in March 2015.

OBJECTIVE(S): To describe the efficacy, loss of response and safety of biosimilar infliximab (CT-P13) at 24 months after switching from originator infliximab in patients with inflammatory bowel disease. The manuscript extends the previous report at 12 months.**

PATIENT CHARACTERISTICS: 100 patients, Crohn's disease = 64, ulcerative colitis = 36; median duration of treatment with originator infliximab prior to switching = 70 months (Crohn's Disease), 50 months (ulcerative colitis); percent receiving concomitant thiopurines = 42.4% (Crohn's Disease), 36.1% (ulcerative colitis); percent receiving concomitant methotrexate = 21.8% (Crohn's Disease), 8.3% (ulcerative colitis); percent in remission at time of switch = 78%.

OUTCOME(S): Change in Harvey-Bradshaw (HB) index (Crohn's Disease) and partial Mayo score (ulcerative colitis).

RESULTS: There were no significant changes in the Harvey Bradshaw index ($p=0.128$) at 12, 18- and 24-months post-switching whilst the median partial Mayo score was decreased at 18 and 24 months compared to baseline ($p=0.001$ and $p=0.003$, respectively). Remission was maintained at 18- and 24-months post-switching in 69.9% (65/93) and 68.5% (63/92) of patients respectively. Over the 24 months follow-up an increase in dose was required in 22% of patients (16 CD and 6 UC). At 24 months 10 patients with Crohn's disease and five patients with ulcerative colitis had discontinued biosimilar infliximab due to loss of response whilst three patients with Crohn's disease and five patients with ulcerative colitis had discontinued having achieved remission. No significant changes were observed in median infliximab drug concentrations at 12, 18 and 24 months. Two patients developed anti-drug antibodies by 18 months.

REVIEWER COMMENTARY: The result related to infliximab concentrations needs to be considered in the context of the dose modification that occurred, but this is consistent with clinical practice. The authors consider that the rate of loss of response observed in this study is *"...consistent with the ones in the literature since the incidence of loss of response varies between 10-20% and 13-30% ..."*.

¹⁷ Arguelles-Arias F, Guerra Veloz MF, Perea Amarillo R et al. Switching from reference infliximab to CT-P13 in patients with inflammatory bowel disease: 12 months results. Eur J Gastroenterol Hepatol 2017; 29: 1290-5.

Gheorghe et al: Effectiveness and safety of biosimilar infliximab (CT-P13) in a real-life setting in patients with Crohn's disease or ulcerative colitis¹⁸

SPONSOR: Egis Pharmaceuticals PLC (medical writing assistance)

LOCATION(S): Romania, the Czech Republic, and Bulgaria

DESIGN: Multi-centre, observational study

DATES: Not specified

OBJECTIVE(S): To describe the effectiveness and safety of biosimilar infliximab (CT-P13) in adults with moderate-to-severe active Crohn's disease or ulcerative colitis.

PATIENT CHARACTERISTICS: 85 patients, Crohn's disease = 38, ulcerative colitis = 47; percent with no prior treatment with infliximab = 63.2% (Crohn's Disease), 93.6% (ulcerative colitis).

OUTCOME(S): The percentage of patients with a clinical response, defined as a decrease of >70 points from the baseline Crohn's Disease Activity Index score (Crohn's Disease) or a decrease of at least 3 points from the baseline in the partial Clinical Activity Index score and an absolute sub-score for bleeding not greater than 1 point (ulcerative colitis), at week 30.

RESULTS: A total of 67 patients (Crohn's Disease = 27, ulcerative colitis = 40) completed 30 weeks of follow-up. At week 30, the response rate was 65.8% in patients with Crohn's Disease and 55.3% in patients with ulcerative colitis. The mean Crohn's Disease Activity Index score decreased from 359 ± 175 at baseline to 190 ± 170 ($p < 0.0001$) whilst the mean partial Clinical Activity Index score decreased from 9.8 ± 3 at baseline to 3.1 ± 4.0 ($p < 0.0001$). Eight patients withdrew due to therapeutic failure and three withdrew due to adverse events.

REVIEWER COMMENTARY: The exact treatment history of patients who were reported as not being infliximab-naïve is unclear as the treatment history is variously described as "*new to infliximab treatment*", "*De novo treatment*" and "*previous exposure to anti-TNF agents*". It is reported that of the 17 patients that have been exposed to infliximab, or possibly an alternative anti-TNF alpha agent, 14 were evaluable and of these nine patients had a clinical response and six were in remission.

ETANERCEPT

Bonifati et al: Effectiveness of etanercept biosimilar SB4 in maintaining low disease activity in patients with psoriatic arthritis switched from etanercept originator: an open label one year study¹⁹

SPONSOR: None

LOCATION(S): Italy, single-centre

DESIGN: Prospective, observational

DATES: Not specified

OBJECTIVE(S): To assess the outcomes of switching from originator etanercept to biosimilar etanercept in patients with psoriatic arthritis.

PATIENT CHARACTERISTICS: 87 patients with a clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) score ≤ 13 (possible range 0-154); patients with Minimal Disease Activity (MDA) = 81/87 (93%)

ENDPOINT(S): The proportion of patients maintaining a cDAPSA score ≤ 13 1 year after switching from originator etanercept to biosimilar etanercept.

RESULTS: At 12 months following switching from originator etanercept to biosimilar, 11 (12.4 %) out of 87 patients did not maintain a cDAPSA score ≤ 13 . In five patients the failure to maintain a cDAPSA ≤ 13 was attributed to “...*slight increase in the tender and swollen joint count...*” (median value at baseline: 0 vs median value post switching: 2, maximum possible value = 154) and “...*a significant increase in the above-mentioned measure’s subjective domains...*”. Of the 81 patients with MDA prior to switching to biosimilar etanercept, 17 patients did not maintain this at 12 months which included 10 participants that did not maintain cDAPSA ≤ 13 . Loss of MDA was “...*was mainly due to an increase in the subjective domains...*”.

REVIEWER COMMENTARY: The prominence of the subjective measures of disease activity as the driver for the reported decrease in disease control following switching to biosimilar etanercept in many of these participants could be influenced by the nocebo effect. Details are not provided as to how participants that experienced reduced disease control, particularly those with increases in subjective measures, were subsequently managed.

Giunta et al: Etanercept biosimilar SB4 in the treatment of plaque-type psoriasis and psoriatic arthritis: a single-center, observational, retrospective, real-life study²⁰

SPONSOR: None

LOCATION(S): Italy, single-centre

DESIGN: Retrospective, observational

DATES: October 2016 - March 2017

OBJECTIVE(S): To describe the outcomes of treatment with biosimilar etanercept (SB4®) in patients with plaque-type psoriasis and psoriatic arthritis.

PATIENT CHARACTERISTICS: 14 patients with plaque-type psoriasis, mean Psoriasis Area and Severity Index (PASI) at baseline = 9.6; 26 patients with psoriatic arthritis, mean PASI = 4.69, mean DAS28-ESR = 5.27; participants with prior treatment with originator etanercept = 10 (25%), mean duration of treatment with originator etanercept = 50.4 weeks (range 24-96), mean wash-out period from originator etanercept = 12.1 weeks (range 8-24).

ENDPOINT(S): Change in PASI and DAS28-ESR.

RESULTS: At week 24 the mean PASI had decreased from 9.61 to 1.27 in patients with plaque-type psoriasis and from 4.69 to 1.19 in participants with psoriatic arthritis. DAS28-ESR decreased from 5.45 to 3.27. There were no statistically significant differences in PASI and DAS28-ESR between those who had received originator etanercept previously and those who were etanercept-naïve. A single patient experienced an injection site reaction.

FILGRASTIM

Aapro et al: Treatment patterns and outcomes in patients with non-small cell lung cancer receiving biosimilar filgrastim for prophylaxis of chemotherapy-induced/febrile neutropenia: Results from the MONITOR-GCSF study²¹

SPONSOR: Hexal AG

LOCATION: Europe-wide

DESIGN: Prospective, non-interventional, multi-level, pharmaco-epidemiological study

OBJECTIVE(S): To describe the outcomes of treatment with biosimilar filgrastim in patients receiving chemotherapy for non-small cell lung cancer.

PATIENT CHARACTERISTICS: 345 patients, chemotherapy regimen (percent of patients): docetaxel = 4.1%, topotecan = 3.2%, cisplatin/etoposide = 21.4%, carboplatin/etoposide = 13.3%, carboplatin/paclitaxel = 7.2%, cisplatin/gemcitabine = 5.2%, cisplatin/vinorelbine = 5.2%, cisplatin/paclitaxel = 2.6%, carboplatin/docetaxel = 2.3%

OUTCOME(S): Incidences of chemotherapy induced neutropenia (any grade) and febrile neutropenia (any grade).

RESULTS: Throughout the duration of the study a total of 126 (36.5%) patients experienced one or more episodes of chemotherapy induced neutropenia (any grade) and 18 (5.2%) patients experienced febrile neutropenia (any grade).

REVIEWER COMMENTARY: This manuscript presents a sub-group analysis of the larger MONITOR-GCSF study from which a number of different manuscripts have been published. Very limited detail is provided in this manuscript, perhaps reflecting the now established place of biosimilar filgrastim in prophylaxis of chemotherapy induced neutropenia.

Buyukavci et al: The comparison of the efficacy and safety of original and biosimilar filgrastim in prevention of chemotherapy-induced neutropenia in children with cancer²²

SPONSOR: None

LOCATION: Turkey

DESIGN: retrospective

OBJECTIVE(S): To compare the efficacy and safety of originator and biosimilar filgrastim for the prophylaxis of chemotherapy induced neutropenia in children.

PATIENT CHARACTERISTICS: 30 patients receiving chemotherapy for acute leukaemia, Ewing sarcoma, astrocytoma, germ cell tumour, and Wilms' tumour; 15 patients received originator filgrastim (Neupogen®) and 15 patients received biosimilar filgrastim (Leucostim®).

OUTCOME(S): White blood cell count on days 1, 5 and 10 post-chemotherapy, duration of febrile neutropenia (defined as axillary temperature $>38.5^{\circ}\text{C}$ recorded once, or of $>38^{\circ}\text{C}$ recorded on 2 or more occasions over a 12-hour period in patients with absolute neutrophil count $<500/\text{mm}^3$, or $500\text{-}1000/\text{mm}^3$ but expected to decline to $<500/\text{mm}^3$ within the next 48 hours).

RESULTS: There were no statistically significant differences in white blood cell counts at days 1, 5 and 10 between the two groups. There was no difference in duration of febrile neutropenia between the two groups.

REVIEWER COMMENTARY: The specific design of this study is unclear. It appears that analysis is based upon a total of 25 cycles of chemotherapy in each group and as such some individual patients will have contributed data from more than one chemotherapy cycle, but details are not provided. Numbers of patients in each group are small and given the number of cancer types included there are numerical differences in these between the two groups. Details regarding the chemotherapeutic regimens are not provided.

ERYTHROPOIETIN

Belleudi et al: Effectiveness and safety of switching originator and biosimilar epoetins in patients with chronic kidney disease in a large-scale Italian cohort study²³

SPONSOR: Italian Ministry of Health

LOCATION: Italy

DESIGN: Retrospective record-linkage cohort study

OBJECTIVE(S): To compare the effectiveness and safety of switching versus non-switching in patients treated with epoetin alpha and of changing therapy from epoetin alpha (originator or biosimilar) to other erythropoiesis stimulating agents (epoetin and darbepoetin).

PATIENT CHARACTERISTICS: New users with at least one epoetin alpha dispensing between 1 January 2009 and 31 December 2015. A matched cohort was created to compare outcomes in switchers versus non-switchers. Switchers were matched 1:1 with non-switchers by propensity score and duration of epoetin alpha treatment. Only subjects without lack of effectiveness and without safety events during the 90 days prior to switching were considered.

OUTCOME(S): Frequency of blood transfusions and anaemia (indicator of lack of effectiveness), frequency of major cardiovascular events, dyscrasias or hypersensitivity reactions (safety).

RESULTS: A total of 1559 patients were examined that switched from originator epoetin alpha to another agent who were matched 1:1 with a patient that remained on originator epoetin alpha. Of these, 221 patients switched from originator to biosimilar epoetin alpha for which there was no statistically significant difference in effectiveness (HR = 0.86, 95%CI: 0.44 to 1.66) or safety (HR= 1.18, 95%CI: 0.49 to 2.83).

A total of 524 patients were examined that switched from biosimilar epoetin alpha to another agent who were matched 1:1 with a patient that remained on biosimilar epoetin alpha. Of these, 226 patients switched from biosimilar to originator for which there was no statistically significant difference in effectiveness (HR = 1.38, 95%CI: 0.66 to 2.89) or safety (HR= 1.52, 95%CI: 0.54 to 3.90).

No statistically significant differences in effectiveness or safety were observed in any pattern of changes in therapy.

STAKEHOLDER PERCEPTIONS

During the quarterly update period, six papers have explored the topic of evaluating and improving stakeholder awareness, confidence, attitudes and acceptance of biosimilar medicines.

HEALTH PROFESSIONALS

Pouillon et al: Consensus report: clinical recommendations for the prevention and management of the nocebo effect in biosimilar-treated IBD patients²⁴

SPONSOR: Meeting was funded by Sandoz and Pfizer. Authors declare multiple competing interests and consultancy roles.

LOCATION(S): NOCE-BIO Consensus group meeting of Milan, Italy

DESIGN: Literature review on the nocebo effect in inflammatory bowel disease using Medline/PubMed, EMBASE and Cochrane CENTRAL conducted by 3 group members to produce preliminary consensus statements, which were then voted upon by the consensus group.

DATES: All years until July 2018

OBJECTIVE(S): Review literature and develop clinical recommendations for the prevention and management of the nocebo effect in biosimilar-treated IBD patients.

PARTICIPANTS: NOCE-BIO consensus group was composed of gastroenterologists with expertise in IBD, pharmacists, oncologists, rheumatologists, methodologists, dermatologists, psychologists and nurse specialists. 13/19 members (Belgium, Portugal, UK, Italy and France) attended the consensus meeting. All 19 members participated in final manuscript development.

RESULTS: Consensus was achieved on 11 recommendation statements categorised as “General statements”, “Prevention and management of the nocebo effect” and “Future Directions”. General statements of consensus included that the nocebo effect is under-recognised and can occur at biosimilar initiation or when switching to a biosimilar. The group agreed that caution is needed “*not to attribute every side effect directly to the treatment, because some effects may be related to nocebo*” and that this may lead to unnecessary cessation of biologic treatment, altering IBD patient outcomes and a negative impact on biosimilar cost savings. Under the prevention and management of the nocebo effect consensus was achieved that all healthcare providers need to adopt strategies to minimise the impact of the nocebo effect. It was identified that the “*patient-health-care provider relationship was a key driver of acceptance of biosimilars and limits the risk of negative bias*” and that a lack of knowledge of patients and health-care providers regarding the effectiveness and safety of biosimilars contributes to the nocebo effect. Consensus was also achieved that positive framing can reduce the nocebo effect and that patient education regarding biosimilars should be individually tailored to account for a patient’s risk of the nocebo effect. The evidence supporting these statements was described by the authors as being of very low quality and was often extrapolated from studies about the nocebo effect from other indications.

Williamson et al: Addressing oncologists' gaps in the use of biosimilar products²⁵

SPONSOR: None declared

LOCATION(S): Live meetings (Multiple US locations) and online activity

DESIGN: Education training session (live and online) with pre- and post-activity assessments designed for health-care professionals involved in the care of patients with cancer.

DATES: September 2017 – July 2018

OBJECTIVE(S): To assess the impact of clinical medical education on the ability of clinicians to assess the risks and benefits of biosimilars and to mitigate barriers to their adoption in clinical practice.

PARTICIPANTS: American health-care professionals including oncologists, haematologists, pharmacists, and nurses involved in the care of patients with cancer.

RESULTS: 9599 participants undertook the activities (114 live and 9485 online). Attendees at the live meetings were predominantly physicians with greater than 10 years' experience. The web course participants were predominantly nurses. Participant knowledge immediately post-activity was increased in all topics covered, including awareness of the FDA biosimilar approval process, awareness of the current number of US approved biosimilars and familiarity with the relative immunogenicity, safety and effectiveness of biosimilar trastuzumab and reference product. In the pre-activity test 25% of participants self-identified as "Confident, Very Confident or Expert" in utilising biosimilars in practice, whereas in the post-activity test this increased to 36% of participants.

REVIEWER COMMENTARY: The post-activity assessments were conducted immediately after the training sessions. No longitudinal follow up of biosimilar knowledge or understanding was reported.

Hadoussa et al: Perception of hematologists and oncologists about the biosimilars: A prospective Tunisian study based on a survey²⁶

SPONSOR: None

LOCATION(S): Tunisia

DESIGN: Questionnaire containing 15 multiple choice questions

DATES: Unknown

OBJECTIVE(S): Evaluate the knowledge and perceptions of Tunisian oncologists and haematologists on biosimilars.

PARTICIPANTS: Oncologists and haematologists in public and private practice settings across Tunisia.

RESULTS: 107 out of 150 physicians responded to the questionnaire. Most respondents were able to differentiate between a biosimilar and a generic drug, however only 11% were able to identify the full correct definition and 14% were able to identify the legislative requirements for biosimilarity. 68% of physicians stated that indication extrapolation was allowed, and more than half stated that they were in favour of substitution and interchangeability. 89% of respondents were in favour of prescribing biosimilars for their patients and 69% stated they would prefer to prescribe a biosimilar medicine. The majority of respondents correlated biosimilars with “*better access for patients*” and a “*lower price*”. The authors stated that “*only 4% of doctors believed that they are clearly informed about biosimilars drugs*”.

REVIEWER COMMENTARY: The results of the questionnaire are difficult to interpret as the precise questions asked are ambiguous. It is stated that Tunisia adopts the EU and WHO guidelines on biosimilar regulation, however the authors identify that a “*lack of concise Tunisian regulations*” impacts on the level of information available to Tunisian healthcare providers regarding biosimilars. Tunisian oncologists and haematologists appear to have a positive outlook on biosimilars, extrapolation of indication and substitution, however that should be viewed in the context of lack of choice due to the hospital tender processes whereby only the cheapest brand is made available.

Pawlowska et al: Perspectives of hospital pharmacists towards biosimilar medicines: A survey of Polish pharmacy practice in general hospitals²⁷

SPONSOR: None

LOCATION(S): Poland

DESIGN: Anonymous questionnaire containing 12 binary/multiple choice questions

DATES: September 2017

OBJECTIVE(S): Assess hospital pharmacist's attitudes towards biosimilars in Poland and their usage in practice.

PARTICIPANTS: Hospital pharmacists working in general hospitals across Poland.

RESULTS: 271 hospitals were contacted and 61 pharmacists completed the questionnaire (response rate 22.5%). 40 pharmacist respondents self-described as well acquainted with biosimilar medicines, 20 somewhat familiar, with one participant declaring themselves as 'not familiar' with biosimilars. In relation to practice in their hospitals 90% stated that originator biologic medicines were used and 77% identified that biosimilars were used. Participants were asked when biosimilars should be used via a multiple response closed question; respondents identified at the initiation of therapy (n=41), when the originator was ineffective (n=23), to substitute an originator (n=14), with 1 respondent stating they should never be used. Respondents identified advantages of biosimilars as lower price (n= 52), pharmacoeconomic issues (n=41), similar efficacy (n=31) and a wider therapeutic usage (n=4). No respondents stated there was a "*lack of advantages*". Respondents identified disadvantages of biosimilars as the drug being similar but not identical (n= 53), immunogenicity (n=29), other pharmacokinetic properties (n=26) and a lower efficacy (n=7). Three respondents stated there was a "*lack of disadvantages*" and no respondents stated they had "low quality". When the participants were asked if pharmacists can interchange a biologic to a biosimilar without the doctor's permission 75% stated no, 15% yes if the originator was not available and 10% responded as "*yes, similarly to chemical medicines*". The authors explained that Polish law does not regulate biosimilar substitution and that no national guidelines existed addressing this issue.

REVIEWER COMMENTARY: This survey did not report any measure of participant's biosimilar understanding. The questionnaire style was directive limiting investigation of attitudes. Questions were ambiguous, when respondents were asked if they thought pharmacists can interchange biosimilars, it is unclear if this question referred to local legal/protocol permission or their personal attitude towards interchangeability.

Greene et al: Strategies for overcoming barriers to adopting biosimilars and achieving goals of the Biologics Price Competition and Innovation Act: A survey of managed care and specialty pharmacy professionals²⁸

SPONSOR: Sandoz

LOCATION(S): US

DESIGN: 28 item online survey

DATES: October 2018

OBJECTIVE(S): Assess perceptions regarding strategies for overcoming barriers to biosimilar adoption.

PARTICIPANTS: Members and contacts of the Academy of Managed Care Pharmacy (AMCP) including managed care professionals working in health plans and pharmacy benefit managers.

RESULTS: 10,000 invitations to participate were sent, with the first 300 respondents qualifying and receiving a \$100 gift card. 84% of respondents agreed or strongly agreed that barriers to biosimilar adoption rated as most difficult to overcome included concerns about biosimilar safety and efficacy amongst prescribers (61% difficult or extremely difficult on a Likert scale) and pricing and contract issues (57% difficult or extremely difficult on a Likert scale). The strategies that were rated as the most likely to overcome barriers to biosimilar adoption included prescriber education on switching studies (91% likely or extremely likely on a Likert scale) and clear FDA guidance on substitution (90%). Whereas the strategy that was rated as least likely to overcome barriers to adoption included required drug monitoring for patients who switch (39% likely or extremely likely) and incentivising providers by quotas (40%).

PATIENTS

Gasteiger et al: The effects of message framing on patients' perceptions and willingness to change to a biosimilar in a hypothetical drug switch²⁹

SPONSOR: None

LOCATION(S): New Zealand

DESIGN: Parallel four-armed randomized controlled trial. Participants were randomized to receive one of four videos explaining a switch to a hypothetical biosimilar using positive framing, positive framing plus analogy, negative framing or negative framing plus analogy and then immediately completed a post-presentation questionnaire assessing their willingness to switch.

DATES: April - July 2018

OBJECTIVE(S): Measure the effect of positive framing and analogy on patient perception and willingness to switch to a hypothetical biosimilar.

PARTICIPANTS: Rheumatology patients currently using a biologic agent (n=96).

RESULTS: At the time of the study no biosimilars were available for the recruited patient group, the intervention was therefore hypothetical. The most common biologic being used by the participants was rituximab, with the most common indication RA. Other biologics currently used by the participants included adalimumab, tocilizumab, infliximab and etanercept. A statistically significant relationship was reported between positive framing (with or without analogy) and willingness to switch to biosimilar ($\chi^2_{(1)} = 4.27$, $P = 0.039$). Framing was determined to significantly predict willingness to switch, with participants in the positive framing group 2.36 times more likely to be willing to switch to hypothetical biosimilar. However, the use of analogy in this study did not affect willingness to switch.

REVIEWER COMMENTARY: The authors described limitations including that a hypothetical situation may not reflect genuine willingness to switch. The explanations were shorter than the ideal duration indicated by participants and outcomes were measured immediately prior to being surveyed without any follow up. The biologic history of the participants in the four arms were not controlled and may have influenced their willingness to switch.

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2. Wu X, Wynne C, Xu C et al. A Global Phase I Clinical Study Comparing the Safety and Pharmacokinetics of Proposed Biosimilar BAT1706 and Bevacizumab (Avastin) in Healthy Male Subjects. *Biodrugs* 2019; **33**: 335-42.
3. Chen X, Li C, Ewesuedo R et al. Population pharmacokinetics of PF-05280014 (a trastuzumab biosimilar) and reference trastuzumab (Herceptin) in patients with HER2-positive metastatic breast cancer. *Cancer Chemotherapy & Pharmacology* 2019; **84**: 83-92.
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5. Jaworski J, Matucci-Cerinic M, Schulze-Koops H et al. Switch from reference etanercept to SDZ ETN, an etanercept biosimilar, does not impact efficacy, safety, and immunogenicity of etanercept in patients with moderate-to-severe rheumatoid arthritis: 48-week results from the phase III, randomized, double-blind EQUIRA study. *Arthritis Research & Therapy* 2019; **21**: 130.
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7. Shim SC, Bozic-Majstorovic L, Berrocal Kasay A et al. Efficacy and safety of switching from rituximab to biosimilar CT-P10 in rheumatoid arthritis: 72-week data from a randomized Phase 3 trial. *Rheumatology* 2019; **10**: 10.
8. Hagino H, Narita R, Yokoyama Y et al. A multicenter, randomized, rater-blinded, parallel-group, phase 3 study to compare the efficacy, safety, and immunogenicity of biosimilar RGB-10 and reference once-daily teriparatide in patients with osteoporosis. *Osteoporosis International* 2019; **26**: 26.
9. Lee SM, Jung JH, Suh D et al. Budget Impact of Switching to Biosimilar Trastuzumab (CT-P6) for the Treatment of Breast Cancer and Gastric Cancer in 28 European Countries. *Biodrugs* 2019; **14**: 14.
10. Xue W, Lloyd A, Falla E et al. A cost-effectiveness evaluation of the originator follitropin alpha compared to the biosimilars for assisted reproduction in Germany. *International Journal of Women's Health* 2019; **11**: 319-31.
11. Patel D, Shelbaya A, Cheung R et al. Cost-Effectiveness of Early Treatment with Originator Biologics or Their Biosimilars After Methotrexate Failure in Patients with Established Rheumatoid Arthritis. *Advances in Therapy* 2019; **30**: 30.
12. Moorkens E, Simoens S, Troein P et al. Different Policy Measures and Practices between Swedish Counties Influence Market Dynamics: Part 1-Biosimilar and Originator Infliximab in the Hospital Setting. *Biodrugs* 2019; **33**: 285-97.
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28. Greene L, Singh RM, Carden MJ et al. Strategies for Overcoming Barriers to Adopting Biosimilars and Achieving Goals of the Biologics Price Competition and Innovation Act: A Survey of Managed Care and Specialty Pharmacy Professionals. *Journal of Managed Care & Specialty Pharmacy* 2019: 1-9.
29. Gasteiger C, Jones ASK, Kleinstaubler M et al. The effects of message framing on patients' perceptions and willingness to change to a biosimilar in a hypothetical drug switch. *Arthritis care & research* 2019; **24**: 24.

APPENDIX 1

The following list contains manuscripts that were published during the review period that are of an educational or review nature. These manuscripts did not contribute new information to literature on biosimilar medicines. Some manuscripts provide a broad, relatively superficial, overview of biosimilar medicines. Other manuscripts provide an in-depth review of specific biosimilar medicines, reporting only on previously published data, but not contributing new information. This list includes several network meta-analyses, the results of which are consistent with the individual studies previously reported.

1. Abad Hernandez MA, Andreu JL, Balsa Criado A et al. Update of the Position Paper of the Spanish Society of Rheumatology on Biosimilar Drugs. *Reumatologia Clinica* 2019; 01: 01.
2. Barbier L, Declerck P, Simoens S et al. The arrival of biosimilar monoclonal antibodies in oncology: clinical studies for trastuzumab biosimilars. *Br J Cancer* 2019.
3. Barker J, Girolomoni G, Egeberg A et al. Anti-TNF biosimilars in psoriasis: from scientific evidence to real-world experience. *Journal of Dermatological Treatment* 2019: 1-7.
4. Bellinvia S, Cummings JRF, Ardern-Jones MR et al. Adalimumab Biosimilars in Europe: An Overview of the Clinical Evidence. *Biodrugs* 2019; 33: 241-53.
5. de Mora F. Biosimilars: A Value Proposition. *Biodrugs* 2019; 07: 07.
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12. Klein K, Stolk P, De Bruin ML et al. The EU regulatory landscape of non-biological complex drugs (NBCDs) follow-on products: Observations and recommendations. *European Journal of Pharmaceutical Sciences* 2019; 133: 228-35.
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14. Lyman GH. New Biosimilar Approvals for Myeloid Growth Factors and Anemia. *Journal of the National Comprehensive Cancer Network* 2019; 17: 622-4.
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17. Santha D, Illes A, Aradi I et al. RGB-02 (biosimilar pegfilgrastim) in the treatment of chemotherapy-induced neutropenia. *Future Oncology* 2019; 18: 18.
18. Steinberg J, Fragoso YD, Duran Quiroz JC et al. Practical Issues Concerning the Approval and Use of Biosimilar Drugs for the Treatment of Multiple Sclerosis in Latin America. *Neurology & Therapy* 2019; 24: 24.

19. Zharkov A, Barton B, Heinzmann D et al. Development pathways for subcutaneous formulations of biologics versus biosimilar development. *Expert Review of Precision Medicine and Drug Development* 2019; 1-8.
20. Gecse KB, D'Haens GR. Infliximab biosimilar CT-P13 in Crohn's disease. *Lancet* 2019; 393: 1671-2.
21. Baumgart DC, Misery L, Naeyaert S et al. Biological Therapies in Immune-Mediated Inflammatory Diseases: Can Biosimilars Reduce Access Inequities? *Frontiers in Pharmacology* 2019; 10: 279.
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33. Lu TX, Cohen RD. Maneuvering Clinical Pathways for Crohn's Disease. *Current Gastroenterology Reports* 2019; 21: 20.
34. Markus R, McBride HJ, Ramchandani M et al. A Review of the Totality of Evidence Supporting the Development of the First Adalimumab Biosimilar ABP 501. *Advances in Therapy* 2019; 10: 10.
35. McClellan JE, Conlon HD, Bolt MW et al. The 'totality-of-the-evidence' approach in the development of PF-06438179/GP1111, an infliximab biosimilar, and in support of its use in all indications of the reference product. *Therapeutic Advances in Gastroenterology* 2019; 12: 1756284819852535.
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40. Smolen JS, Goncalves J, Quinn M et al. Era of biosimilars in rheumatology: reshaping the healthcare environment. *RMD Open* 2019; 5: e000900.
41. Thill M. Biosimilar Trastuzumab in Clinical Trials: Differences or Not? *Breast Care* 2019; 14: 17-22.
42. Wormann B, Sinn M. Position of Scientific Oncological Societies Towards Biosimilar Antibodies. *Breast Care* 2019; 14: 5-8.
43. Yang J, Yu S, Yang Z et al. Efficacy and Safety of Supportive Care Biosimilars Among Cancer Patients: A Systematic Review and Meta-Analysis. *Biodrugs* 2019; 03: 03.
44. Yang J, Yu S, Yang Z et al. Efficacy and Safety of Anti-cancer Biosimilars Compared to Reference Biologics in Oncology: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *BioDrugs* 2019.

APPENDIX 2

The following list contains manuscripts that were published during the review period that are of a technical nature and relate to topics such as the physicochemical and pharmacological characterisation of potential biosimilar medicines.

1. Brown KA, Rajendran S, Dowd J et al. Rapid characterization of structural and functional similarity for a candidate bevacizumab (Avastin) biosimilar using a multipronged mass-spectrometry-based approach. *Drug Testing & Analysis* 2019; 30: 30.
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3. Hutterer KM, Polozova A, Kuhns S et al. Assessing Analytical and Functional Similarity of Proposed Amgen Biosimilar ABP 980 to Trastuzumab. *Biodrugs* 2019; 33: 321-33.
4. Lee JH, Paek K, Moon JH et al. Biological Characterization of SB3, a Trastuzumab Biosimilar, and the Influence of Changes in Reference Product Characteristics on the Similarity Assessment. *Biodrugs* 2019; 12: 12.
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