OPTIMIZING THE CLINICAL EFFICACY AND SAFETY OF BIOLOGICAL MEDICINES AND THEIR BIOSIMILARSA WITHIN AVAILABLE RESOURCES IN EUROPE

Thesis submitted for the degree of Doctor of Philosophy at the Open University, UK

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Abstract

Introduction: Biological medicines contain active principles made by large and complex molecular structures, produced or extracted from a biological source. Biosimilars offer significant opportunities to reduce the price of biological medicines especially in an area of spiralling healthcare expenditure. Given the complexity of these medicines, their role in the management of many diseases, and their high price, there is the need to promote their appropriate use and develop tools and policies to increase access to high quality and affordable medicines.

Aims: With a multidisciplinary approach, I took into account different facets this topic.
1. Analysis of the development and marketing authorisation of biosimilars in the EU to explore how the regulatory framework affects biosimilar clinical development, policies and uptake.
2. Analysis of the evidence supporting the switch between originator and biosimilars and the switch among biosimilars, in chronic clinical conditions.
3. Development and testing of an innovative analytical technique to monitor the appropriate use of biological medicines in order to maximise patient outcomes.
4. Development of education and training programmes for healthcare professionals regarding biological medicines and biosimilars in collaboration with local health authorities.

Methods: I applied a combination of different methodologies, tailored to each different aim.
1. Analysis of pivotal clinical trials of EU approved biosimilars that compare their efficacy and safety to originators.
2. Series of systematic reviews that evaluate efficacy and safety of switching between biologics and their biosimilars of insulin analogues and anti-TNFs. Identification of studies through systematic searches on Medline, EMBASE, and The Cochrane Library. Update of anti-TNFs review (2022) to retrieve studies on switching among biosimilars.
4. Definition of training objectives and modalities of educational sessions on biological medicines. Identification of clinical areas where these medicines are commonly used. Development of key metrics of prescription performance used as starting point for the course content.

Main results:
1. Up to April 2022, I retrieved 68 biosimilars approved in the EU, corresponding to 18 active principles. The comparability exercise and subsequent approval of the majority of them is based on one or more pivotal phase III trials comparing their clinical efficacy to the originators. Often
trials adopted an equivalence design, while insulin analogue biosimilars approval based on non-inferiority trial design. Two third of these trials included data on immunogenicity. The requirement for showing similarity in terms of clinical efficacy and safety provides a robust demonstration of comparable clinical outcomes.

2. I retrieved 22 studies addressing the insulin review questions. Three randomised controlled trials, on insulin glargine, collected evidence on equivalent efficacy, safety and immunogenicity when switching to biosimilar. Data on switching between different analogues, or from analogues to human insulins are very limited (one RCT). Studies comparing switching from originators to biosimilars of anti-TNF (infliximab, adalimumab, etanercept) in chronic inflammatory diseases are many and consistent. I included 32 records, corresponding to three systematic reviews, 14RCTs, 8 OLEs and three cohort studies. Substantial amount of evidence from RCTs is available for IFX and ADMB, versus one RCT of ETN. All these studies suggest switching is safe and effective. With regards of switching among biosimilars, I included 19 clinical studies: 11 cohort studies and 8 single-arm studies: none of these studies highlights significant concerns on switching between biosimilars.

3. The study involved 76 patients receiving infliximab for IBD. Concentration of biological drug and anti-drug-antibodies in each sample determined by SPR in triplicate by two researchers with different experience. Measurements with both ELISA and SPR indicated very similar IFX serum concentrations, with differences of ADA. All the sera showing ADA by ELISA also showed ADA by SPR. 8 patients showed ADA only with SPR: these ADA had significantly faster dissociation rate constants than those detectable by both methods. Measurement of IFX and ADA can support informed decisions for a more rational management of biological therapies.

4. Education programme was replied four times with 30-40 participants each. There was a case-mix of specialties: gastroenterologists, dermatologists, rheumatologists but also oncologists, internal medicine physicians and general practitioners. The majority was confident in prescribing biosimilars in naive patients, with some restraint to switching. All the participants were in favour of better integration of the gained experience with different specialities.

**Conclusions:** Altogether, the different strategies exploited in my project could support a clinical decision-making based on a more rational use of biological medicines, with benefits for both the patient’s outcome and the health budgets.
Author’s contribution of the thesis

With the assistance and co-operation of my supervisors Dr. Rita Banzi, Dr. Marco Gobbi and Dr. Brian Godman, I conceptualized my thesis project defining the research questions and defined the methodology I applied to pursue the objectives of the PhD program.

Specifically, I conceptualized Chapter 1 and Chapter 2 with the assistance and supervision of Dr. Rita Banzi and Dr. Brian Godman. I did the data collection and analysis included in chapter 3 and 4, with the support of Dr. Rita Banzi and Dr. Chiara Gerardi. I helped carrying out the experiments regarding the laboratory part of the PhD program (chapter 5) under the supervision of Dr. Marten Beeg and Dr. Marco Gobbi. Tuscany Regional Healthcare Authorities proposed the education and training project described in Chapter 6. I helped in developing and performing the project, in collaboration with my supervisor Dr. Rita Banzi. I conceptualized and wrote Chapter 7 with the assistance and supervision of all my supervisors, Dr. Rita Banzi, Dr. Bran Godman and Dr. Marco Gobbi.

I wrote the first draft of the thesis, and revised it after the comment of my supervisors and myself. Dr. Rita Banzi and Dr. Brian Godman supervised the writing process. Dr. Chiara Gerardi and Dr. Vittorio Bertele’ also helped me in the writing process.
List of published papers by the PhD candidate

All the papers listed below contain part of the work presented in the thesis.

For the following publications, I was responsible for conceptualization, methodology, data collection and analysis, data interpretation, writing, reviewing and editing.


Allocati E, Godman B. Key patient related factors in the management of inflammatory bowel disease. J Med Econ. 2020 Dec;23(12):1606-1609;


For the following publications, I contributed to methodology, data collection and analysis, data interpretation, reviewing.


For the following publications, I contributed to analysis and interpretation, reviewing.


Tubic B, Marković-Peković V, Jungić S, Allocati E, Godman B. Availability and accessibility of monoclonal antibodies in Bosnia and Herzegovina: Findings and implications. Medicine Access @ Point of Care. 2021;5.
**Glossary**

ACR: American College of Rheumatology

ACR20: 20% improvement in American College of Rheumatology core set measurement

ADA: Antidrug Antibody

ADBM: Adalimumab

AE: adverse event

AIFA: Agenzia Italiana del Farmaco (Italian Medicines Agency)

AS: Ankylosing Spondylitis

ASDAS: Ankylosing Spondylitis Disease Activity Score

ASL: Azienda Sanitaria Locale (Local Health Authority)

AUC: Area under the serum concentration-time curve

AUCinf: Area under the serum concentration-time curve from time 0 to infinity

AUClast: Area under the serum concentration-time curve from time 0 to the last quantifiable concentration

AUEC: Area under the unit-dose-response curve

AxSpA: Axial Spondyloarthritis

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

CAI: cytokine activity index

CDAI: Clinical Disease Activity Index

CHMP: Committee for Medicinal Products for Human Use

CG Chiara Gerardi

CI Confidence Interval

Cl(R)D: chronic inflammatory (rheumatic) diseases

Cmax: Maximum plasma concentration

CRP: C-reactive protein

Cthrough: Through concentration

DSN: Duration of severe neutropenia

DTSQ: Diabetes Treatment Satisfaction Questionnaire

EA: Eleonora Allocati

EEA: European Economic Area
ELISA: Enzyme-Linked Immunosorbent Assays
EMA: European Medicine Agency
EML: Essential Medicine List
EPAR: European Public Assessment Reports
ESR: erythrocyte sedimentation rate
ETN: Etanercept
EU: European Union
FDA: Food and Drug Administration
GRADE: Grading of Recommendations Assessment, Development and Evaluation
HAQ-DI: Health Assessment Questionnaire Disability Index
HbA1c: Glycated hemoglobin
HTA: health technology assessment
IBD: Inflammatory Bowel Disease
IDeg: Insulin Degludec
IDet: Insulin Detemir
IFX: Infliximab
IgG: Immunoglobulin G
IGla: Insulin Glargine
IMM: Immunomodulator
IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico
ITR-QoL: Insulin Therapy-Related Quality of Life
KD: equilibrium dissociation constant
Kon: association rate constant
Koff: and dissociation rate constants
MAA: Marketing Authorization Application
MMAS: Morisky Medication Adherence Scale
mAb: Monoclonal Antibody
MB: Marteen Beeg
MODD: Means Of Daily Differences
NAb: Neutralizing Antibodies
NHS: National Health Services
NPH: Neutral Protamine Hagedorn
OOR: Overall response rate
PASI: Psoriasis Area and Severity Index
PASI 50: >50% improvement in Psoriasis Area and Severity Index
PASI75: > 75% improvement in Psoriasis Area and Severity Index
pCR: Pathologic complete response
PD: Pharmacodynamic
PGA: Physician’s Global Assessment
PK: Pharmacokinetic
PPS: Per Protocol Study
PS: Plaque Psoriasis
PsA: Psoriatic Arthritis
PsO: Plaque Psoriasis
RA Rheumatoid Arthritis
RU: Resonance Unit (time course of the SPR signal in RU (1000 RU = 1 ng/mm2)
QoL: quality of life
RB: Rita Banzi
RCT: Randomised Control Studies
R&D: Research and Development
RR: Risk Ratio
SD: Standard Deviation
SE: Standard Error
SIBDQ: Short Inflammatory Bowel Disease Questionnaire
SIPBS: Strathclyde Institute of Pharmacy and Biomedical Sciences
SPR: Surface Plasmon Resonance
T1DM: Type 1 Diabetes Mellitus
T2DM: Type 2 Diabetes Mellitus
TEAE: treatment-emergent adverse event
TDIM: Therapeutic Drug and Immunogenicity Monitoring
TDM: Therapeutic Drug Monitoring
TGA: Therapeutic Good Administration
TNF: Tumour Necrosis Factor
UK: United Kingdom
USA: United States of America
WED: Well-being Enquiry for Diabetes
WHO: World Health Organization
CHAPTER 1. Background

1.1. Definition of biological medicines

The introduction of biological medicines has changed the management of many serious and rare conditions including immune conditions, cancer and orphan diseases. Biological medicines (also called biotechnology products or biologicals) are medicines whose active principle consists of large and complex molecular structure, produced or extracted from a biological source, such as living cells or organisms (human, animals and microorganisms such as bacteria or yeast). Because these medicines are prepared using biotechnology methods or extracted from a biological source, there is the possibility of significant structural variations in the final product (e.g. different glycosylation profiles), which can give rise to important immunogenic differences (AIFA website; EMA healthcare professionals; EMA doc 26643). Moreover, the characterization of biological medicines is particularly difficult and cannot be disregarded from the production process, due to the intrinsic variability of the biologicals and the complexity of production techniques operating on living systems (Figure 1).

Biological medicines include a wide range of different products including recombinant therapeutic proteins, enzymes naturally produced in the human body, immunological medicinal products as vaccines, blood components and advanced technology products as gene therapy. The size and the complexity of biologicals span from simple proteins such as insulin or growth hormone to more complex ones such as coagulation factors or monoclonal antibodies. Biologicals include biotechnological medicines whose active substances are derived through procedures including recombinant DNA technologies, controlled expression of genes coding for biologically active proteins and monoclonal antibody methods (EMA biological guidelines; FDA biological products; AIFA website).
Complexity and high costs of development and manufacturing of biologics are key drivers of high requested prices, posing an important challenge for the sustainability of healthcare systems worldwide as their usage grows certainly across Europe (Godman B, Hill A, 2021). Indeed, cost and price pressures may lead to decreased patient access and use of these medicines as seen with the anti-TNFs for rheumatoid arthritis, psoriasis and inflammatory bowel disease among Central and Eastern European countries compared to Western European countries (EMA healthcare professional; EMA doc 26643; Aletaha D, 2010; Putrik P, 2014; Kostić M, 2017; Baumgart DC, 2019; Tubic B, 2021). In the USA, expenses related to biologic treatments currently represent almost 40% of the net drug spending and rising (Stiff KM, 2019). In addition in the USA, expenditures on new oncology medicines, typically biological medicines, for those approved just in 2018 could be as high as US$39.5 billion if all these new medicines were prescribed to all eligible patients that year (DeMartino PC, 2021).

Biosimilars offer significant opportunities to reduce price of biological medicines in an area of spiraling healthcare expenditure. Economic modeling has predicted considerable savings through the introduction of biosimilars (IQVIA, 2021; Kvien TK, 2022). In addition to benefiting health
systems generally, these cost savings may benefit patients directly by increasing or enabling earlier access to biologic therapies or by enabling dose intensification (Allocati, 2020; Dutta B, 2020).

1.2. Definition of biosimilar medicines
Over the past few years, the expiry of patents and/or other data protection certificates for biological medicines in Europe has fueled interest in developing biosimilars, i.e. biological agents that are similar to previously authorized biological medicines. Biosimilar medicines are highly similar to another already approved biological medicine called a “reference medicine” or “originator” in terms of their quality, efficacy and safety. According to the EMA “Guideline on similar biological medicinal products”, a biosimilar is “a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product in the EEA” and is not subject to patent coverage (EMA guidelines). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established for a biosimilar before marketing authorization can be granted. A biosimilar and its reference product, despite being the same biological substance, may have minor differences due to a certain degree of natural variability to their complex nature and to production techniques. Due to these characteristics, biosimilars cannot be considered as a generic of biological medicines (EMA healthcare professional; AIFA website) in the same way as traditional oral medicines including proton pump inhibitors or statins can (Godman B, 2014).

In Europe, the first biosimilar, approved in 2006, was somatotropin. Since then, more than 60 biosimilars of 18 biological drugs have been licensed by the EMA for the treatment of chronic and often disabling conditions including diabetes, autoimmune diseases and cancers. In addition, the period of data exclusivity of several other biologics is due to expire in the next few years (2022-2026) further enhancing potential savings.

The rationale behind the introduction of biosimilars is to increase price competition, leading to lower prices and improving sustainability and accessibility to medicines in Europe (Moorkens E, 2017; Matusewicz W, 2015; Godman B, 2013).

Given the rapid evolution of pharmaceutical technologies over the past decade and patent expiration of previously approved biologic molecules, biosimilar drugs have been developed as less costly alternatives to their reference biological medicine. It is believed that biosimilars can accelerate market competition, positively impacting the global healthcare system through improved
healthcare affordability and increased patients’ access to effective and safe medicines. However, despite the cost-saving potential of biosimilar drugs, there are still diverging perceptions regarding the efficacy, safety, and immunogenicity of biosimilars resulting in limited use in some countries despite affordability issues (Godman B, Fadare J 2021). Topics of considerable debate still include the switching and interchangeability between biologic and biosimilar drugs, i.e., replacing one medicine with another that is expected to achieve the same clinical effect in a given clinical setting (Ascef, 2021).

1.3. Overview of regulation at the European and national levels
As mentioned, the approach established for granting marketing authorization for generic medicines is not suitable for development, evaluation and licensing of biosimilars. Generic medicines need to demonstrate their “bioequivalence” to their reference product for marketing authorisation. Two medicinal products containing the same active substance, usually a simple synthetic molecule, are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailability (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. The manufacturers do not have to perform any clinical study to demonstrate their effectiveness and safety; however, such studies have been performed to enhance their acceptance and use (Gagne JJ, 2014; Manzoli L, 2016).

Biological medicines are relatively large and complex proteins produced following complex manufacturing processes, which may lead to molecules that are similar but not identical to the originator. For these reasons, biosimilars should demonstrate their “biosimilarity” compared to the reference product. The assessment of biosimilarity with respect to the originator slightly differs in the different world regions; however, it is basically based on the demonstration of similar analytical, pre-clinical and clinical performance (WHO 2019).

The EU pioneered in the development of a legal and regulatory framework for marketing authorization of biosimilars. This is one of the reasons why the European biosimilars market is highly mature especially compared to that of the United States. The EMA is responsible for the approval of biosimilars in the EU, following a formal regulatory pathway and extensive scientific guidelines that since 2001 outline the general requirements for marketing approval for specific biological products (EMA website; EMA guidelines). An amendment to Directive 2001/83/EC entered into force in 2005, provided the legal basis for a specific marketing authorization procedure for biosimilars (Directive, 2004). In the following years, additional overarching guidelines for biosimilars
were published, as well as product specific guidelines, for example for monoclonal antibodies (EMA guidelines).

The EU biosimilar approval pathway implies that the regulatory assessment is individually tailored to the evidence provided by the pharmaceutical company seeking marketing authorization for a biosimilar and to the type of product and therapeutic area (EMA guidelines). As for any other medicine, on the basis of EMA’s opinion, the European Commission grants marketing authorizations that are valid throughout the EU (Directive, 2004).

With twenty years of experience in approving biosimilars for use in the EU and advancements in technology, the EMA continues to revise its guidelines for the development of biosimilars, with a trend towards reduction of clinical data requirements (Wolff-Holz E, 2019).

The robust regulatory framework for biosimilars in Europe and other countries has led to the licensing of high-quality biosimilars. As a result, it has been proposed to further improve efficiency and evolve from the current ‘totality of evidence’ approach to a ‘confirmation of sufficient likeness’ paradigm based on analytical and pharmacokinetic evidence, allowing timely patient access with lower development costs, while maintaining the same scientific standards for approval (Webster CJ, 2019).

After an EU-wide marketing authorization is obtained, the individual Member States coordinate pricing and reimbursement of biosimilars and have the responsibility for implementing specific policy measures related to the use of off-patent biologicals, including biosimilars. Though responsible for assessing biosimilarity and allowing biosimilars onto the market, the EMA does not provide opinions on the interchangeability with the originator, which is established by each member state (EMA marketing authorization). The adoption of different policies and practices by European countries to manage the entry of biosimilars has contributed to considerable variation in their use, both between and within countries (Troein P, 2019). In general, competition in a therapeutic class, the use in acute or chronic treatment, and the use of the product in the hospital or retail setting, are factors that play a role in variation in biosimilar use between different active substances (Troein P, 2019). In addition, issues of trust in a biosimilar among both physicians and patients with concerns with the nocebo effect (Rezk MF, 2018; Colloca L, 2019).

It should be noted, while the EMA does not regulate interchangeability between the reference product and biosimilars, in the US the FDA considers the originator and its biosimilars
therapeutically interchangeable if the manufacturer has demonstrated no clinically meaningful
differences from the reference product (FDA guidelines).

1.4. Comparability exercise
The process for producing biological medicines is so highly distinctive that it can be said that "the
product is the production process" (Carson K, 2005; AIFA website).
Manufacturers of biological products frequently make changes to the manufacturing process both
during development and after approval. This applies to reference products as well as to biosimilars.
Such changes are needed to improve the manufacturing process, increase the scale of production,
improve product stability, and comply with changes in regulatory requirements. Balázs Vezer and
colleagues investigated the number and types of manufacturing changes of the originator
monoclonal antibodies and ascertained the level of risk these changes might impart (Balázs Vezer,
2016). The study included 29 monoclonal antibodies approved at the time of the analysis (October
2014) and with publicly available EPAR (a set of documents describing the evaluation of a medicine
authorised via centralised procedure published on the European Medicines Agency website). The
authors found details of 404 manufacturing changes authorized by the EMA. Of these, 22 were
categorized as high risk, 286 as moderate risk and 96 as low risk manufacturing changes. Examples
of high-risk changes were changes in the purification of the active substance, in the manufacture of
active substance or of a starting material/reagent/intermediate, or changes in batch size. Examples
of low-risk changes were changes in the manufacturing process of the finished product, replacement
or addition of a manufacturing site for the finished product, change to in-process tests or limits
applied during the manufacture of the finished product (Balázs Vezer, 2016).
For all these changes made during the manufacturing process, the manufacturer is required to
evaluate the relevant quality attributes of the product to demonstrate that modifications cannot
adversely impact the safety and efficacy of the drug product. These series of studies characterizing
quality attributes are the first step of the so-called comparability exercise and aim to indicate
whether or not confirmatory nonclinical or clinical studies are appropriate. The goal of the
comparability exercise is to ensure the quality, safety and efficacy of the biological medicine
produced by a changed manufacturing process, through collection and evaluation of the relevant
data to determine whether there might be any adverse impact on the biological medicine due to
changes in the manufacturing process. The demonstration of comparability does not necessarily
mean that the quality attributes of the pre-change and post-change product are identical, but that
they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the biological medicine. A determination of comparability can be based on a combination of analytical testing, biological assays and, in some cases, nonclinical and clinical data. If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the post-change product are not warranted (ICH Topic Q 5 E Comparability of Biotechnological/Biological Products). However, physicians or patients may not be aware of the considerable changes that have taken place for a number of originator biological medicines without the need to undertake additional studies to demonstrate similar effectiveness of safety, whilst at the same time having concerns with biosimilars (Godman B, 2019).

Indeed, no approved biological medicine is structurally identical to itself, and although different batches are not identical to each other, they may be considered essentially equal and therapeutically indistinguishable. Consequently, there is a clinically acceptable range of inherent structural heterogeneity for any biological product (de Mora F, 2019).

Biosimilars are licensed according to the same standards of pharmaceutical quality, safety and efficacy that apply to all medicines including biological products.

The comparability exercise has become the scientific norm for biosimilar development. Indeed, the scientific principles for biosimilar development and review were built on experience and regulatory history of originator biologics, especially the comparability concept for regulating process manufacturing changes that was developed in the 1990s and cumulated in the ICH Q5E guideline (Schiestl M, 2020; EMA Q5E_Guide line).

As a result, biosimilars are licensed only after a thorough comparability exercise aimed to detect any differences arising from manufacturing changes that can influence their efficacy and safety versus the originator (EMA guidelines). Notwithstanding natural variability inherent to all biological medicines, biosimilars are approved by the EMA if there are no clinically meaningful differences between the biosimilar and reference medicine in terms of structure, biological activity and efficacy, safety and immunogenicity profile.

As well as the comparability exercise required when changes to the manufacturing process occur, the comparability exercise required for the approval of biosimilars envisages a stepwise approach (Figure 2).
To prove biosimilarity, the stepwise approach starts by the demonstration of structural and functional similarity (including for example amino acid sequence changes, post-translational modifications, higher-order structure, purity, receptor affinity, and potency in cell bioassays). The approach proceeds until the developer is sufficiently confident that the biosimilar molecule has a comparable quality, safety and efficacy to the reference product. Depending upon the level of similarity demonstrated analytically, clinical PK/PD/immunogenicity studies, and comparative clinical effectiveness studies may be required by regulatory agencies. Differences that may affect clinical safety, efficacy or immunogenicity need to be further studied through comparative non-clinical studies and/or comparative clinical studies.

In particular, comparative non-clinical studies include pharmacodynamic studies in vitro, which look at the binding and activation (or inhibition) of physiological targets and immediate physiological effects in cells. Pharmacodynamic studies in animal models are only done if no suitable in vitro model exists. On the other hand, comparative clinical studies are tailored to confirm biosimilarity and to address any questions that remained from previous analytical or functional studies. An inherent variability is associated with a production process relying on living cells (Schiestl M, 2011). In addition, the production process is highly sensitive to different process variables such as growth conditions. First, a production cell line must be developed that produces the biological molecule. Following this, the physicochemical features of the molecule are characterised and compared with
those of the reference product (Niazi S, 2016). Biological activity is also tested in vitro in bioassays in comparison with the reference product. The development of a biosimilar is a re-iterative process. Adaptation of the cell line, optimization of the culture conditions and a purification process are all required to ultimately achieve a biological medicine that is physio-chemically and in vitro biologically as close to the reference product as possible. Based on these outcomes, a phase I PK/PD study must be carried out, which most of the time is followed by a phase III confirmatory efficacy study (EMA guidelines). The chosen indication for the phase III study will be the indication that is most sensitive to demonstrate possible differences with the reference product; however, it is not intended to prove efficacy per se. The basis for demonstrating biosimilarity is thus the extensive comparative physicochemical and biological characterization (EMA guidelines).

1.5. Facilitators and barriers to biosimilar prescriptions
Beyond the R&D and regulatory path allowing biosimilars onto the market, a number of important aspects are associated with the use of biosimilars. These include health care system sustainability and market dynamics, interchangeability policies, and labelling and prescribing information to physicians and patients.

Biosimilars are increasingly seen as an attractive alternative to innovator biological medicines. They attain comparable quality, safety and efficacy, typically at a lower cost, creating competition in the pharmaceutical market. This competition may as well lead to a shift in market shares, revision of market strategies and attraction of new players to the biopharmaceutical market (Rader RA, 2013; Malkin BJ, 2015; Troein P, 2019). Biosimilar competition may also lead to a reduction of the price of the respective innovator biological medicine. For instance, delivered savings for NHS England following the use of adalimumab, infliximab, etanercept and rituximab biosimilars were estimated at over GB£220 million in the year 2018/2019 (NHS England, 2019). In addition to cost savings, biosimilar competition may serve to enlarge the number of patients who can be treated with biological medicines, decreasing patient access barriers and representing an important opportunity for earlier, optimal and equal access to very effective biological treatments (Inotai A, 2019). Furthermore, biosimilars can improve the cost effectiveness of a therapy, stimulate incremental innovation and contribute to the prevention of drug shortages (Dutta B, 2020). Savings can also be used to ensure access to other new, expensive treatments; alternatively increase the number of professionals treating a disease where resources are finite.
On the other hand, the mistrust in efficacy and safety of biosimilars may affect their adoption, discouraging competition and contributing to a limited reduction of drug prices (Tricco AC, 2021). This mistrust is a result of concerns surrounding the use of biosimilars, which stems from their molecular complexity despite the rigorous regulatory processes necessary to achieve authorization (Kaplan GG, 2020; Luber RP, 2021).

Reportedly prescribers have little knowledge of the manufacturing, approval requirements, and ongoing regulation of biologic and biosimilar products (Jimenez-Pichardo L, 2018; Leonard E, 2019; Hemmington A, 2017; Aladul MI, 2018). Medical specialists generally have positive attitudes towards biosimilars, with differences between specialties, but they seem to be less confident about the extrapolation of indications and switching patients from an originator biologic to its biosimilar (Leonard E, 2019; Hemmington A, 2017; Aladul MI, 2018). Positive attitudes towards biosimilars may be enhanced by studies re-affirming their equivalence in clinical practice as seen with the NOR-SWITCH study with infliximab in Norway sponsored by the Norwegian Ministry of Health (Jørgensen KK, 2017).

Immunogenicity constitutes another important concern of the use of biosimilars, especially in chronic conditions where patients may be required to switch from the reference products to biosimilar medicines. It is known that the presence of ADAs is associated with the decrease of trough-serum drug levels, lower clinical response and more side effects. Infliximab is one of the most immunogenic anti-TNF therapies; consequently, the prevention of the immunization and the clinical management of its consequences is a key clinical issue. Due to potential differences between originator and its biosimilars, both physicians and patients fear that switching could lead to increased immunogenicity risk due to potential differences (Park W, 2016). This was the basis of the NOR-SWITCH study with infliximab in Norway (Jørgensen KK, 2017). Since then, multiple studies have been undertaken to demonstrate the clinical effectiveness of biosimilars as well as lack of immunogenicity concerns when patients are switched between biosimilars (Allocati E, 2022).

Physician and patient education and information remains essential to reduce the mistrust against biosimilar medicines, to strengthen patients’ relationship with the doctor and to accept the treatment. Shared decision-making and improving the quality of information given to both physicians and patients have demonstrated benefit for improving treatment adherence (Lofland JH, 2017; Trystram N, 2021).
CHAPTER 2. Aims of the project
The general aim of this project was to provide reliable tools to support the introduction of biological medicines and their biosimilars, and to optimize their clinical use (Figure 3). Moreover, this project aimed at exploring whether it may be appropriate to use potential surrogate measures in current clinical practice to select and monitor the appropriate use of all biological medicines. In particular, the project had the following specific aims:

2.1. To analyse the clinical development and marketing authorisation of biosimilars in the EU
I sought to explore how the regulatory framework affects biosimilar clinical development, policies and uptake, to provide physicians and health professionals with an overview of the approval of biosimilars by the EMA. The broad objective was to establish the basis for streamlining the approval processes and facilitating prompt availability of biosimilars and their subsequent moderating effects on expenditure on biological medicines.

2.2. To analyse the switching between originator and biosimilars in chronic clinical conditions
I sought to evaluate the evidence that reduces uncertainties about the use of biosimilars, evidence of strategies focused on potential mandatory interchangeability at the procurement and clinical level, and tackling new approaches to develop, license and monitor biosimilars to improve efficiency of market approval and accelerate access. In order to do this, I reviewed all the studies that assessed the outcomes of switching between biologics and their biosimilars focusing on those treatment considered by the Expert Committee of EML, in particular on insulins and anti-TNFs.

2.2.1. The case of switching among insulins
I sought to analyse the evidence regarding the switching between insulin analogues and their biosimilars and human insulin. The objective was to inform the WHO EML Expert Committee in charge of issuing recommendations on switching from human insulin to insulin analogues and vice versa, as well as interchangeability of insulin analogues and their biosimilar products as more biosimilars became available to lower the costs of long-acting insulin analogues.
2.2.2. The case of switching among anti-TNFs
I sought to analyse the evidence supporting the switch between originator and biosimilars of anti-TNFs to understand key issues and barriers to full interchangeability for wider access to affordable biologic medicines and their biosimilars.

2.3. To support appropriate use of biologic drugs and their biosimilars (therapeutic drug and antibodies monitoring of biologic drugs and their biosimilars)
I sought to explore whether and how the proactive measurement of TNF inhibitors and ADA in the blood (proactive TDIM) can support informed decisions for a more rational management of biological therapies, improving the appropriateness and personalization of care, with important advantages for the patients and European National Health Services.

2.4. Education and training of health professionals/liaison with health authorities
I aimed to provide health professionals with knowledge regarding the bases of biosimilar medicines, the research and development path as well as scientific and regulatory requirements underlying their marketing authorization. I also provided information about the context of the supply of biosimilar drugs in Italy, their appropriateness and therapeutic monitoring.

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**Figure 3:** the introduction of biological medicines and their biosimilars, and to optimize their clinical use
This figure represents a sort of system map that describes the path to a needed widespread adoption for a better introduction of biological medicine and their biosimilars as well as for their optimization in clinical use.
CHAPTER 3. Clinical development and marketing authorisation of biosimilars in the EU

3.1. Purpose and methodology

In order to review the marketing authorization of biosimilars and provide a critical analysis of the pivotal trials supporting their approval, I searched the EMA database and identified all biosimilars approved for any indication up to June 2019 for which the EPAR were available (Allocati E, 2020). For each biosimilar, I identified the pivotal trials, i.e. those had contributed the most to form the basis for their subsequent marketing approval, focusing on those reported in the clinical efficacy section of the EPAR along with supportive trials. Indeed, although the regulatory authorities’ decision to grant the marketing authorization to a biosimilar is based on the whole body of evidence supporting the similarity at the quality, preclinical and clinical levels, we assumed the clinical efficacy data were pivotal when available. I analyzed clinical trials assessing their efficacy and safety when available, as well as pharmacokinetics/pharmacodynamics (PK/PD) data when considered pivotal. For each trial I extracted the design and its duration, the type and number of participants, information on intervention and control arms, primary outcome and comparability margins, and the main results. I also extracted summary information on the immunogenicity as reported in the pivotal trials.

A second reviewer (RB) supervised and independently checked all the steps of data collection and analysis to ensure quality and consistency. If any doubt or discrepancy would have emerged with the second reviewer (RB), it would have been solved through discussion. We did not need to consult a third independent reviewer.

Through this analysis, I sought to explore how the regulatory framework affects biosimilar clinical development, policies and uptake, to establish the basis for streamlining the approval processes and facilitating prompt availability of biosimilars and their subsequent moderating effects on expenditure on biological medicines.

Since the first analysis reported in the publication of Allocati et al (Allocati E, 2020), the EMA has approved several other biosimilars. Consequently, in this thesis, I will provide an update of the analysis up to April 2022. Indeed, I searched the EMA database and identified all biosimilars approved for any indication from June 2019 up to April 2022, for which the EPAR were available.
3.2. Results
In the initial analysis, I found that the EMA evaluated 55 biosimilars, corresponding to 16 biologic medicinal products. Between July 2019 and April 2022, the EMA evaluated 19 biosimilars corresponding to six biological medicinal products. Biosimilars of insulin aspart and ranibizumab entered for the first time since the patent and further extension of their reference products had recently expired. I report here the analysis of 74 biosimilars, 68 still on the market (April 2022), and corresponding to 18 biologic medicinal products. Seventeen biosimilars were excluded from the analysis: two had a negative opinion from the EMA CHMP, while 15 had been withdrawn by the marketing authorisation holders before the CHMP opinion or after the marketing approval (Flow chart 1 above).
The first finding from this analysis is that the 68 current biosimilars, as of April 2022, correspond to only 18 active principles – the compound responsible for the activity of the medicine (Evidence Table 1 above).

Indeed, different applications for the same biosimilar were often submitted to the EMA, leading to the approval of one medicinal product but with different commercial names. For instance, six biosimilars of rituximab were approved in 2017, but they contain only two different active principles. Similarly, ten biosimilars of adalimumab were approved between 2017 and 2022, but
they contain only eight different active principles. To note, two other biosimilars of adalimumab that entered the market were later withdrawn due to commercial reasons. Their active principles were the same as other adalimumab products still on the market. Different biosimilars of infliximab, epoetin alfa and zeta, filgrastim, and teriparatide, containing the same active principle, were marketed by different companies. This also happened for biosimilars belonging to different marketing authorisation holders: the XM02-02-INT trial involving patients with breast cancer receiving chemotherapy which formed the basis for the approval of both Ratiograstim (Ratiopharm) and Tevagrastim (Teva).
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<th>active principle</th>
<th>N active principle</th>
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<th>Design</th>
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**Epoetin alfa**

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**Epoetin alfa Hexal**

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<td>04-04 (maintenance phase)</td>
<td>anemia (chronic kidney failure)</td>
<td>III</td>
<td>equivalence</td>
<td>weekly dosage of epoetin</td>
<td>1</td>
<td>609</td>
<td>95% CI diff in mean weekly dosage: -14 to 14 IU/kg/week</td>
<td>difference: 0.1 (95% CI -4.67 to 4.29)</td>
<td>Y</td>
</tr>
<tr>
<td>Silapo 1  2007  SB309</td>
<td>04-05 (correction phase)</td>
<td>anemia (chronic kidney failure)</td>
<td>III</td>
<td>equivalence</td>
<td>weekly dosage of epoetin</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>04-04 (maintenance phase)</td>
<td>anemia (chronic kidney failure)</td>
<td>III</td>
<td>equivalence</td>
<td>weekly dosage of epoetin</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Filgrastim Table**

| Nivestim 1  2010  PLIVA/Ma yne filgrastim | GCF071 | neutropenia (cancer) | III | equivalence | DNS | 1 | 279 | 95% CI diff DSN: -1 to 1 | day | difference: 0.38 (95% CI 0.08 to 0.68) | N |
| Ratiogranств 1  2008  XM02 | XM02-02-INT | neutropenia (breast cancer) | III | equivalence | DNS | 1 | 378 | 95% CI diff DSN: -1 to 1 | day | difference: 0.032 (95% CI -0.262 to 0.325) | N |
| Tevagranств 1  2008  XM02 | XM02-02-INT | neutropenia (breast cancer) | III | equivalence | DNS | |
| Accofil 1  2014  Neukine | KWI-300-103 | healthy volunteers | PK/PD | bioequivalence | AUC, Cmax | 1 | 78 | 90% CI AUC, Cmax: 80 to 125% | AUC0-24: 99.0 (90% CI 89.25 to 109.82); Cmax: 99.7 (90% CI 88.74 to 112.03); AUC-S5: 103.1 (90% CI 92.04 to 115.37) | N |
|             | KWI-300-104 | neutropenia (breast cancer) | III | single arm | DSN, adverse events | 1 | 120 | not applicable | DSN: 1.40 (SD=1.07) | N |
| Grastofil 1  2013  Neukine | KWI-300-103 | healthy volunteers | PK/PD | bioequivalence | AUC, Cmax | |
|             | KWI-300-104 | neutropenia (breast cancer) | III | single arm | DSN, adverse events | |
|             | EP06-301 | neutropenia (breast cancer) | III | single arm | DSN, adverse events | 1 | 170 | not applicable | not reported | N |
|             | EP06-301 | neutropenia (breast cancer) | III | single arm | DSN, adverse events | |

**Pegfilgrastim**
<p>| Pelgraz | 1 | 2018 | APO-Peg | 1 | Pelgraz-03 | neutropenia (breast cancer) | III | equivalence | DNS | 1 | 589 | 95% CI diff DSN: -0.5 to 0.5 day | difference vs EU orig: -0.01 (95% CI -0.29 to 0.26) | difference vs US orig: 0.23 (95% CI -0.04 to 0.50) | Y |
| Fulphila | 1 | 2018 | MYL-1401H | 1 | MYL-1401H-3001 | neutropenia (breast cancer) | III | equivalence | DNS | 1 | 194 | 95% CI diff DSN: -1 to 1 day | difference: 0.01 (95% CI -0.285 to 0.298) | Y |
| Udenyca | 1 | 2018 | CHS-1701 | 1 | CHS-1701-05 (PK/PD BE) | healthy volunteers | PK/PD | bioequivalence | AUC, Cmax | 1 | 122 | 90% CI AUC, Cmax: 80 to 125% | AUCO-inf: 92.8 (90% CI 83.6 to 103.1) | Cmax: 100.4 (90% CI 90.5 to 111.4) | AUCO-last: 96.7 (95% CI 91.4 to 102.4) | AUCO-48h: 99.8 (95% CI 97.3 to 102.4) | Y |
| Peleg | 1 | 2018 | B121019 | 1 | B12019-101 | healthy volunteers | PK/PD | bioequivalence | AUC, Cmax, AUEC | 1 | 172 | 94.32% CI AUC, Cmax: 80 to 125% | AUCO-last: 95.23 (94.32% CI 86.60 to 104.73) | Cmax: 92.84 (94.32% CI 84.36 to 102.18) | AUCO-inf: 92.07 (94.32% CI 82.94 to 102.21) | AUEC: 100.20 (95% CI 98.67 to 101.75) | Y |
| Ziextenzo | 1 | 2018 | LAEP2006 | 1 | LA-EP06-301 | neutropenia (breast cancer) | III | equivalence/no-inferiority | DSN | 1 | 316 | 95% CI diff DSN: -1 to 1 day Equiv. | 95% CI diff DSN: -0.6 day Ni | difference vs EU orig: 0.08 (95% CI -0.17 to 0.33) | Y |
| Grasustek | 1 | 2019 | Grasustek | 1 | PEGF/USV/P3/003 | neutropenia (breast cancer) | III | equivalence | DSN | 1 | 254 | 95% CI ratio mean DSN: 0.65 to 1.55 | Difference vs EU orig: 0.96 (95% CI 0.78 to 1.18) | Y |
| Bemfola | 1 | 2014 | AFOLIA | 1 | FIN3001 | LH/FSH deficiency, hypogonadism | III | equivalence | number of oocytes | 1 | 372 | 95% CI diff No. oocytes: -2.9 to 2.9 | difference: 0.27 (95% CI -1.34 to 1.32) | N |</p>
<table>
<thead>
<tr>
<th>Study Name</th>
<th>Year</th>
<th>Code</th>
<th>Type</th>
<th>Condition</th>
<th>Design</th>
<th>Endpoint</th>
<th>Hba1c</th>
<th>No.</th>
<th>95% CI Difference</th>
<th>95% CI</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovaleap</td>
<td>2013</td>
<td>XM17</td>
<td>LH/FSH deficiency, hypogonadism</td>
<td>III</td>
<td>equivalence</td>
<td>number of oocytes</td>
<td>1</td>
<td>299</td>
<td>upper 95% CI diff from baseline Hba1c: below 0.4%</td>
<td>difference: 0.03 (95% CI -0.76 to 0.82)</td>
<td>Y</td>
</tr>
<tr>
<td>Abasaglar</td>
<td>2014</td>
<td>LY2963016</td>
<td>ABEB study</td>
<td>T1DM</td>
<td>III</td>
<td>non-inferiority</td>
<td>Hba1c</td>
<td>1</td>
<td>536</td>
<td>upper 95% CI diff from baseline Hba1c: below 0.4%</td>
<td>difference: 0.106 (95% CI -0.005 to 0.217)</td>
</tr>
<tr>
<td>ABEC study</td>
<td></td>
<td></td>
<td>T2DM</td>
<td>III</td>
<td>non-inferiority</td>
<td>Hba1c</td>
<td>1</td>
<td>759</td>
<td>upper 95% CI diff from baseline Hba1c: below 0.4%</td>
<td>difference: 0.052 (95% CI -0.070 to 0.175)</td>
<td>Y</td>
</tr>
<tr>
<td>P-006 STUDY</td>
<td></td>
<td></td>
<td>T2DM</td>
<td>III</td>
<td>non-inferiority</td>
<td>Hba1c</td>
<td>1</td>
<td>526</td>
<td>upper 95% CI diff from baseline Hba1c: below 0.4%</td>
<td>difference: 0.03 (95% CI -0.12 to 0.18)</td>
<td>Y</td>
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<tr>
<td>Semglee</td>
<td>2018</td>
<td>MYL-1501D</td>
<td>MYL-GAI-3001</td>
<td>T1DM</td>
<td>III</td>
<td>non-inferiority</td>
<td>Hba1c</td>
<td>1</td>
<td>558</td>
<td>upper 95% CI diff from baseline Hba1c: below 0.4%</td>
<td>difference: 0.03 (95% CI -0.066 to 0.117)</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>2017</td>
<td>SAR342434</td>
<td>EFC12619</td>
<td>T1DM</td>
<td>III</td>
<td>non-inferiority</td>
<td>Hba1c</td>
<td>1</td>
<td>507</td>
<td>upper 95% CI diff from baseline Hba1c: below 0.3%</td>
<td>difference: 0.06 (95% CI -0.084 to 0.197)</td>
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<tr>
<td>EFC13403</td>
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<td>T2DM</td>
<td>III</td>
<td>non-inferiority</td>
<td>Hba1c</td>
<td>1</td>
<td>505</td>
<td>upper 95% CI diff from baseline Hba1c: below 0.3%</td>
<td>difference: -0.07 (95% CI -0.215 to 0.067)</td>
<td>Y</td>
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<tr>
<td>Rituximab</td>
<td>2017</td>
<td>GP2013</td>
<td>GP13-301</td>
<td>follicular lymphoma</td>
<td>III</td>
<td>equivalence</td>
<td>response rate (ORR)</td>
<td>1</td>
<td>629</td>
<td>95% CI diff ORR: -12 to 12%</td>
<td>difference: -0.40 (95% CI -5.94 to 5.14)</td>
</tr>
<tr>
<td>Rixathon</td>
<td>2017</td>
<td>GP2013</td>
<td>GP13-301</td>
<td>follicular lymphoma</td>
<td>III</td>
<td>equivalence</td>
<td>response rate</td>
<td>1</td>
<td>173</td>
<td>90% CI AUC: 80 to 125%</td>
<td>AUCO-inf: 1.064 (90% CI 0.968 to 1.169)</td>
</tr>
<tr>
<td>Riximyo</td>
<td>2017</td>
<td>GP2013</td>
<td>GP13-301</td>
<td>follicular lymphoma</td>
<td>III</td>
<td>equivalence</td>
<td>response rate</td>
<td>1</td>
<td>154</td>
<td>90% CI AUC, Cmax: 80 to 125%</td>
<td>AUCO-last: 97.72 (90% CI 89.23 to 107.00) Cmax: 97.57 (90% CI 91.96 to 103.53)</td>
</tr>
<tr>
<td>Blitzima</td>
<td>2017</td>
<td>CT-P10</td>
<td>CT-P10.1.1</td>
<td>RA</td>
<td>I</td>
<td>bioequivalence</td>
<td>AUC, Cmax</td>
<td>1</td>
<td>372</td>
<td>90% CI AUC, Cmax: 80 to 125%</td>
<td>AUCO-last: 94.08 (90% CI 84.63 to 104.58) Cmax: 88.99 (90% CI 82.40 to 96.10) Diff DAS28: -0.05 (90% CI -0.31 to 0.20)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Drug</th>
<th>N (Year)</th>
<th>CT-P10</th>
<th>RA/RAI/RAIII</th>
<th>Follicular lymphoma</th>
<th>I/III</th>
<th>Equivalence/Non-Inferiority</th>
<th>AUC, Cmax, DAS</th>
<th>Response Rate (ORR)</th>
<th>1</th>
<th>121</th>
<th>90% CI AUC, Cmax: 80 to 125% Point Estimate difference ORR: Below 7%</th>
<th>AUCO-last: 95.32 (90% CI 81.03 to 112.14) Cmax: 101.38 (90% CI 93.49 to 109.94) OOR: 5.7 (95% CI -3.4 to 15.4)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truxima</td>
<td>1 2017</td>
<td>CT-P10</td>
<td>RA</td>
<td>I</td>
<td>bioequivalence</td>
<td>AUC, Cmax</td>
<td></td>
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<tr>
<td>Ritemvia</td>
<td>1 2017</td>
<td>CT-P10</td>
<td>RA</td>
<td>I</td>
<td>bioequivalence</td>
<td>AUC, Cmax</td>
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</tr>
<tr>
<td>Rituzena</td>
<td>1 2017</td>
<td>CT-P10</td>
<td>RA</td>
<td>I</td>
<td>bioequivalence</td>
<td>AUC, Cmax</td>
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</tbody>
</table>

| Enoxaparin   |         |        |              |                     |                  |                      |               |                      |   |     |                                                                 |                                                  |   |
| Inhixa       | 1 2016  | enoxaparin 1 | 411/13   | healthy volunteers | PD                | bioequivalence        | AUC, Cmax     |                      |   | 20 | 90% CI AUC, Cmax: 80 to 125%                                   | AUCO-t: 105.72 (95% CI 97.12 to 115.09) Cmax: 104.79 (95% CI 99.45 to 110.43) | N |
| Thorinane    | 1 2016  | enoxaparin 1 | 411/13   | healthy volunteers | PD                | bioequivalence        | AUC, Cmax     |                      |   |     |                                                                 |                                                  | N |

| Somatropin   |         |        |              |                     |                  |                      |               |                      |   |     |                                                                 |                                                  |   |
| Omnitrope    | 1 2006  | API Sandoz 1 | EP2K-99-PhIII, EP2K-00-PhIIIfo and EP2K-00-PhIIIAQ | GH-deficiency     | III                | equivalence          | HSDS          |                      |   | 89 | not reported                                                      |                                                  | Y |

<p>| Teriparatide |         |        |              |                     |                  |                      |               |                      |   |     |                                                                 |                                                  |   |
| Movymia      | 1 2017  | RGB 10 | RGB-10-001  | healthy premenopausal women | I                | bioequivalence        | AUC, Cmax     |                      |   | 56 | 94.12% AUC, Cmax CI: 80 to 125%                                  | AUCO-last: 91.66 (94.14% CI 85.20 to 98.60) Cmax: 92.25 (94.12% CI 85.51 to 99.52) | N |</p>
<table>
<thead>
<tr>
<th>Terrosa</th>
<th>1</th>
<th>2017</th>
<th>RGB 10</th>
<th>RGB-10-001</th>
<th>healthy pre-menopausal women</th>
<th>I</th>
<th>bioequivalence</th>
<th>AUC, Cmax</th>
</tr>
</thead>
</table>

List of abbreviation: ACR20: 20% improvement in American College of Rheumatology core set measurement; AUC: Area under the serum concentration-time curve; AUC\text{inf}: Area under the serum concentration-time curve from time 0 to infinity; AUC\text{last}: Area under the serum concentration-time curve from time 0 to the last quantifiable concentration; AUEC: Area under the unit-dose-response curve; C\text{max}: Maximum plasma concentration; C\text{through}: Through concentration; DSN: Duration of severe neutropenia; HbA1c: Glycated hemoglobin; OOR: Overall response rate; PASI75: $\geq$ 75% improvement in Psoriasis Area and Severity Index; pCR: Pathologic complete response; PPS: Per Protocol Study; PS: Plaque psoriasis; RA: Rheumatoid arthritis.
The biosimilars approved by the EMA cover a wide range of clinical indications (Table 1 below). Most biosimilars are intended for treating cancers or chronic inflammatory diseases including inflammatory bowel diseases and rheumatic disorders. Other biosimilars are used for the treatment of diabetes and osteoporosis. The approved biosimilars usually have the same indications as the originator, with minor differences. This is due to the so-called extrapolation of indications that is part of the comparability exercise of any biologic agents, and has been used for several years to prove similarity after manufacturing changes (EMA Q5E_Guideline). The scientific and regulatory principle at the basis of the extrapolation of indications is that the approval of a biosimilar in one indication held by the reference product can be extended to the other indications of the originator without the need of comparative clinical trials in each indication. For instance, adalimumab biosimilars entered the market after the assessment of one or two pivotal clinical trial(s) that compared efficacy and safety in patients with plaque psoriasis and/or RA. Indeed, RA is the indication for which the adalimumab originator Humira® obtained the initial marketing authorization and the condition where most clinical evidence had been accumulated. Moreover, after the demonstration of comparable physicochemical and functional characteristics through quality and pre-clinical data between biosimilars and its originator, extrapolation can be agreed in the various indications granted for the originator. Through the analysis of the EPARs, restricted to 55 biosimilars that entered the market from 2006 to April 2019, we highlighted that the comparability exercise and subsequent approval of the majority of them (49/55, 89%) were based on one or more pivotal phase III trials testing their clinical efficacy (Allocati E, 2020). In all, biosimilars were approved on the basis of 55 trials, mostly phase III (42/55, 76%) assessing clinical efficacy, which were mainly equivalence trials (31/55, 56%). This was different to the approvals of biosimilars of insulin glargine and insulin lispro, which were based on trials with a non-inferiority design, i.e., simply aimed at demonstrating that the biosimilar product was not much worse than its originator. The different study design chosen for the insulin lispro and glargine pivotal clinical trials, shows that not for all the approved biosimilars the comparability exercise was based on comparative efficacy trials. This complies with specific EMA guidelines, stating that a dedicated comparative efficacy trial is not always considered necessary (EMA guideline heparin).

The pivotal phase III trials assessed surrogate measures of clinical effect and 71% reported immunogenicity data, measured as the production of ADAs and NAb. The immunogenic responses
were similar between biosimilars and originators and none of the trials showed evidence of differences in the therapeutic effects or induction of adverse effects due to ADA or NAb. As I did not assess safety supportive studies, I cannot exclude that additional data on immunogenicity were reported in supportive safety studies.

This trend in our findings is confirmed by the analysis of the 19 biosimilars approved between July 2019 and April 2022. For the biologic medicines that already had at least one biosimilar approved before 2019, pivotal phase III studies testing clinical efficacy were usually the basis of the approval. This was the case for the newer approved biosimilars of adalimumab, etanercept, trastuzumab, bevacizumab and rituximab but not for teriparatide and pegfilgrastim. Indeed, the first teriparatide biosimilars were approved on the basis of PK phase I studies, while the latest teriparatide (Livogiva) has been approved on the basis of a phase III immunogenicity study (Livogiva EPAR). This was made possible since the applicant followed the EMA advice to present a comparative immunogenicity study at the time of MAA with the ADA incidence as the primary objective. The applicant provided an estimate for the difference in ADA incidences between treatment groups at time-points 12 and 24 weeks by making use of a confidence interval (95% two-sided). In the assessment of uncertainties of biosimilarity, the upper limits of these derived confidence intervals were taken into consideration for a worst-case evaluation: for week 12 the upper limit was 15.4%-points ADA incidence in the investigated population, whereas for week 24 the upper limit was 18.3%-points, which appears a rather large difference (Livogiva EPAR).

On the other hand, for the approval of the biosimilar of Forsteo®, no analysis of immunogenicity parameters was performed because the Applicant was of the opinion that “a clinically relevant immunogenic potential of RGB-10 appeared to be highly unlikely as the immunogenic potential of Forsteo® has proved to be negligible in the clinical studies for registration purposes as well as over the past ten years on the market” (Terrosa EPAR).

The same applies to the latest biosimilar pegfilgrastim, approved on the basis of phase III equivalence trial, while all the older pegfilgrastim were approved on the basis of PD study only. The comparability exercise for the biosimilars of ranibizumab and insulin aspart were based on one or more pivotal phase III trial testing their clinical efficacy, as their safety and immunogenicity (Ranibizumab EPAR; Insulin aspart EPAR).
<table>
<thead>
<tr>
<th>Active substance (originator, MA Holder)</th>
<th>Biosimilar commercial name – PA</th>
<th>MA holder</th>
<th>MA year</th>
<th>EMA indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira, AbbVie Ltd)</td>
<td>Amgevita&lt;sup&gt;1&lt;/sup&gt; - ABP 501</td>
<td>Amgen Europe B.V</td>
<td>2017</td>
<td>Rheumatoid arthritis and juvenile idiopathic arthritis, axial spondyloarthritis and ankylosing spondylitis, psoriatic arthritis, psoriasis and pediatric plaque psoriasis, hidradenitis suppurativa, Crohn’s disease, ulcerative colitis, uveitis</td>
</tr>
<tr>
<td>Imraldi - SB5</td>
<td>Samsung Bioepis UK Limited</td>
<td></td>
<td>2017</td>
<td>Rheumatoid arthritis and juvenile idiopathic arthritis, enthesitis-related arthritis, axial spondyloarthritis and ankylosing spondylitis, psoriatic arthritis, psoriasis and pediatric plaque psoriasis, hidradenitis suppurativa, Crohn’s disease, ulcerative colitis, uveitis</td>
</tr>
<tr>
<td>Hefiya&lt;sup&gt;b&lt;/sup&gt; - GP2017</td>
<td>Sandoz GmbH</td>
<td></td>
<td>2018</td>
<td>Rheumatoid arthritis and juvenile idiopathic arthritis, enthesitis-related arthritis, axial spondyloarthritis and ankylosing spondylitis, psoriatic arthritis, psoriasis and pediatric plaque psoriasis, hidradenitis suppurativa, Crohn’s disease, ulcerative colitis, uveitis</td>
</tr>
<tr>
<td>Hulio - FKB327</td>
<td>Mylan S.A.S.</td>
<td></td>
<td>2018</td>
<td>Rheumatoid arthritis and juvenile idiopathic arthritis, enthesitis-related arthritis, axial spondyloarthritis and ankylosing spondylitis, psoriatic arthritis, psoriasis and pediatric plaque psoriasis, hidradenitis suppurativa, Crohn’s disease, ulcerative colitis, uveitis</td>
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<tr>
<td>Idacio – MSB11022</td>
<td>Fresenius Kabi Deutschland GmbH</td>
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<td>2019</td>
<td>Rheumatoid arthritis and juvenile idiopathic arthritis, enthesitis arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, pediatric plaque psoriasis, hidradenitis suppurativa, Crohn’s disease, pediatric Crohn’s disease, ulcerative colitis, uveitis, pediatric uveitis</td>
</tr>
<tr>
<td>Amsparity - PF-06410293</td>
<td>Pfizer Europe MA EEIG</td>
<td></td>
<td>2020</td>
<td>Rheumatoid arthritis and juvenile idiopathic arthritis, enthesitis-related arthritis, ankylosing spondylitis, axial spondyloarthritis, psoriatic arthritis, psoriasis, pediatric plaque psoriasis, hidradenitis suppurativa, adolescent hidradenitis suppurativa, Crohn’s disease, pediatric Crohn’s disease, ulcerative colitis, uveitis, pediatric uveitis</td>
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<tr>
<td>Libmyris - AVT02 Hukyndra - AVT02</td>
<td>Stada Arzneimittel AG</td>
<td></td>
<td>2021</td>
<td>Plaque psoriasis, psoriatic arthritis, rheumatoid arthritis and juvenile idiopathic arthritis, enthesitis-related arthritis, axial spondyloarthritis and ankylosing spondylitis, hidradenitis suppurativa, Crohn’s disease, ulcerative colitis, uveitis, pediatric uveitis</td>
</tr>
<tr>
<td>Yuflyma - CT-P17</td>
<td>Celltrion Healthcare Hungary Kft.</td>
<td></td>
<td>2021</td>
<td>Plaque psoriasis, psoriatic arthritis, rheumatoid arthritis and juvenile idiopathic arthritis, enthesitis-related arthritis, axial spondyloarthritis and ankylosing spondylitis, hidradenitis suppurativa, Crohn’s disease, ulcerative colitis, uveitis, pediatric uveitis</td>
</tr>
<tr>
<td>Etanercept (Enbrel, Pfizer Limited, UK)</td>
<td>Benepali SB4</td>
<td>Samsung Bioepis UK Limited</td>
<td>2016</td>
<td>Rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis and ankylosing spondylitis, non-radiographic spondyloarthritis, plaque psoriasis</td>
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<tr>
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<td>Erelzi GP2015</td>
<td>Sandoz GmbH</td>
<td>2017</td>
<td>Rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis and ankylosing spondylitis, non-radiographic spondyloarthritis, plaque psoriasis and pediatric plaque psoriasis</td>
</tr>
<tr>
<td><strong>Product</strong></td>
<td><strong>Brand Name</strong></td>
<td><strong>Manufacturer</strong></td>
<td><strong>Year</strong></td>
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<td>------------</td>
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<tr>
<td><strong>Infliximab</strong> (Remicade, Janssen Biologics B.V.)</td>
<td>Nepexto - YLB113</td>
<td>Mylan IRE Healthcare Limited</td>
<td>2020</td>
<td></td>
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<tr>
<td></td>
<td>Flixabi - SB2</td>
<td>Samsung Bioepis UK Limited</td>
<td>2016</td>
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<td>Inflectra - CT-P13</td>
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<td>Sandoz GmbH</td>
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<td><strong>Bevacizumab (Avastin, Roche)</strong></td>
<td>Mvasi - ABP 215</td>
<td>Amgen Europe B.V.</td>
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<td>2018</td>
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<td>Abemvmy - MYL-1402O</td>
<td>Mylan IRE Healthcare Limited</td>
<td>2021</td>
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<td>Zirabev</td>
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<td>Kanjinti - ABP 980</td>
<td>Amgen Europe B.V., Breda</td>
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<td>Zercepac - HLX02</td>
<td>Accord Healthcare S.L.U.</td>
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<td><strong>Epoetin alfa (Eprex, Janssen-Cilag GmbH) and Erypro (Ortho Biotech Janssen-Cilag GmbH)</strong></td>
<td>Abseamed - X575</td>
<td>MediceArzneimittelPütter GmbH &amp; Co</td>
<td>2007</td>
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<td>Binocrit - X575</td>
<td>Sandoz GmbH</td>
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<td><strong>Epoetin Zeta</strong></td>
<td>Retacrit - SB309</td>
<td>Hospira UK Limited</td>
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<tr>
<td><strong>Epoetin alfa (Erypro, Ortho Biotech Janssen-Cilag GmbH)</strong></td>
<td>Silapo - SB309</td>
<td>StadaArzneimittel AG</td>
<td>2007</td>
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</tr>
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</table>

Rheumatoid arthritis, adult and pediatric Crohn’s disease, ulcerative colitis and pediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, psoriasis

Metastatic carcinoma of colon, rectum, cervix, breast cancer, non-small cell lung cancer, renal cell cancer, epithelial ovarian, fallopian tube, or primary peritoneal cancer

HER2-positive early breast cancer, metastatic breast cancer, metastatic gastric cancer

Breast cancer, metastatic breast cancer, early breast cancer, metastatic gastric cancer

Anemia due to cancer therapies and chronic kidney failure; increasing the yield of autologous blood for patients in a pre-donation program, reduction of transfusions in major elective orthopedic surgery

Anemia due to chronic renal failure in adult and pediatric patients on hemodialysis and adult patients on peritoneal dialysis, severe anemia of renal origin, anemia due to cancer therapies for solid tumors
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Company</th>
<th>Date</th>
<th>Indications</th>
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<tr>
<td>Filgrastim (Neupogen, Amgen Europe B.V.)</td>
<td>Nivestim</td>
<td>Hospira UK Ltd</td>
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<tr>
<td>Ratiogristim - XM02</td>
<td>Ratiogristim - XM02</td>
<td>Ratiopham GmbH</td>
<td>2008</td>
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<tr>
<td>Tevagristim - XM02</td>
<td>Tevagristim - XM02</td>
<td>Teva GmbH</td>
<td>2013</td>
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<tr>
<td>Accofil - Apo-filgastrim</td>
<td>Grastofil – Apo-filgrastim</td>
<td>Accord Healthcare Ltd</td>
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<tr>
<td>Nivestim</td>
<td>Hospira UK Ltd</td>
<td>2010</td>
<td>Neutropenia and febrile neutropenia reduction due to myelosuppressive chemotherapy or congenital, idiopathic, HIV, hematopoietic stem cell transplantation</td>
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<tr>
<td>Fulphila</td>
<td>Fulphila</td>
<td>MYL - 1401H</td>
<td>2018</td>
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<td>Udenyca</td>
<td>Udenyca</td>
<td>CHS - 1701</td>
<td>2020</td>
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<td>Pelgraz</td>
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<td>2018</td>
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<tr>
<td>Drug Name</td>
<td>Company</td>
<td>Year</td>
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<td>Grasustek</td>
<td>USV Europe Limited</td>
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<td>Cegfila (previously Pegfilgrastim Mundipharma) – B12019</td>
<td>Mundipharma Corporation (Ireland) Limited</td>
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<td>Nyvepria - PF-06881894</td>
<td>Pfizer Europe MA EEIG</td>
<td>2020</td>
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<td>Stimufend - MSB11455</td>
<td>Fresenius Kabi Deutschland GmbH</td>
<td>2022</td>
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<td>Rituximab (MabThera, Roche Registration)</td>
<td>Rixathon - GP2013 Sandoz GmbH (Austria)</td>
<td>2017</td>
<td>Non-Hodgkin lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis</td>
</tr>
<tr>
<td></td>
<td>Blitzima/Truxima/Ritemvia/Rituzena e-CT-P10 Celltrion Healthcare Hungary Kft</td>
<td>2017</td>
<td>Non-Hodgkin lymphoma, chronic lymphocytic leukaemia, granulomatosis with polyangiitis and microscopic polyangiitis</td>
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<td>Ruxience - PF-05280586 Pfizer Europe MA EEIG</td>
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<td>Non-Hodgkin lymphoma, chronic lymphocytic leukaemia, granulomatosis with polyangiitis and microscopic polyangiitis, rheumatoid arthritis, Pemphigus vulgaris</td>
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<td>Somatropin (Genotropin, Pfizer)</td>
<td>Omnitrope - API Sandoz GmbH</td>
<td>2006</td>
<td>Growth disturbance in children (insufficient secretion of growth hormone, Turner syndrome, chronic renal insufficiency, Prader-Willi syndrome), growth hormone deficiency in adults</td>
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<td>Enoxaparin sodium (Clexane EU/Lovenox Sanofi Aventis, US)</td>
<td>Inhixa Techdow Europe AB (Sweden) Thorinane Pharmathen S.A. (Techdow Pharma NL)</td>
<td>2016</td>
<td>Venous thromboembolism, deep vein thrombosis, unstable angina and non-Q-wave myocardial infarction, acute ST-segment elevation myocardial infarction, blood clot prevention</td>
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<tr>
<td>Ranibizumab (Lucentis Novartis Europharm Limited)</td>
<td>Byooviz - SB11 Samsung Bioepis NL B.V.</td>
<td>2021</td>
<td>Neovascular (wet) age-related macular degeneration, proliferative diabetic retinopathy, visual impairment due to: diabetic macular oedema, macular oedema secondary to retinal vein occlusion AND choroidal neovascularisation</td>
</tr>
<tr>
<td>Teriparatide (Forsteo, Eli Lilly)</td>
<td>Movymia – STADA - RGB 10 Arzneimittel AG Terrosa Gedeon Livogiva - PF708 Theramex Ireland Limited</td>
<td>2017</td>
<td>Osteoporosis in postmenopausal women and in men at increased risk of fracture or associated with sustained systemic glucocorticoid therapy</td>
</tr>
</tbody>
</table>

MA: marketing authorisation. a Amgevita and not approved for entesitis-related arthritis; b Hefiya not approved for rheumatoid arthritis and Crohn’s disease; c Halimatoz not approved for Crohn’s disease; d Kromeya hidradenitis suppurativa; e Riximo not approved for chronic lymphocytic leukaemia; f Blitzima/ Truxima/Ritemvia/ Rituzena not approved for rheumatoid arthritis

N=6 (red) withdrawn between July 2019 and April 2022; N= 19 (blue): approved between July 2019 and April 2022
### 3.3. Discussion

Since the approval of the first biosimilar Omnitrope® (somatotropin) in 2006, the number of biosimilars authorised in Europe has rapidly increased, more than in other markets. The US FDA approved its first biosimilar in 2015 (Zarxio, filgastrim) and as of July 2022 it had licensed only 36 biosimilars. Of these, 24 were also approved by the EMA: eight in the same year by the two agencies, 12 licensed first in EU, and four first in the US (FDA biosimilar guideline). It appears that the two regulatory frameworks (EMA guideline; USA Innovation act 2009) share similar views and the dossiers submitted to the two agencies often include the same clinical studies.

Whilst the central regulatory approval by the EMA is backed by a robust regulatory framework and guidelines on pre-clinical and clinical development, the penetration of biosimilars is greatly affected by national policies implemented among the different European countries, which currently vary widely (Moorkens E, 2017). Differences exist in pricing and reimbursement procedures, levels of education, populations covered and incentives, leading to differences in uptake of biosimilars and in savings from biosimilar use across Europe, and even within the same country (Moorkens E, 2017; QuintilesIMS 2017; Ingrasciotta Y, 2015; Godman B, Haque M, 2021a; Godman B, Wladysiuk M, 2021). Some countries such as Italy and Spain have quite low biosimilar uptake compared to other countries including Austria, Germany, The Netherlands and Sweden (IQVIA 2021). However, this is changing as seen with increasing regional activities in Italy to grow the biosimilar market (Godman B, 2020).

Looking at the indications for which biosimilars are approved, these are mostly the same indication as their originator. However, this is not the case for some of the biosimilars of adalimumab and rituximab, for which important indications such as rheumatoid arthritis are lacking although pivotal trials in that indication were included in the applications. This creates a blurred scenario, which in some cases may affect patients’ and public health trust. In many cases, several biosimilars of the same biologics are licensed by the same or different marketing authorisation holders, using different commercial names even when the active molecule (and the relevant pivotal trial) is the same. We could find no plausible scientific or regulatory reasons for this, though it may be due to different local legal requirements across countries in the EU (Mielke J 2018), or commercial reasons. Partnerships among biosimilar manufacturers are common, with large companies adopting agile go-
to-market strategies to compete locally and reach the European market with different products (Chen Y 2018).

The analysis of the current regulatory process and approval of biosimilars in Europe, highlighted that almost all the biosimilars were authorised on the basis of clinical evidence from phase III comparative trials, mainly adopting an equivalence design (Evidence Table 1). These trials are not primarily intended to detect meaningful differences in the efficacy and safety profiles of biosimilars (Frapaise FX, 2018). Indeed, they were meant to demonstrate that the efficacy of the biosimilar and its comparator did not really differ (worse or better) in terms of outcomes and equivalence margin. The EMA guidelines rarely require showing similarity on a given population and never suggest a specific equivalence margin to be used in clinical efficacy pivotal trials.

The current approach provides demonstration of comparable efficacy and safety for biosimilars and their originators; however, this poses a burden for biosimilar manufacturers and may delay their introduction.

While clinical evidence confirming the similarity of biosimilars and their originator is often available and helps reassure prescribers and patients, marketing pressure seems to make people believe that uncertainties only apply to biosimilars and not to biologics in general. As mentioned, changes to the manufacturing process of biologic drugs, including originators, are common. However, there are typically only concerns with biosimilars despite successive batches of originators potentially being seen as biosimilars (Balázs Vezér, 2016).

As mentioned, the data supporting the regulatory approval in the EU does not address issues that might be important for clinicians and patients, such as interchangeability and switching. Exploring the consequences of switching from the originator to a biosimilar, or between different biosimilars in clinical trials, is challenging considering the various possible scenarios in clinical practice. Evidence indicates that the risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine (Feagan BG 2019; Cohen HP 2018). However, this can only be assumed but not proved for switching from one batch of the originator to another. This has now been addressed in recent studies (Allocati E, 2022).
CHAPTER 4: Switching between originator and biosimilars in chronic clinical conditions

4.1. Introduction and purpose

The availability of biosimilars, and their role to decrease pharmaceutical expenditure, have increased the possibility for physicians and patients to switch between the originator and its biosimilars, for non-medical reasons, such as economic or procurement decisions, not related to patient care. In the context of biologic medicines and biosimilars, interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect (EMA professionals’ guideline). This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. This latter scenario is now more frequent, considering the availability of an increased number of biosimilars of the same active principle. Replacement can be done by:

- Switching, which is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.
- Substitution (automatic), which is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.

Changes in pharmaceutical pricing and/or administrative/reimbursement policies may trigger subsequent switches, leading to a complex switching scenario (Feagan BG, 2020).

Specific guidelines related to biosimilars and switching have been developed by regulatory authorities such as the EMA, the FDA, Health Canada and the Australian Therapeutic Good Administration (TGA).

In Europe, the EMA in collaboration with the European Commission prepared an information guideline, defining interchangeability - the practice of replacing one medicine with another that is expected to achieve the same clinical effect in a given clinical setting - and the two forms of replacing (switching and substitution).

While the EMA is in charge of assessing the market authorization of both biologics and biosimilars, it does not regulate interchangeability, switching and/or substitution. Indeed, the responsibility on the definition of policies regarding both switching and substitution rests within the different European national health authorities (EMA 2019). Given this regulatory framework, the EMA does not require specific studies assessing whether alternating or switching from the biosimilar and its originator affect safety and/or efficacy in chronic conditions. In other words, biosimilars are
expected to produce the same clinical results as their reference products in any patient, providing that biosimilarity has been demonstrated.

While switching of biologics is becoming relatively common in different European countries, the possibility to substitute one biological medicine with its biosimilars at pharmacy level is less frequent. This stands in contrast to small molecule-generics, which via substitution have rapidly gained market share rapidly, led to considerable cost savings especially among European healthcare systems (Druedahl LC, 2022; Godman B, 2010; Woerkom M, 2012; Martin A, 2014).

Several countries announced that they consider EU biosimilars interchangeable with their reference products; however, in general, they do not allow automatic substitution or even recommend against it. In some countries including Poland, the absence of specific guidance or laws has allowed automatic substitution. As of 2020, biosimilar substitution is only permitted in the Czech Republic (though not recommended by practitioners) (Vogler S, 2021). Most of the EU member states either prohibit pharmacy-level automatic substitution or allow for limited substitution only (GaBi, 2017).

France had introduced, as part of the 2014 Social Security Financing Law, a new legal framework for restricted automatic substitution of biosimilars. This law permits the substitution in treatment-naïve patient of an originator and its biosimilar if the biosimilar belongs to the same group as the prescribed product and if the prescribing physician has not explicitly prohibited substitution (Biosimilar Development, 2019).

In Germany, despite the existence of prescribing quotas, office-based physicians do not always meet these quotas. To resolve this problem, payers highlighted the need to force biosimilar’s substitution at the pharmacy level, which could also equalize the substantial differences in biosimilar prescription quotas between regions. A law was passed in 2019 but negotiations are still ongoing; however two sets of guidance, provided the Federal Joint Committee (highest decision-making body of the self-governance of health insurers and providers) are likely to become available: one for physicians, detailing how to conduct switching, and the other for pharmacists, listing the biosimilars eligible for automatic substitution (Biosimilar Development, 2019; Vogler S, 2021).

In other countries including Italy and Spain, automatic substitution at pharmacy level seems to be a far off prospective since currently there is no legal framework in place. The AIFA in Italy released a position paper in April 2018 recommending the use of biosimilars in naïve patients and the practice of switching, reinforcing the concept that prescribing should be handled by physicians only. In other
words, AIFA considers biosimilars as interchangeable but not *sic et simpliciter* as for generics for which automatic substitution is allowed (AIFA, 2018; Biosimilar Development, 2019).

Unlike the EMA, the FDA grants a designation of interchangeability separately from biosimilarity. FDA applications for a biosimilar administered more than once to an individual generally include data from one or more switching studies. These are aimed at demonstrating that the risk in terms of safety or diminished efficacy of alternating or switching between the use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternation or switch (FDA biosimilar guideline). The FDA has created a regulatory designation pathway for the scientific evaluation of interchangeability, requiring that the proposed interchangeable product “can be expected to produce the same clinical result as the originator in any given patient; and for a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its originator is not greater than the risk of using the originator without such alternation or switch” (FDA biosimilar interchangeability). To date (June 2022), two biosimilars (FDA biosimilar insulin 2021; FDA biosimilar adalimumab 2021) have been deemed interchangeable by the FDA: the first one was the biosimilar insulin glargine Semglee (July 2021) and more recently it approved the first adalimumab biosimilar Cyltezo (October 2021).

As well as the FDA, Health Canada authorization of interchangeability is independent of biosimilarity. This is due to the fact that with the term interchangeability, Health Canada refers to the pharmacist’s ability to switch a patient from one drug to its biosimilar (Biosimilar biologic drugs in Canada: fact sheet. Ottawa: Heath Canada; Aug 23, 2019).

Despite switching becoming more common in practice, a debate on its safety and effectiveness in clinical practice is still ongoing, in particular the possibility of switching between biosimilars has exacerbated the uncertainties of switching (Mysler E, 2021; Barbier L, 2021).

Clinical evidence on safety and effectiveness of switching among biosimilars may reduce uncertainties about the use of biosimilars and support health policies aimed at encouraging interchangeability at the procurement and clinical level. To understand issues and barriers to interchangeability for wider access to affordable biologic medicines and their biosimilars, I focused on chronic conditions for which biologic medicines represent the pillar of pharmacological treatment in my research. The two case models are illustrated in the following sections – insulins
and anti-TNF agents. These were translated in two formal reports for the WHO with the aim to inform the Expert Committee in charge of issuing recommendations on interchangeability of biosimilar products (Allocati E, Gerardi C, 2020a; Allocati E, Gerardi C, 2020b). Guidance provided by WHO and its Expert Committee will support countries in making evidence-based, timely and informed choices when considering the inclusion of biological and biosimilar medicines on their national lists and reimbursement schemes. This is now happening (Godman B, Haque M, 2021a; Godman B, Wladysiuk M, 2021; Godman B, Leong T, 2021).

4.1.1. The case of insulin, insulin analogues and their biosimilars
Diabetes is the seventh leading cause of death and a major case of costly and debilitating complications including heart attacks, stroke, kidney failure, blindness and lower limb amputations (Allocati E, Gerardi C, 2020a). People affected by T1DM need insulin to survive and maintain their blood glucose at lower enough levels to reduce the risk of common complications. Moreover, people affected by T2DM increasingly need insulin for controlling blood glucose levels to avoid complications when oral diabetes medicines become less effective as the illness progresses (WHO diabetes 2020; Allocati E, Gerardi C, 2020a).

There are several types of insulin available to treat diabetes categorised by how quickly they work, when they peak and how long their effects last. Recombinant human insulin is available in two forms, a short acting (regular) form and an intermediate acting (NPH) form.

Insulin analogues are recombinant proteins that have been designed to mimic the body’s natural pattern of insulin release. However, they have minor structural or amino acid changes that give them special desirable characteristics when injected under the skin. Long-acting insulin analogues were developed to reduce hypoglycaemia and improve adherence to treatment. However, their considerably higher costs compared to human insulin when first launched have limited their use, especially in low- and middle- income countries. The availability of biosimilars of insulin analogues was expected to reduce the costs of diabetes management. However, compared with other therapeutic biologics, their entry has resulted in variable pricing competition. Among other reasons, it is important to note that the originator companies have dropped their prices in a number of markets, as well as promoting newer patented and more concentrated insulin analogues, to reduce the attractiveness of the market for biosimilar manufacturers (Godman B, Haque M, 2021a; Godman B, Wladysiuk M, 2021; Godman B, 2022). There can also be concerns with different devices between the manufacturers impacting on physician and patient confidence: biosimilars administered
subdermally come along with new devices different from the ones used for the administration of the originator. Finally, only three large companies (Eli Lilly, Novo Nordisk and Sanofi) account for the majority of insulin manufacturing (Godman B, Haque M, 2021a).

The mistrust in efficacy and safety of biosimilars may be among the reasons for the limited impact of biosimilars of insulin analogues across different world regions, discouraging competition and contributing to a limited reduction in prices (WHO insulin). However, the WHO has now introduced a prequalified scheme to enhance competition in an attempt to lower the price of biosimilars especially among low- and middle-income countries (WHO rituximab, 2020).

4.1.2. The case of anti-TNF

The introduction of monoclonal antibody biosimilars represented a major milestone in the treatment of patients with different chronic diseases as they significantly reduce the direct cost of biological therapies and improve therapy access for a larger population of patients. The effect could be greatest in those countries where affordability is a key issue with high-cost therapies (Putrik P, 2014; Danese S, 2017; Baumgart DC, 2019; Mazza S, 2022).

Agents able to block the cytokine-TNF, a key mediator of inflammation, represent the cornerstone of treatment of several chronic inflammatory diseases. Biologic medicines such as etanercept, infliximab, adalimumab, golimumab and certolizumab that are able to antagonize the effect of TNF are widely used in a variety of inflammatory conditions including rheumatic disorders (e.g., rheumatoid arthritis), dermatologic diseases (e.g., psoriasis), and inflammatory bowel disease (e.g., Crohn’s disease, ulcerative colitis) (Barbier L, 2020). These medicines have shown significant efficacy and are usually used for long periods, increasing the burden on healthcare systems given their high costs, with for instance adalumimab the top selling prescription medicine globally in 2019 (Pharmaceutical technology, 2019). Biosimilars of etanercept, infliximab, and adalimumab are currently available in several world’s regions, including the European and North America markets. The first biosimilars of infliximab, etanercept and adalimumab were licensed by the EMA in 2013, 2016, and 2017 respectively (Allocati E, 2020).

Given the chronic prescription of anti-TNF agents in inflammatory diseases and the rather long experience of using biosimilars, this drug class is a key case model for assessing the evidence supporting the safety and efficacy of switching from originators to biosimilars. This model is also interesting because anti-TNF biologic medicines are used by different physicians in different clinical
disorders, i.e., rheumatic, dermatologic and inflammatory bowel conditions that may reflect a range of attitudes concerning biosimilars.

Finally, there have been multiple activities across countries to increase the use of biosimilars of anti-TNFs. For instance, in Norway the price of biosimilar infliximab was already approximately 70% lower than the originator price soon after the launch of the biosimilar (Matusewicz W, 2015; Godman B, Fadare J, 2021). In Denmark, expenditure on adalimumab had decreased by 83% following aggressive contracting, with similar expectations for the UK with estimated savings of over GB£300 million per year (Jensen TB, 2020).

4.2. Methodology
To address the effectiveness and safety of switching among originators and biosimilars, I applied a common methodological approach to both case studies to systematically retrieve, appraise, and summarize data from the various clinical studies.

I collected the evidence through a comprehensive review of studies that assessed the outcomes of switching between biologics and their biosimilars for both insulin analogues and anti-TNFs. Box 1 reports the review questions. I considered both pre-marketing trials and post-marketing drug-utilization data helping to consolidate the practice of switching/substituting from reference to biosimilar medicines. Studies were identified through systematic searches of the major literature databases, i.e. MedLine, EMBASE, and The Cochrane Library. I also retrieved information on ongoing or unpublished studies through searching the main trial registries and the International Clinical Trials Registry Platform. The full search strategies for both insulin analogues and anti-TNF reviews are reported in the Appendix 1 and Appendix 2 (Allocati E, Gerardi C, 2020a; Allocati E, Gerardi C, 2020b).
**Box 1: review questions**

**Insulins**

Review question 1: In people of all ages under active treatment for diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), does the switch from one insulin analogue to another insulin analogue and from insulin analogue to its biosimilar compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?

Review question 2: In people of all ages under active treatment for diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), does the switch from insulin analogues to human insulin or vice versa compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?

*Both questions are extended to the switch from one biosimilar to another.*

**Anti-TNF**

Review question: In people of all ages under active treatment for rheumatic disorders, dermatologic diseases, and inflammatory bowel diseases with anti-TNF biologic medicines (etanercept, infliximab, adalimumab) does switching to their biosimilar (e.g., CT-P13, PF-06438179, GP1111, ABP 501, GP2015, MSB11022, GP2017) [OR a switch from a biosimilar to another of the same biologic medicine] compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?

For both insulin and anti-TNFs, the literature search was up to October 2020, i.e., when we (EA, CG) finalized the preparation of the WHO reports on insulin analogues and anti-TNFs (*Allocati E, Gerardi C, 2020a; Allocati E, Gerardi C, 2020b*).

After the publication of the WHO anti-TNF report, I decided to update the literature search up to March 2022 to check whether further studies on switching among biosimilars had been published. I again searched Medline, Embase and the Cochrane Library for studies on anti-TNF agents assessing the clinical efficacy and safety of biosimilar-to-biosimilar switches in chronic inflammatory diseases including Crohn’s disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, and psoriasis. I included studies on anti-TNF agents as multiple biosimilars had been marked in the European Union for infliximab, adalimumab, and etanercept by March 2022.
I applied a hierarchal approach to inclusion of primary studies, focusing on the most robust designs, i.e., RCTs with appropriate control arms and prospective controlled cohort studies, evaluating safety, immunogenicity or efficacy of switching from a biologic medicine to its biosimilars or from different biosimilars of the same biologics. I also considered eligible retrospective cohort studies, uncontrolled and controlled transition studies, and cross over studies if no evidence from prospective controlled studies are available. I included secondary and tertiary literature such as up-to-date systematic reviews and other types of evidence syntheses (i.e., HTA reports and clinical guidelines if developed following a systematic approach).

The selection of the studies to be included in the analysis was firstly made by two independent reviewers that screened the titles and abstracts of the retrieved records to exclude any clearly irrelevant records (EA, CG). Secondly, I retrieved and checked the full publications of possibly eligible records to confirm or not their inclusion in the analysis. All the discrepancies were resolved by discussion with a second reviewer (CG).

The key features of each review or study were summarised in a tabular format and the effect of switching on the three clinical areas of drug efficacy, safety, and immunogenicity was noted for each published study. Whenever possible and appropriate, I extracted numeric information on the results and performed a meta-analysis.

I also assessed the risk of bias of included evidence synthesis reports by using different tools (AMSTAR; Cochrane Collaboration’s tool and ROBINS-I) depending on the type of study. These tools were designed as practical critical appraisal tools for use by health professionals and policy makers to enable them to carry out rapide and reproducible assessments of the quality of conduct of systematic reviews of controlled trials of interventions (AMSTAR), of randomized trials (Cochrane Collaboration’s tool) and of non-randomised trials (ROBINS-I) (Shea BJ 2017 and AMSTAR-2 2017; Higgins JP 2011; Sterne 2016).

Whenever possible, I prepared a summary of findings for each dyad class product-indications, considering the following outcomes: measure of clinical efficacy (e.g., clinical remission, response, biomarker levels, and hypoglycemic events), persistence in treatment (discontinuation), rate of adverse event, and any measure of immunogenicity (e.g., anti-drug antibody levels) (GRADE working group).

The collected data were checked by a second reviewer (CG) who assured quality data and consistency.
4.3. Results

4.3.1. The case of insulin analogues

This section reports a summary of the main results of the systematic review that I prepared for the WHO report (Allocati E, Gerardi C, 2020a; Allocati E, Gerardi C, 2020b). This report includes the full details on the included studies, their quality assessment and the list of excluded studies with reasons for exclusion. Searches launched in April 2020 resulted in 2321 records, after duplicates were discarded, while 99 records were selected for the full text reading. Overall, the systematic review included 22 studies (Flow chart 2 below). No additional publications were retrieved from the HTA reports/guideline search (November 2020).

Flow chart 2: the case of insulin analogues
**Evidence Table 2**: the case of insulin analogues

<table>
<thead>
<tr>
<th>1st author (year); reference</th>
<th>Design, setting</th>
<th>Study duration (and follow up)</th>
<th>Population</th>
<th>Total random</th>
<th>Switch</th>
<th>Intervention</th>
<th>Control (non-switchers)</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blevins, 2020 Diabetes Obes Metab (INSTRIDE 3)</td>
<td>RCT, open-label, USA</td>
<td>36 weeks (safety FUP at week 40)</td>
<td>T1DM</td>
<td>127</td>
<td>Originator to biosimilar (IGla to MYL-1501D)</td>
<td>MYL-1501D (N= 64)</td>
<td>MYL-1501D (N= 64)</td>
<td>HbA1c; hypoglycaemic events; nocturnal hypoglycaemic events; immunogenicityTEAEs</td>
</tr>
<tr>
<td>Hadjiyianni, 2016 (2) Diabetes Obes Metab ELEMENT 2 (NCT01421459)</td>
<td>Randomized, 2-arm; post hoc analysis; Europe, Japan, USA</td>
<td>52 weeks (24 weeks primary efficacy outcomes)</td>
<td>T2DM (subgroup of ELEMENT 2, participants who had prestudy IGla)</td>
<td>298</td>
<td>Originator to biosimilar</td>
<td>Biosimilar IGla (N= 154)</td>
<td>Originator IGla (N= 144)</td>
<td>HbA1c; hypoglycaemia incidence; SAEs, TEAEs, AEs, TEAR</td>
</tr>
<tr>
<td>Hadjiyianni, 2016 (1) Diabetes Obes Metab ELEMENT 1 (NCT01421147)</td>
<td>Randomized, 2-arm; post hoc analysis; Europe, Japan, USA</td>
<td>52 weeks (24 weeks primary efficacy outcomes)</td>
<td>T1DM (subgroup of ELEMENT 1, participants who had prestudy IGla)</td>
<td>452</td>
<td>Originator to biosimilar</td>
<td>Biosimilar IGla (N= 218)</td>
<td>Originator IGla (N= 234)</td>
<td>HbA1c; hypoglycaemia incidence; SAEs, TEAEs, AEs, TEAR</td>
</tr>
<tr>
<td>Jprn, Umin, 2018</td>
<td>Randomized parallel group study; Japan</td>
<td>6 months (6 months)</td>
<td>T2DM adults aged between 20 and 80 years</td>
<td>100</td>
<td>Originator to biosimilar</td>
<td>Biosimilar IGla</td>
<td>Gla U-300</td>
<td>QoL; hypoglycaemia</td>
</tr>
</tbody>
</table>

RCTs exploring the switch one insulin analogue to another
<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
<th>Duration</th>
<th>Type</th>
<th>Age</th>
<th>Comparator</th>
<th>N</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamada, 2014</td>
<td>Randomized cross-over study; Japan</td>
<td>4 weeks (4 weeks)</td>
<td>T1DM</td>
<td>21</td>
<td>Analogue to analogue Dosage of IDeg equal to the dosage of IGla</td>
<td>IGla-IDeg-IDeg (N= 10)</td>
<td>IGla-IDeg-IDeg (N= 11)</td>
</tr>
<tr>
<td>Berard, 2015 (ACCORD)</td>
<td>RCT, open-label, single site; Canada</td>
<td>6 months</td>
<td>T2DM Adults aged between 40 and 79 years (from ACCORD study)</td>
<td>66</td>
<td>Analogues to human (IGla to NPH)</td>
<td>NPH (N= 34)</td>
<td>IGla (N= 32)</td>
</tr>
<tr>
<td>Luo, 2019</td>
<td>Retrospective cohort study; USA</td>
<td>3 years: Jan 1 2014 to Dec 31, 2016 (729 days)</td>
<td>T2DM</td>
<td>1966</td>
<td>Analogues to human</td>
<td>Human insulin (N= 983)</td>
<td>Insulin analogues (N= 983)</td>
</tr>
<tr>
<td>Curington, 2017</td>
<td>Prospective cohort pilot study; USA</td>
<td>24 weeks</td>
<td>T2DM; underserved and financially disadvantaged; adults aged ≥18 years</td>
<td>29</td>
<td>Analogues to human (IGla to NPH)</td>
<td>NPH (N= 14)</td>
<td>Glargine (N= 15)</td>
</tr>
<tr>
<td>Yamada, 2007</td>
<td>Open-label, prospective, randomized, Japan</td>
<td>4 months</td>
<td>T2DM</td>
<td>30$^1$</td>
<td>Human to analogues (premixed human to ILisp)</td>
<td>50/50 premixed ILisp (N=15)</td>
<td>70/30 premixed human (N=13) 50/50 premixed human (N=2)</td>
</tr>
<tr>
<td>Manini, 2007</td>
<td>Cohort study, historically controlled; Italy</td>
<td>6-8 months</td>
<td>T1DM (at least 1 year duration)</td>
<td>87</td>
<td>Human to analogue (NPH to IGla)</td>
<td>IGla (N= 47)</td>
<td>NPH (N= 40)</td>
</tr>
<tr>
<td>Reaney, 2012</td>
<td>Prospective, multicentre, observational, 9 European countries</td>
<td>4 years (12 months)</td>
<td>T2DM; adults aged ≥18 years</td>
<td>2389</td>
<td>Human to analogues Analogues to human</td>
<td>H-A 2203 A-H$^1$ 186</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
1ITR-QoL: Insulin Therapy-Related Quality of Life; DTSQ: Diabetes Treatment Satisfaction Questionnaire

1MMAS: Morisky Medication Adherence Scale

1for both groups doses adjusted every month, if needed

1WED: Well-being Enquiry for Diabetes

2QoL: in this specific case, questionnaire derived from the Diabetes-specific QoL Scale and Diabetes QoL Measure

1H: human insulin; A: insulin analogue; both prescribed in accordance with usual clinical practice; control and intervention formulation are branded
We also identified 11 studies including paediatric populations: one cross-over RCT (Urakami T, 2017), four prospective cohort studies (Kosteria I, 2017, Urakami T, 2015, Elbarbary NS, 2017, Dündar BN, 2009), five retrospective cohort studies (Jinno K, 2012, Bosco A, 2016, Päiväranta M, 2008, Braun D, 2008, Predieri B, 2018) and one single arm study in which it was unclear if the data collection was prospective or retrospective (Xatzipsalti M, 2017). All studies included patients with T1DM and the majority assessed the switch between insulin analogues.

4.3.1.1. **Switching between insulin analogues**

**Review question 1:** In people of all ages under active treatment for diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), does the switch from one insulin analogue to another insulin analogue and from insulin analogue to its biosimilar safely compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?

Overall, I found five RCTs with results and one ongoing study exploring the switch between insulin analogues. Four studies - INSTRIDE 3 (Blevins TC, 2020), the post hoc analyses of ELEMENT 1 and 2 trials (Hadjiyianni I, 2016), and an ongoing Japanese study (Jpn, Umin 2018) - focused on the switch from an insulin analogue originator to its biosimilar. One RCT (Yamada K, 2014) focused on the switch between IDeg and IGla.

Evidence on the switch between insulin originators and biosimilars derived from the INSTRIDE 3 trial, in which the completers of 52-week reference IGla treatment in the INSTRIDE 1 study were randomised to continue with the reference insulin originator or switch to its biosimilar (Blevins TC, 2020). This study demonstrated that participants switching multiple times between reference IGla and its biosimilar MYL-1501D achieved similar glucose control (change in HbA1c (Mean, SE) switching group: −0.05 (0.032); reference IGla: −0.06 (0.034) mean difference: 0.01 (95%CI, −0.085 to −0.101)), with a similar safety profile since the incidence of any hypoglycaemic event was similar between the two groups, with no statistically significant differences.

Moreover, post hoc analyses of ELEMENT 1 and 2 trials - two RCTs comparing IGla biosimilar (LY IGla) to originator (IGla) in patients with TD1M and TD2M respectively (Blevins TC, 2015; Rosenstock
P 2015) - suggesting that patients who had pre-study IGla treatment had similar efficacy and safety outcomes if randomised to LY IGla or continued with the originator (Hadjiyianni 2016).

However, post hoc analyses should be interpreted with caution, as neither study was designed to prospectively to compare biosimilar and reference glargine. Consequently, the study results in isolation should be not considered sufficient to support interchangeability.

Overall, these studies showed that switching from the originators to their biosimilars does not affect safety and efficacy of the treatment. However, there are methodological issues with these studies (i.e., small sample size, post hoc analysis) that affect our ability to draw firm conclusions. Nevertheless, the use of long-acting insulin analogue biosimilars are growing across countries (Godman B, Haque M, 2021a).

We are unable to draw any conclusion about the switch between insulin analogues as we only retrieved one small, randomised trial that evaluated the switch from IDeg to IGla (Yamada K, 2014). The study reported a small, 4-week, cross-over study in 21 Japanese patients with T1DM. Eleven patients in the intervention group switched to IGla treatment and after two weeks switched back to IGla for other two weeks (IGla-IDeg-IGla). The 10 patients in the control group remained under IGla treatment for the first two weeks of the study and then switched to insulin degludec (IGla-IDeg). Data from this study suggested that in T1DM, IGla reduces glucose levels before lunch more effectively than insulin glargine. The steady-state day-to-day variability of glucose was evaluated by absolute means of daily differences (MODD) which were 59.8 ± 39.1 and 46.9 ± 31.6 mg/dl during IGla treatment and IDeg treatment, respectively (p = 0.25). No severe hypoglycaemia occurred during the study period.

Data in paediatric population was very scarce. We found only one cross-over RCT evaluating the efficacy and safety of switching between insulin analogues, from IGla to IDeg in 18 children (Urakami T, 2017). Results from this study suggested that IDeg, injected once at bedtime, may provide similar glycaemic control as IGla while better reducing the risk of nocturnal hypoglycaemia in children with T1DM. Three single-arm prospective cohort studies (Kosteria I, 2017, Urakami T, 2015, Elbarbary NS, 2017) and one study with a poorly defined study design (Xatzipsalti M, 2017) evaluated the efficacy and safety of switching between insulin analogues. Overall, the glycaemic control was similar comparing the period before and after-switch, with less hypoglycaemic episodes.
Finally, two retrospective studies provided very poor evidence on the switch from IGla to IDeg (Predieri B et al., 2018; 37 patients mean age 11.7 (SD=4.22)) and from IGla to IDeg (Bosco A et al., 2018; 58 patients). Methodological concerns, small sample size and lack of generalizability (i.e. most studies conducted in Asian patients) made it again difficult to fully assess the efficacy and safety of switching in the paediatric population.

4.3.1.2. Switching from insulin analogues to human insulin (and vice versa)

**Review question 2:** In people of all ages under active treatment for diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), does the switch from insulin analogues to human insulin or vice versa safely compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?

Overall, we found two RCTs (Berard L, 2015, Yamada S, 2007) and three cohort studies (Luo J, 2019, Curington R, 2017, Manini R, 2007) that reported data on this review question.

Evidence from one randomised study (Berard L, 2015) and two cohort studies (Lou J, 2019 and Curington R, 2017) in T2DM patients from low-income settings suggested that the switch back to human insulin from IGla may result in a small increase in the risk of hypoglycaemia events and HbA1c levels.

In particular, the paper by Berard 2015 et al., reports a one-site extension of the ACCORD trial (ACCORD 2008) in which patients treated with IGla in the ACCORD trial were randomised to continue once-daily IGla or switch to once-daily NPH. The study demonstrated a significant decrease in HbA1c in the IGla group compared with the NPH group (mean + SE, IGla: -0.34\%±0.11; NPH: -0.01\%±0.10), even though neither group achieved the HbA1c target of <7.0% recommended by the Canadian Diabetes Association Clinical Practice Guidelines. The rates of symptomatic (IGla: 37.5 ± 2.2; NPH: 31.1 ± 2.1) and nocturnal (IGla: 4.2±0.7; NPH 4.4±0.8) hypoglycaemia did not differ significantly between groups; while the rates of severe hypoglycaemia showed a meaningful difference (NPH 6.1±0.9; IGla 2.7±0.6).

Both the cohort studies of Lou 2019 et al., and Curington 2017 et al., compared patients who switched from analogue insulin to human insulin with patients who continued taking insulin analogues. Non-significant differences in glycaemic control, hypoglycaemic and hyperglycemic
episodes and adherence between NPH and IGla were reported. The clinical impact of these findings is uncertain and should be considered in the light of a possible increase in patients’ access to less costly interventions.

It was unable to draw any conclusion about the switch from human insulin (NPH) to analogues as only one small, randomised trial (Yamada S, 2007) and one historically controlled cohort study (Manini R, 2017) were included.

We found only one study, the SWING study, which was the only study assessing the switching from human insulin to its analogue or from analogue to human insulin (Reaney M, 2012), reporting no significant differences in glycaemic control or hypoglycaemia between the two groups. Data in paediatric population are very scarce. We found only one prospective cohort study (Dundar BN, 2009) that assessed the switch from human insulin NPH to insulin analogues. Daily insulin requirements, mean fasting blood glucose levels and frequency of severe hypoglycaemia before and after treatment with IGla and IDet were not significantly different. Both IGla and IDet proved to be safe and well tolerated in children and adolescents.

We also retrieved two retrospective studies providing very poor evidence on the switch between NPH and IDet (Braun D, 2008) and IGla (Päivärinta M, 2008). Methodological concerns, small sample size and lack of generalizability (i.e. most studies conducted in Asian patients) again made it difficult to assess the efficacy and safety of switching.

4.3.2. The case of anti-TNF

This section reports a summary of the main results of the systematic review prepared for the WHO report (Allocati E, Gerardi C, 2020b). This report includes the full details on the included studies, their quality assessment, and the list of the excluded studies with reasons for exclusion. The systematic searches launched on 5th December 2019 and updated on 2nd October 2020 resulted in 570 records, after duplicates were discarded. Moreover, five records were retrieved from other sources. After applying the eligibility criteria 56 records were selected for the full text reading.

We were able to include in our analysis seven up-to-date reviews, published between 2018-2020, summarising studies on switching from originators to biosimilars of anti-TNF agents (Barbier L, 2020; Bernard L, 2020; Queiroz NFS, 2020; Mezones-Holguin E, 2019; Bakalos G, 2019; Ebbers HC, 2019; Feagan 2019).
We also identified 14 RCTs (seven on infliximab, six on adalimumab, one on etanercept) and 11 open-label extensions (five on infliximab, two on adalimumab, four on etanercept). In addition, we also identified two ongoing trials with no results at the time of this report (ADA-SWITCH_ NCT04131322 and ACTRN 12618000279224).

We also identified three single-arm cohort studies (Gervais L, 2018; Sieczkowska J, 2016; Kang B, 2018) involving paediatric populations (Flow chart 3 below).

**Flow chart 3: the case of anti-TNF**

SR: systematic review, RCT: randomised controlled trial, OLE: open-label extension
Review question: In people of all ages under active treatment for rheumatic disorders, dermatologic diseases, and inflammatory bowel diseases with anti-TNF biologic medicines (etanercept, infliximab, adalimumab) does switching to their biosimilar (e.g., CT-P13, PF-06438179, GP1111, ABP 501, GP2015, MSB11022, GP2017) compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?

4.3.2.1. Systematic reviews

In adults, we found consistent evidence from systematic reviews that switching from the originators of anti-TNF biologic medicines to their biosimilars does not affect safety, immunogenicity, or the efficacy of the treatment (Evidence Table 3 below).
### Evidence Table 3: up to date systematic reviews – the case of anti-TNF

<table>
<thead>
<tr>
<th>1st author (year)</th>
<th>Date of last research</th>
<th>Authors’ affiliation</th>
<th>Indications</th>
<th>Biologic(s)</th>
<th>Outcomes</th>
<th>Design of included studies</th>
<th>Number of included studies</th>
<th>Total participants</th>
<th>Main results (efficacy)</th>
<th>Main results (safety)</th>
<th>Main results (Immunogenicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbier 2020*</td>
<td>December 2019</td>
<td>University of Leuven, MEB Agency, The Netherlands</td>
<td>Chronic, inflammatory conditions</td>
<td>Infliximab, adalimumab, etanercept</td>
<td>Efficacy, safety, immunogenicity</td>
<td>RCTs, OLEs, prospective and retrospective observation, registries, case series</td>
<td>Infliximab RCTs and OLEs: 21; other study design: 91</td>
<td>Overall, approximately 20,000</td>
<td>Infliximab and etanercept RCTs and OLEs: switch did not negatively affect efficacy; other study design showed some differences, in discontinuations probably because of nocebo effects Adalimumab: RCTs and OLEs: the switch did not negatively affect efficacy</td>
<td>the switch did not negatively affect efficacy, with the exception of some observational studies on infliximab Short study duration precludes the assessment of rare AEs</td>
<td>Apparently, the switch did not negatively affect the immunogenicity profile (less data available)</td>
</tr>
<tr>
<td>Queiroz 2020</td>
<td>June 2018</td>
<td>San Paulo University, Brazil</td>
<td>IBD</td>
<td>Infliximab, adalimumab?</td>
<td>Discontinuation at 6-24 months and reasons for discontinuation</td>
<td>(before and after) observational studies, case series</td>
<td>30</td>
<td>3954</td>
<td>Risk of discontinuation at 6 months 8%, 12 months 14%, 24 months 21%; Remission 4%; disease worsening 2%, loss of response 7%, loss of adherence 4%, AEs 5% (quality from very low to low)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Last name</td>
<td>Date</td>
<td>Location</td>
<td>Disease or Condition</td>
<td>Treatment</td>
<td>Efficacy, effectiveness, response, safety</td>
<td>Study Design</td>
<td>Safety Concerns</td>
<td>Immunogenicity Concerns</td>
<td></td>
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</tr>
<tr>
<td>Bernard</td>
<td>April 2018</td>
<td>University Montreal, Canada</td>
<td>IBD (CD, UC)</td>
<td>Infliximab/CT-P13</td>
<td>Efficacy, response, safety (disease worsening, loss of response, sustained remission)</td>
<td>RCTs and observational studies, case series</td>
<td>NR</td>
<td>Most studies revealed no efficacy concerns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mezones-Holguin</td>
<td>June 2018</td>
<td>University, HTA Agency, Peru</td>
<td>Chronic inflammatory conditions</td>
<td>infliximab</td>
<td>Efficacy, safety (+financial analysis)</td>
<td>Controlled studies</td>
<td>1723</td>
<td>No difference between maintenance and switching groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebbers</td>
<td>January 2019</td>
<td>Biogen Intern, UK</td>
<td>RA, PsA or AxSpA, AS, PsO</td>
<td>etanercept (originator vs SB4)</td>
<td>acceptance, effectiveness, safety</td>
<td>prospective and retrospective observation, registries</td>
<td>13552 (11053 switching)</td>
<td>DANBIO registry: no major safety signals, no data available (low rate of ADAs for etanercept)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bakalos</td>
<td>May 2018</td>
<td>Hoffman La Roche Ltd</td>
<td>rheumatic diseases and IBD</td>
<td>mAbs (all studies on infliximab)</td>
<td>discontinuation rate</td>
<td>observation</td>
<td>NR</td>
<td>discontinue rate: range from 2.8% to 28.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feagan 2019</td>
<td>January 2018</td>
<td>Janssen</td>
<td>rheumatic diseases psoriasis, IBD</td>
<td>Infliximab</td>
<td>efficacy, safety</td>
<td>transition study (controlled and uncontrolled), RCTs, observational</td>
<td>6 RCTs, 53 observational studies (most uncontrolled)</td>
<td>NR</td>
<td>no clinically important efficacy or safety signals associated with switching</td>
<td>no clinically important efficacy or safety signals associated with switching</td>
<td>NR</td>
</tr>
</tbody>
</table>

AS: ankylosing spondylitis; AxSpA: axial spondyloarthritis; DAS28: disease activity score; IBD: inflammatory bowel disease; mAbs: monoclonal antibodies; NR: not reported; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; RCT: randomised controlled trial.

* the reviews assessed the efficacy, safety and immunogenicity of switching in several classes of biologics; data are reported only for anti-TNF agents.
Most of the reviews included only studies on infliximab (Bernard L, 2020; Queiroz NFS, 2020; Mezones-Holguin E, 2019; Feagan BG, 2019; Bakalos G, 2019), while Barbier L et al., 2020 analyzed every therapeutic class for which a European market authorization has been granted. Ebbers HC, et al., 2019 focused on etanercept (Ebbers HC, 2019).

Four reviews included both RCTs and observational studies (Barbier L, 2020; Bernard L, 2020; Mezones-Holguin E, 2019; Feagan BG, 2018), while three reviews only included prospective and retrospective cohort studies as their primary aim was to assess the effect of switching in clinical practice, (Queiroz NFS, 2020; Bakalos G, 2019; Ebbers HC, 2019).

Overall, these reviews did not show any significant differences between biosimilars and originators. Indeed, switching was not associated with an increase in safety signals or immunogenic reactions, nor with a decreased efficacy of treatments, while biosimilarity in terms of efficacy, safety, and immunogenicity have been confirmed.

The reviews by Souto A, et al., 2016; Bakalos G, et al., 2019 and Queiroz NFS et al., 2020, included many uncontrolled studies and case series that reported large variation in post switch discontinuation rate across studies. Discontinuation rate is suggested as meaningful marker of treatment efficacy and tolerability that can also provide insight into clinical and patient-reported consequences of non-medical switching.

### 4.3.2.2. RCTs

The included RCTs demonstrated that switching from the originators of anti-TNF biologic medicines to their biosimilars does not affect the safety, immunogenicity or efficacy of the treatment in adults (Evidence Table 4 below).
### Evidence Table 4: Included RCTs – the case of anti-TNF

<table>
<thead>
<tr>
<th>Study, year, (name)</th>
<th>Design &amp; setting</th>
<th>Follow up</th>
<th>Population</th>
<th>Total randomised</th>
<th>Intervention</th>
<th>Control</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFLIXIMAB</strong></td>
<td></td>
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</tr>
<tr>
<td>Alten 2019 (REFLECTIONS B537-02) and Cohen 2020</td>
<td>multicenter, double blind, 174 centers, 28 countries</td>
<td>24 weeks (up to 78 OLE)</td>
<td>RA, adults aged ≥18 years</td>
<td>286 (treatment period 2) 505 (treatment period 3)</td>
<td>PF-06438179/GP1 111 (n=143)</td>
<td>infliximab EU (Remicade) (n=143)</td>
<td>ACR 20 (primary), ACR &gt;20,50,70; DAS28-CPR, HAQ-DI, TEAES; % of ADAs ≤ NAB</td>
</tr>
<tr>
<td>Ye 2019</td>
<td>multicenter, non-inferiority, 58 centres, 16 countries</td>
<td>54 weeks</td>
<td>Crohn's disease, adults 18-75 years</td>
<td>110 (switch groups)</td>
<td>CT-P13–infliximab (n=55 of the 110 firstly randomised to CTP13)</td>
<td>infliximab–CT-P13 (n=55 of the 109 firstly randomised to infliximab)</td>
<td>CDAI 70 response at week 6 (primary), CDAI 70 response at week 14 (after switch), clinical remission week 6/14 SIBDQ, incidence causality severity of AE, PO2</td>
</tr>
<tr>
<td>Kaltsonoudis 2019</td>
<td>open label, prospective observational cohort study, single centre (Greece) with random allocation (not clear)</td>
<td>18 months</td>
<td>ankylosing spondylitis, adults</td>
<td>88</td>
<td>Inflectra/Remsima (n=45)</td>
<td>reference infliximab (Remicade?) (n=43)</td>
<td>efficacy and safety: BASDAI, ASDAS, ESR (mm/h), CRP (mg/l)</td>
</tr>
<tr>
<td>Smolen 2018</td>
<td>double-blind, parallel group (transition study), 11 countries from Europe and Africa</td>
<td>78 weeks</td>
<td>moderate to severe RA, 18-75 year</td>
<td>195 (re-random)</td>
<td>SB2 (n=94)</td>
<td>Remicade (n=101)</td>
<td>ACR20, DAS28, AEs, immunogenicity</td>
</tr>
<tr>
<td>Roder 2018*</td>
<td>double-blind, IBD centre (Munich, Germany)</td>
<td>52 weeks</td>
<td>Crohn's disease, ulcerative colitis adults</td>
<td>200</td>
<td>CT-P13 (n=111)</td>
<td>infliximab originator (Remicade?) n=89</td>
<td>clinical remission (CAI and CDAI)</td>
</tr>
<tr>
<td>Jorgensen 2017 (NORSWITCH)</td>
<td>double-blind, parallel group, non-inferiority, comparative, phase IV - 24 Norwegian hospitals (17 gastroenterology,12 rheumatology, 5 dermatology hospital departments)</td>
<td>52 weeks</td>
<td>Crohn's disease, ulcerative colitis, spondyloarthritis, RA, psoriatic arthritis, chronic plaque psoriasis, adults</td>
<td>482</td>
<td>CT-P13 (n=241)</td>
<td>infliximab originator (Remicade?) (n=241)</td>
<td>disease worsening, safety (AEs), ADA</td>
</tr>
<tr>
<td>Volkers 2017* [ongoing?]</td>
<td>randomized, controlled, double-blind, phase IV, non-inferiority</td>
<td>30 weeks</td>
<td>CD and UC</td>
<td>47</td>
<td>CT-P13 (n=15)</td>
<td>Infliximab (n=6)</td>
<td>remission</td>
</tr>
</tbody>
</table>

**ADALIMUMAB**
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Region/Countries/Length</th>
<th>Design/Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hercogova 2019</td>
<td>double-blind phase III equivalence trial, North and South America, Europe</td>
<td>50 weeks</td>
<td>moderate-to-severe chronic plaque-type psoriasis 202 (re-random reference adalimumab)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Switch to MSB11022 (n=101)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continued reference adalimumab (n = 101)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PASI 75 (primary), mean change PASI -16, PGA, QoL TEAES-SAFTY, ADA</td>
</tr>
<tr>
<td>Blauvelt 2018</td>
<td>double-blind, Europe and US</td>
<td>51 weeks</td>
<td>active, clinically stable, moderate-to-severe chronic plaque psoriasis, adults</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>379 multiple switch GP 2017/originator (n=126)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>continue treatment GP 2017/originator (n=253)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PASI 75-week 16, (primary) PASI 50/75/90/100 response rate, PGA disease activity, PK, immunogenicity, tolerability</td>
</tr>
<tr>
<td>Cohen 2018b</td>
<td>double-blind, parallel-group, equivalence trial, 15 countries</td>
<td>58 weeks</td>
<td>moderate to severe RA, adults</td>
</tr>
<tr>
<td></td>
<td>(VOLTAIRE-RA)</td>
<td></td>
<td>645 BI695501 (n=324)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Humira (n=321)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACR20, DAS28, AE, immunogenicity</td>
</tr>
<tr>
<td>Weinblatt 2018</td>
<td>phase III, double-blind, parallel group (transition study), 7 countries (Bosnia and Herzegovina, Bulgaria, Czech Republic, Lithuania, Poland, Republic of Korea and Ukraine)</td>
<td>52 weeks</td>
<td>moderate to severe RA, adults 18-75 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>254 (re-random)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SBS (n=125)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>adalimumab originator (Humira?) (n=129)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACR20, DAS28, AE, immunogenicity</td>
</tr>
<tr>
<td>Papp 2017</td>
<td>phase III, double-blind, active-controlled (single transition), Australia, Canada, Hungary</td>
<td>52 weeks</td>
<td>severe plaque psoriasis, adults 18-75 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>156 ABP501 (n=79)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>adalimumab originator (Humira?) (n=77)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PASI, AE, immunogenicity</td>
</tr>
<tr>
<td>Hodge 2017</td>
<td>Phase III, double blind, multicentric (global)</td>
<td>24 weeks</td>
<td>Moderate to severe plaque psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>545 Switch to CHS 1420 (n=124)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CHS 1420/CHS 1420 Originator/originator (n=129)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PASI, TEAE, ADA</td>
</tr>
</tbody>
</table>

* Volkers 2017 and Roder 2018 published only as poster.

ACR: American college of rheumatology; ADA: anti-drug antibody; AE: adverse event; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CAI: cytokine activity index; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: disease activity score; ESR: erythrocyte sedimentation rate; EU: European union; HAQ-DI: Health Assessment Questionnaire Disability Index; IBD: inflammatory bowel disease; mAbs: monoclonal antibodies; NAB: neutralising antibody; NR: not reported; PASI: Psoriasis Area and Severity Index; PGA: Physician’s Global Assessment; PK: pharmacokinetics; QoL: quality of life; RA: rheumatoid arthritis; RCT: randomised controlled trial, SIBDQ: Short Inflammatory Bowel Disease Questionnaire TEAE: treatment-emergent adverse event.
A substantial amount of evidence from RCTs is available for infliximab (seven studies), adalimumab (six) and etanercept (one). They show that continuing the originator or switching to a biosimilar does not result in differences in response, ADA development or discontinuation (Table 2 and 3; and Figure 4). The certainty of the pooled estimates, assessed using the GRADE approach, was judged high for all the three outcomes. High certainty in evidence means that we can be very confident that the effect found across studies is close to the true effect (GRADE working group).
### Table 2: Summary of Findings - continuing reference IFX compared to switching to biosimilar

**Patient or population**: chronic inflammatory diseases  
**Intervention**: continuing ref-IFX  
**Comparison**: switching to biosimilar

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE) *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with switching to biosimilar</td>
<td>Risk with continuing ref-IFX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>665 per 1.000 (612 to 718)</td>
<td>RR 1.00 (0.92 to 1.08)</td>
<td>1112 (5 RCTs)</td>
<td>⬠⬤⬤⬤ HIGH</td>
</tr>
<tr>
<td>Anti-drug antibodies</td>
<td>306 per 1.000 (279 to 392)</td>
<td>RR 1.08 (0.91 to 1.28)</td>
<td>863 (3 RCTs)</td>
<td>⬠⬤⬤⬤ HIGH</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>105 per 1.000 (71 to 144)</td>
<td>RR 0.96 (0.68 to 1.37)</td>
<td>1054 (4 RCTs)</td>
<td>⬠⬤⬤⬤ HIGH</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio.

### Table 3: Summary of Findings - continuing ref ADMB compared to switching to biosimilar

**Patient or population**: chronic inflammatory diseases  
**Intervention**: continuing ref-ADMB  
**Comparison**: switching to biosimilar

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE) *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with switching to biosimilar</td>
<td>Risk with continuing ref-ADMB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>831 per 1.000 (781 to 905)</td>
<td>RR 1.01 (0.94 to 1.09)</td>
<td>584 (3 RCTs)</td>
<td>⬠⬤⬤⬤⬤ HIGH</td>
</tr>
<tr>
<td>Anti-drug antibodies</td>
<td>495 per 1.000 (441 to 560)</td>
<td>RR 1.01 (0.89 to 1.13)</td>
<td>764 (4 RCTs)</td>
<td>⬠⬤⬤⬤ HIGH</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>57 per 1.000 (40 to 107)</td>
<td>RR 1.13 (0.69 to 1.86)</td>
<td>941 (4 RCTs)</td>
<td>⬠⬤⬤⬤ HIGH</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio.
**Figure 4**: study design for exploring switch between originator biological drugs and biosimilars. (Faccin et al 2016)

*Infliximab*

Three of the seven RCTs included patients with rheumatoid diseases (Alten R, 2019 and Cohen SB, 2020; Kaltsonoudis E, 2019; Smolen JS, 2018)

The Reflection study (Alten R, 2019; Cohen SB, 2020) was divided into three different treatment periods. In the first one, patients were randomised to infliximab originator or biosimilar; during the second period, patients in the originator group were re-randomised to continue the originator or switch to the biosimilar. In the third period, all patients received biosimilar infliximab. During all these treatment periods, no clinically meaningful differences in the safety profiles between the groups were found. The percentage of patients who were antidrug antibody-positive was generally stable through the treatment period. In the study of Smolen et al., 2018, patients were first randomised to receive infliximab originator or biosimilars and after the first period of time patients in the originator group were re-randomised to switch to biosimilar or to continue on the originator. Roder H, et al., 2018 (Roder H, 2018) and Volkers A, et al, 2017 (Volker A, 2017) included patients with gastrointestinal disorders. Their preliminary results were broadcasted through poster presentations, and the authors concluded that switching is feasible and safe.

The NOR-SWITCH study (Jorgensen KK, 2017; Jorgensen KK, 2020) selected patients with six different chronic inflammatory diseases and demonstrated that switching was not inferior to continuing treatment with infliximab originator according to a prespecified non-inferiority margin of 15%. As a subgroup analyses of participants with Crohn’s and ulcerative colitis displayed a close to significant difference favouring originator infliximab, the authors provided further analysis of the
efficacy, safety and immunogenicity in these subgroups. Both analyses showed the absence of significant concerns related to switching from originator infliximab to biosimilar. These six RCTs evaluated switching from originator to biosimilar and patients treated with the originator were randomised to switch to the biosimilar or continue the originator (single transition studies).

The study of Ye DB, et al., 2019 (Ye DB, 2019) assessed the switch from biosimilar to originator and vice versa and demonstrated that also switching back and forth is safe and effective. Indeed, efficacy was well maintained and similar between groups after switching.

Adalimumab

All the six adalimumab studies included participants with rheumatoid diseases. Four RCTs (Hercogova J, 2019; Cohen SB, 2018; Weinblatt ME, 2018; Papp K, 2017) evaluated the switching from originator to four different adalimumab biosimilars (single transition studies). Regardless of the biosimilar chosen in these studies, all these four studies agreed that switching from the originator to any adalimumab biosimilar is safe and effective.

In the AURIEL-PsO trial (Hercogova J, 2019), patients were randomised to biosimilar MBS11022 or originator. After a first period, patients with a ≥50% improvement in PASI were eligible to enter a double-blind extension period: patients receiving biosimilar continued treatment, and patients receiving the originator were re-randomised to continue either the originator or switch. The same study design was applied in the VOLTAIRE-RA (Cohen SB, 2018) study (BI695501), in the Weinblatt ME, et al., 2018 study (SB5) and in the Papp K, et al., 2017 study (ABP501). Indeed, after a first randomisation to biosimilar adalimumab or its originator, patients in the originator group were re-randomised to continue their assigned treatment or switch from the originator to a biosimilar. Switch from originator to BI 695501 had no impact on efficacy, safety and immunogenicity. The results of all these studies highlighted that no clinically meaningful differences in efficacy, safety or immunogenicity were seen between the treatment arms through to the end of the observation period.

Hodge J, et al., 2017 compared the switching to a fifth adalimumab biosimilar (CHS-1420), but the results were reported only in a poster presentation (Hodge J, 2017).

Blauvelt A, et al., 2018 was the first study that assessed the impact of multiple switches between biosimilar GP2017 and its originator (Blauvelt A, 2018). The study consisted of four periods: screening, treatment period 1 in which patients were randomised to originator or biosimilar;
treatment period 2 in which patients achieving ≥ 50% improvement in PASI 50 were eligible for re-randomisation to continue their originally assigned treatment or to receive either the biosimilar or the originator. During the extension, all patients received the treatment originally assigned at randomisation. Switching up to four times between originator and the reference adalimumab had no impact on the incidence of adverse events or injection-site reactions. The frequency of ADA development was similar between the switching and continuing treatment groups, and there was no impact on efficacy.

*Etanercept*

The EGALITY trial (*Gerdes S*, 2017; *Griffiths CEM*, 2017) assessed the switch between etanercept originator and its biosimilar, and showed no differences in terms of response, discontinuation, or ADA development in adult patients with psoriasis. In a first treatment period, patients with stable chronic plaque psoriasis were randomised to etanercept biosimilar or the originator, after which, patients who had achieved at least a 50% improvement in PASI were re-randomised to either continue the same treatment or undergo a sequence of three treatment switches between the biosimilar and the originator. The mean (SD) PASI score and mean percentage change from baseline in PASI score were comparable between switching and continuing treatment groups at all-time points. No patients from both treatment groups were positive for ADAs during the second period of treatment. Additional evidence on the switching from the etanercept originator to three different biosimilars are available from the open-label long term extensions of RCTs.

### 4.3.2.3. Open-label long-term extension studies

Open-label long-term extensions of the pivotal trials is a clinical trial that typically enrols participants of a previous clinical trial and is designed to gather the long-term safety and tolerability data on a medicine after the time period of the main study. The OLEs we retrieved, all confirmed the equivalence between switching to a biosimilar or continuing with the biologic originator. In total, we included in our analysis five open label long-term extension of RCTs pivotal for each anti-TNF: five on infliximab (*PLANETAS, PLANETRA, Japan-PLANETRA, NORSWITCH extension, Kay J, 2015*), two on adalimumab (*Cohen S*, 2019, *Alten R*, 2020), and four on etanercept (*Jaworski J*, 2019; *Park MC*, 2019; *Emery P*, 2017; *O’ Dell J*, 2017).
The open-label long-term extensions of the pivotal trials PLANETAS, PLANETRA and Japan-PLANETRA assessed the efficacy and safety of switching to infliximab biosimilar in patients with rheumatoid diseases. In the long-term extensions of the PLANETAS trial and of both the PLANETRA trials, the proportion of patients achieving a clinical response, as well as the proportion of patients with ADAs, were maintained at similar levels to those in the main study in both the maintenance and switch groups and was comparable between groups. Similar results came from the long-term extension of the PLANETRA trial.

The long-term extension of the NORSWITCH study (Goll GL, 2019) compared the maintenance group (patients treated with CT-P13 for 72 weeks) and the switch group (patients treated with the originator for 52 weeks in the double-blind phase then treated with CTP13 for 26 weeks in the open-label phase). Disease worsening during the extension phase occurred at a similar rate in the two groups, with no significant difference amongst those switched at main study baseline and those switched at extension study baseline.

We retrieved two one-label extension studies assessing the switch from adalimumab originator to its biosimilars (Cohen S, 2019 and Alten R, 2020).

The long-term extension study reported by Cohen 2019 included the participants who had completed the randomised phase of the main study. The percentages of patients who reported treatment-emerging adverse events and efficacy were similar in the group that transitioned from originator to ABP501 and the group that continued on the biosimilar. The single switch from originator to ABP501 did not impact immunogenicity.

We also retrieved one-label extension study, which assessed the switch from adalimumab originator to the FKB327 and vice versa. The participants who had completed the 22 weeks of treatment in the main study (Genovese MC, 2019) were re-randomised: participants treated with FKB327 to continue with biosimilar or switch to the originator, while participants treated with the originator to continue the originator or switch to FKB327. In this third period, a small group of patients experienced a double switch (biosimilar-originator-biosimilar), while others a single switch (either originator-biosimilar-biosimilar or originator-originator-biosimilar). Efficacy, safety and immunogenicity were similar for up to 2 years and were not affected by single- or double-switching treatment (Genovese MC, 2020, Alten R, 2020).
We retrieved four open-label extension studies assessing the switch from etanercept originator to different etanercept biosimilars. All the four extension studies selected patients from their reference main studies and randomised them in the maintenance group or in the switch group (Jaworski J, 2019; Park MC, 2019; Emery P, 2017; O’ Dell J, 2017). None of these extension studies highlighted clinically meaningful differences in safety, immunogenicity, or efficacy in patients who were switched from etanercept to one of its biosimilars in comparison with those who remained in the maintenance group.

4.3.2.4. Studies in paediatric population
We were able to retrieve only prospective multicentre observational cohort studies that evaluated the switch from infliximab originator to biosimilar in inflammatory bowel disease in the paediatric population. In these studies, switching appears to be safe and effective.

We retrieved three prospective multicentre observational cohort studies evaluating the switch from infliximab originator to biosimilar (CT-P13) in a paediatric population affected by Crohn's disease, ulcerative colitis and other IBDs (Gervais L, 2018, Kang B, 2018, and Sieczkowska J, 2016). Two were small single-group studies involving 33 and 39 participants respectively (Gervais L, 2018, Sieczkowska J, 2016). No clinically significant changes to disease activity, biomarkers, ADA, and trough levels were recorded. A larger study on 74 patients (38 maintained on originator and 36 switched to CT-P13) showed a similar persistence in treatment and persistent remission at one year, as well as no statistically significant differences in any measures of disease activity, pharmacokinetics, or immunogenicity between the time of switch and 1-year post-switch in the CT-P13 switch group (Kang B, 2018).

The evidence in the paediatric population is scarce, and limited to infliximab used in Crohn's disease, ulcerative colitis and other IBDs. Data suggest a comparable efficacy and safety profile after switching to biosimilar.

4.3.2.5. Switching among biosimilars of anti-TNF
Through the finding of the systematic reviews prepared for the WHO, I was able to address only single switching from originator to biosimilars with few evaluating multiple or “back and forth” switching between originators and biosimilars and none among biosimilars.
Consequently, there is a need to further evaluate current evidence regarding switching between biosimilars, sometimes referred to as cross-switching, to dispel concerns among key stakeholder groups.

In this respect, I focused on anti-TNF agents as multiple biosimilars have been marked in the European Union for infliximab, adalimumab, and etanercept. To this aim, I updated the systematic searches launched in October 2021 for the WHO report (Allocati E, Gerardi C, 2020b), as already highlighted in the methodology part (section 4.2). The full results of this analysis were published in Allocati 2022 (Allocati E, 2022).

**Review question: In people of all ages under active treatment for rheumatic disorders, dermatologic diseases, and inflammatory bowel diseases with anti-TNF (etanercept, infliximab, adalimumab) switching from a biosimilar to another of the same biologic medicine compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?**

From this systematic search, I was able to include a total of 19 studies, either RCTs or observational studies (Flow chart 4 below).
Flow chart 4: switching among biosimilars of anti-TNF

Records identified through database searching
  Medline (n = 189)
  Embase (n = 141)
  Cochrane library (n = 0)

Additional records identified through other sources
  (n = 1)

Records after duplicate removed
  (n = 331)

Records screened
  (n = 331)

Records excluded
  (n = 310)

Full-text articles assessed for eligibility
  (n = 21)

Full text articles excluded with reasons
  (n = 0)

Studies included in qualitative synthesis

21 publications corresponding to 19 clinical studies
### Evidence Table 5: Switching among biosimilars

<table>
<thead>
<tr>
<th>1st author (year)</th>
<th>Country</th>
<th>Study design</th>
<th>Indications</th>
<th>N° pts</th>
<th>Comparisons</th>
<th>Main results</th>
<th>Authors conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFLIXIMAB</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Lovero (2021) (61)</td>
<td>IT</td>
<td>cohort study (R)</td>
<td>IBD</td>
<td>36</td>
<td>CT-P13 to SB2 vs multiple switch</td>
<td>Clinical remission rate, LOR, AEs: no differences</td>
<td>Switching from CT-P13 to SB2 seems to be safe and effective either in pts with single and multiple switches</td>
</tr>
<tr>
<td>Macaluso (2021) (60)</td>
<td>IT</td>
<td>cohort study (P)</td>
<td>IBD</td>
<td>276</td>
<td>CT-P13 to SB2 vs multiple switch vs IFX originator to SB2</td>
<td>SAEs, n (%)*: CT-P13 to SB2: 11 (25.6) Multiple switches: 4 (16.7)</td>
<td>Safety and effectiveness of IFX SB2 similar to those of IFX originator; switching from originator or CT-P13 (and multiple switches) not dangerous</td>
</tr>
<tr>
<td>Hanzel (2021) (58)</td>
<td>NLD</td>
<td>cohort study (P)</td>
<td>IBD</td>
<td>176</td>
<td>CT-P13 to SB2 vs multiple switch vs IFX originator to CT-P13</td>
<td>Clinical remission n (%): CT-P13 to SB2: 55 (69); multiple switch: 58 (84); IFX originator to CT-P13: 25 (93) Discontinuation (HR 95% CI): CT-P13 to SB2: 0.42 (0.16 to 1.12); multiple switch: 0.39 (0.14 to 1.11) ADA (%): CT-P13 to SB2: 8.8% (7/80); multiple switch: 5.8% (4/69); IFX originator to CT-P13: none</td>
<td>No significant differences in clinical, CRP or faecal calprotectin remission at 12 months, lower rates in pts switching from CT-P13 to SB2; multiple switching and switching between biosimilars of IFX seemed effective and safe</td>
</tr>
<tr>
<td>Mazza (2021) (62)</td>
<td>IT</td>
<td>cohort study (R)</td>
<td>IBD</td>
<td>118</td>
<td>multiple switch vs IFX originator to CT-P13</td>
<td>Clinical remission (adjusted OR, 95% CI): 1.3 (0.3 to 6.2) Total AE n (%): multiple switch 5 (9.6); IFX originator to CT-P13 8 (12.4); discontinuation (adjusted HR, 95% CI) 1.3 (0.3 to 6.2)</td>
<td>No significant differences in terms of safety and efficacy when comparing double switch with a single switch; data consistent with the safety profile of IFX</td>
</tr>
<tr>
<td>Luber (2021) (59)</td>
<td>UK</td>
<td>cohort study (P)</td>
<td>IBD</td>
<td>186</td>
<td>CT-P13 to SB2 vs multiple switch</td>
<td>Disease activity n (%) 1 year: CT-P13 to SB2: 6 (9.5); multiple switch: 1 (1.3) ADA 1 year: none in both arms</td>
<td>Biosimilar switching does not have negative influence in terms of infliximab trough levels and disease activity</td>
</tr>
<tr>
<td>Author</td>
<td>Country</td>
<td>Study Type</td>
<td>Disease</td>
<td>Study Design</td>
<td>Comparator</td>
<td>Disease Activity</td>
<td>Discontinuation</td>
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<tr>
<td>Harris (2019) (63)</td>
<td>UK</td>
<td>cohort study (P)</td>
<td>IBD</td>
<td>133</td>
<td>CT-P13 to SB2 vs historic control (no switch)</td>
<td>Disease activity (mean ± SD) week 16-18: Crohn's disease: 3.15 ± 3.17; Ulcerative colitis: 0.91 ± 1.64</td>
<td>Discontinuation rate n (%): CT-P13 to SB2: 5 (11.6); multiple switch: 7 (6.2)</td>
</tr>
<tr>
<td>Trystram (2021) (54)</td>
<td>FR</td>
<td>cohort study (P)</td>
<td>IBD</td>
<td>204</td>
<td>CT-P13 to SB2 vs multiple switch</td>
<td>LOR n (%): 17 (10.8) both groups</td>
<td>Discontinuation rate n (%): CT-P13 to SB2: 36/40 (90); multiple switch: 104/113 (92)</td>
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<tr>
<td>Bouhnik (2020) (53)</td>
<td>FR</td>
<td>Single-arm (R)</td>
<td>IBD</td>
<td>109</td>
<td>IFX (biosimilar or originator) to SB2</td>
<td>LOR n: 19</td>
<td>Discontinuation rate due to AEs n: 9; Discontinuation due to unspecified reasons n: 16</td>
</tr>
<tr>
<td>Mott (2021) (68)</td>
<td>UK</td>
<td>Single-arm (P)</td>
<td>IBD</td>
<td>289</td>
<td>CT-P13 to GP1111</td>
<td>LOR n (%): 17 (6)</td>
<td></td>
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<tr>
<td>Siakavellas (2021) (67)</td>
<td>UK</td>
<td>Single-arm (P)</td>
<td>IBD</td>
<td>246</td>
<td>CT-P13 to GP1111</td>
<td>ADA n (%): 5 (2)</td>
<td>Discontinuation rate n (%): 10 (3.7); LOR n (%): 5 (2)</td>
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<tr>
<td>Lauret (2020) (57)</td>
<td>FR</td>
<td>cohort study (P)</td>
<td>CID</td>
<td>309</td>
<td>CT-P13 to SB2 vs multiple switch</td>
<td>ADA n (%): 3 years: CT-P13 to SB2: 11 (25); multiple switch: 20 (8.5)</td>
<td>Discontinuation rate n (%): 3 years: CT-P13 to SB2: 15 (34); multiple switch: 44 (16.6)</td>
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<tr>
<td>Peters (2021) (70)</td>
<td>NLD</td>
<td>Single-arm (R)</td>
<td>sarcoidosis</td>
<td>86</td>
<td>IFX originator or CT-P13 to SB2</td>
<td>Discontinuation: none; AE n (%): 5 (6.3)</td>
<td>ADA (assessed in 7 pts): none</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Disease</td>
<td>N</td>
<td>Treatment</td>
<td>Outcome Measures</td>
<td>Results</td>
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<tr>
<td>Gisondi (2020) (65)</td>
<td>IT</td>
<td>Single-arm (P)</td>
<td>Psoriasis</td>
<td>96</td>
<td>Multiple switch</td>
<td>mean PASI: no change; LOR n (%): 7 (7.3); AE n (%): 3 (3.1)</td>
<td>did not significantly changed compared with trough levels at baseline</td>
</tr>
<tr>
<td>Khan (2022) (71)</td>
<td>USA</td>
<td>Cohort study (R)</td>
<td>CIRD</td>
<td>271</td>
<td>multiple switch vs IFX originator to SB2</td>
<td>Discontinuation rate n (%): multiple switch: 30 (17.6); IFX originator to SB2: 9 (8.9); LOR n (%): multiple switch: 15 (8.8); IFX originator to SB2: 9 (8.9); Pts not in remission n (%): multiple switch: 16 (9.4); IFX originator to SB2: 12 (11.9)</td>
<td>Switch not associated with significant change in the mean PASI and LOR</td>
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### ADALIMMUNAB

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>Disease</th>
<th>N</th>
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<th>Outcome Measures</th>
<th>Results</th>
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<tr>
<td>Ribaldone (2021) (64)</td>
<td>IT</td>
<td>Single-arm (P)</td>
<td>CID</td>
<td>68</td>
<td>ABP501 to SB5</td>
<td><strong>Success rate (clinical remission) n (%):</strong> 50 (82); <strong>discontinuation n (%):</strong> 7 (11.5); AE n (%): 7 (11.5)</td>
<td>Switching between biosimilars is safe and effective; switch not recommended if positive CRP is found at the time of switching.</td>
<td></td>
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<tr>
<td>Lontai (2022) (56)</td>
<td>HU</td>
<td>Cohort study (P)</td>
<td>IBD</td>
<td>246</td>
<td>ADMB bio 1 to ADMB bio 2 vs ADMB originator to ADMB bio</td>
<td><strong>Clinical remission % (week 20-24):</strong> bio1 to bio2: 77.6; originator to bio: 85</td>
<td>No differences in pts who switched from originator to biosimilar or between biosimilar</td>
<td></td>
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<tr>
<td>Gall (2021) (55)</td>
<td>N/A</td>
<td>Cohort study (P)</td>
<td>CIRD</td>
<td>90</td>
<td>ADMB bio 1 to ADMB bio 2 vs multiple switch</td>
<td>no differences in disease characteristics nor in satisfaction with care</td>
<td>No differences in disease characteristics nor in satisfaction with care</td>
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### ETANERCEPT

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<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>Disease</th>
<th>N</th>
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<th>Outcome Measures</th>
<th>Results</th>
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<tr>
<td>Kilz (2020) (69)</td>
<td>DE</td>
<td>Single-arm (R)</td>
<td>CIRD</td>
<td>100</td>
<td>SB4 to GP2015</td>
<td><strong>DAS28 (RA) mean ± SD:</strong> 3.0 (1.4); <strong>DAS28 (PsA) mean ± SD:</strong> 3.6 (2.6); <strong>BASDAI (axSpA) mean ± SD:</strong> 4.3 (2.4); discontinuation n: 7 pts; AEs n: 8 pts</td>
<td>Retention rate after multiple switches about 90%; No major changes in disease activity and function</td>
<td></td>
</tr>
<tr>
<td>Piaserico (2021) (66)</td>
<td>IT</td>
<td>Single-arm (P)</td>
<td>psoriasis</td>
<td>72</td>
<td>Multiple switch (originator to SB4 to GP2015)</td>
<td>LOR n: 3 pts No treatment-emergent SAEs reported.</td>
<td>Switching from SB4 to GP2015 is both safe and effective</td>
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*results of the groups in which patients switch between biosimilars; Multiple switch: Switch from originator to one biosimilar and then to another

ADA: antidrug antibodies; ADMB: adalimumab; AE: adverse events; BASDAI: Bath Ankylosing Spondylitis Disease Activity; axSpA: axial spondyloarthritis; CI: confidence interval; CI(R)D: chronic inflammatory (rheumatic) diseases; CPR: C-reactive protein; DAS28: Disease Activity Score; IFX: infliximab; LOR: loss of response; P: prospective; PASI: Psoriasis Area Severity Index; PsA: psoriatic arthritis; Pts: patients; R: retrospective; SAE: severe adverse events; SD: standard deviation
None of these though directly compared switching from a biosimilar to another of the same biologic medicine vs the maintenance of the same biosimilar (Evidence Table 5 above). This would have been the optimal study design to assess the efficacy and possible risks of switching between biosimilars (vs non-switch), similar to switching between originators to biosimilars. One study, published as poster, compared a group of patients with inflammatory bowel diseases switching from infliximab CT-P13 to SB2 to an historical cohort of patients treated with CT-P13. This preliminary data did not suggest switching had an impact on drug persistence. Ten controlled cohort studies compared switching between two biosimilars vs switching from originator to a biosimilar or vs multiple switches, e.g., from an originator to biosimilar A to biosimilar B. Eight were single-arm cohort studies, where participants switched from one biosimilar to another and outcome were compared before and after the switch.

Overall, 12 studies adopted a prospective design, six were retrospective and one was a prospective observational study with a retrospective control group.

Most of the studies (74%, 14 out of 19) involved infliximab (originator and its biosimilars CT-P13 and SB2). Moreover, 12 out of 19 of the studies (63%) assessed anti-TNF for the management of inflammatory bowel diseases (IBD), ulcerative colitis or Crohn’s disease in clinical practice setting. It is worth noting that one study analysed the switching between two infliximab biosimilars in patients with sarcoidosis, an inflammatory disorder characterised by a heightened granulomatous immune response. Infliximab is used off-label to treat this condition, as multiple studies demonstrated a clinical improvement, possibly because of the cytokine TNF-α role in the inflammatory process and granuloma formation.

In terms of outcomes, all the included studies evaluated whether the switch between biosimilars impacted on the safety and efficacy of anti-TNF agents. Safety was typically measured as the frequency of adverse events and discontinuations, while efficacy was assessed by measuring clinical responses or worsening of the disease, steroid-free clinical remission, or loss of response, through standard metrics applied to the different diseases. For instance, serum C-reactive protein levels were measured in inflammatory disease and ACR criteria used in rheumatic disorders. Less than a third of the included studies (28%, 5 out of 18) specifically addressed the impact on immunogenicity by measuring infliximab trough levels and antidrug antibodies using ELISA assay.
4.4. Discussion

Through the case models of insulin analogues and anti-TNFs, I tried to assess the clinical evidence supporting the effectiveness and safety of switching from an originator to its biosimilar in chronic conditions.

Overall, these studies suggest that switching from one biosimilar (infliximab, adalimumab or etanercept) to another biosimilar of the same medicinal biologic medicine in patients with chronic inflammatory diseases is safe and effective in terms of disease activity, remission rate, loss of response, adverse events, and immunogenicity (when analysed). Similar conclusions can be drawn from studies assessing multiple switches, i.e., studies in which patients already on treatment with the originator are switched to one biosimilar and then to another one. None of the studies assessing immunogenicity demonstrated that switching between biosimilars leads to a change in the immune response, with similar anti-drug antibodies trough levels either soon after switching or after longer follow-up.

Overall, the data highlights that switching seems not to be associated with major efficacy, safety, or immunogenicity issues. However, the case-models represent two quite different situations.

In regard of insulin analogues, I found only a very limited number of studies that evaluate the switch between insulins. A possible explanation could be that switching between insulin analogues as well as analogue to human, or vice versa, is regularly and confidently undertaken in clinical practice. This reflection came up also from the research done by my external supervisor (Professor Brian Godman), with whom I explored the impact of biosimilars on prices and utilisation of long-acting biosimilar insulin glargine versus the originator across Europe and wider. (Haque M, 2021; Godman B, Haque M, 2021b). Because of this, this area might not represent a research priority nor a clinical question requiring equivalence studies that provide evidence to support clinical practice.

The body of identified switch studies is heterogeneous in its design, and in consequence, in the quality of the generated evidence, and I cannot exclude any potential risks. In addition, the results of the studies analysed cannot be generalised to other products or other disease given the different immunological complexities of the different products, the different disease states and the natural variability among patients.

The most relevant burden against insulin switching seems to be the absence of promotional efforts of the potential saving/cost-effectiveness from increasing the use of biosimilar insulins. In addition, originator companies lowering the price of originators often close to biosimilar prices, coupled with
concerns with different devices used, has further limited biosimilar use (Godman B, Wladysiuk M, 2021).

On the other hand, there is a much larger body of evidence regarding the switch of anti-TNFs between originators and biosimilars in adults with chronic inflammatory diseases, such as rheumatic disorders, inflammatory bowel diseases and psoriasis. Indeed, there is a large body of published evidence for anti-TNFs evaluating the impact of switching as we were able to include 14 RCTs and 11 open-label extension studies. Although the switch studies retrieved through the systematic reviews cannot exclude every potential risk associated with switching from originator to a biosimilar, as well as switching among biosimilars of the same active principle, none of them corroborate the voiced concerns of increased immunogenicity induced by switching. Indeed, the current body of switch data, together with the robust biosimilar approval pathway, helps to considerable reduce any residual uncertainty. In addition to data supporting biosimilarity at the time of approval, these data should reassure professional societies and patient groups who strongly advocate that any decision to exchange an originator with a biosimilar should remain the responsibility of the physicians in consultation with their patients.

There is a need to increase physicians’ and patients’ confidence in biosimilar medicines, including switching between biosimilars, to increase the availability and use of biological medicines especially where there are issues of affordability. This is ongoing (Moorkens E, 2021).

In view of our findings, healthcare professional expectations for routine switching studies now seem unnecessary due to the growing body of evidence suggesting no real problems in practice coupled with stringent regulatory requirements. Increased monitoring of patients prescribed biosimilars in clinical practice through increased use of TDIM (see Chapter 5) could offer an additional tool to support interchangeability and help to further realize possible savings.
CHAPTER 5. Therapeutic drug and antibodies monitoring of biologic drugs and their biosimilars

5.1. Introduction

As already highlighted, biological medicines improved the outcomes of common chronic immune-mediated inflammatory diseases. However, the responsiveness to biological medicines – either originators or biosimilars - is often highly variable among patients, which could be translated in important differences in clinical efficacy or side effects. Various factors can influence the pharmacokinetics of a biological medicine. These include patient-related factors i.e., genetic factors, albumin concentrations, disease activity and treatment, and factors related to the medicine itself i.e., the type of biological agent, the dosing schedule and route of administration, the target antigen (Strand V, 2021).

On one hand, for the same antibody, inter-individual differences lead to the possibility that the organism’s ability to remove (or breakdown) the medicine might be reduced or increased, with the consequence of having higher or lower drug concentrations, possibly leading to more side effects or reduced or no response, respectively. On the other hand, biologic drugs can prime immune responses to themselves and related proteins or induce immunologically related clinical effects or adverse clinical events, affecting either efficacy or safety, or both (Harding FA, 2010).

This propensity to trigger an unwanted immune response, intrinsically linked to the nature of biological medicines, goes under the name of immunogenicity. All biological drugs, even those that are fully human, are immunogenic, that is, they can induce an immune response in the treated patient (Harding FA, 2010).

The understanding and assessment of immune responses and of immunogenicity is of great importance during the drug development of biological medicines. Moreover, relevant changes in the manufacturing process of biological medicines after their launch on the market, and the introduction of biosimilars with the request to compare these drugs with their reference product, have generated the need for providing information on the immunogenicity both before and after the marketing approval along the product lifecycle.

The EMA guidance document and other reviews have classified the factors that can induce immunogenicity into disease-, patient-, or product-related factors (CHMP, 2008; Shankar G, 2008; Mire-Sluis AR, 2004). The reason for the variable occurrence of ADAs in different disorders is unclear, but may be related to the pathogenic mechanisms of the disease itself or different degree
of cells activation (Matucci A, 2021). Examples for disease-related factors include dysregulation of immune responses in autoimmune conditions, inflammatory responses due to an infectious agent, or an existing immune response in a patient due to a disease condition (CHMP, 2008). Indeed, certain diseases including rheumatoid arthritis and Crohn’s disease among others are known to be particularly associated with immunogenicity.

The mode of administration is also relevant since it has been demonstrated that subcutaneous administration is more immunogenic than intravenous infusion as it permits prolonged contact between the molecule and dendritic cells. (Carrascosa JM, 2013; Schellekens H, 2010).

The molecular structure of a medicine also has a significant role as immunogenicity varies depending on whether the biologic agent is a fusion protein, a chimeric, humanised or fully human antibody (Carrascosa JM; 2013). In theory, humanised monoclonal antibodies should be less immunogenic than chimeric or murine antibodies owning to the presence of less non-human protein sequences that might be recognized as foreign. Nevertheless, despite being a fully humanised monoclonal antibody, adalimumab has shown to be immunogenic (Strand V, 2021).

Compared to monoclonal antibodies, the relatively small, structurally uncomplicated and well-characterised nature of insulin products, leaves little or no residual uncertainty regarding the risk of clinical impact from immunogenicity. Moreover, extensive experience and the literature confirm that there is minimal or no clinical relevance of immunogenicity with insulin product use (CDER, 2019).

As mentioned, when the patient’s immune system recognizes these medicines as non-self, it leads to the development of ADA. In some patients, ADAs are associated with reduced therapeutic efficacy, either because of immune complex formation and accelerated drug clearance and/or because of the neutralizing antibodies that block the binding of the biological drug to its target (Strand V, 2021). ADA formation is also linked to adverse events including injection site reaction and/or infusion reactions (Strand V, 2021).

In both cases, the ultimate result is the loss of function of the medicine that may trigger a change in the prescriptions. The physician may choose another active principle of the same class of drug, or another class of drug. This latter option might lead to losing therapeutic options, i.e. other effective agents in the same class, especially in chronic inflammatory conditions where it is typically required to administer the drug over a long period of time. (Vande Casteele N, 2015).
Due to the interindividual variability, some patients may not respond to treatments (primary non-responders) or experience a secondary loss of response to biological therapy. For example, one-third of patients treated with infliximab for common immune-mediated inflammatory diseases do not respond to induction therapy (primary non-responders), while up to half of the patients (30% to 50%) who initially respond to the drug will lose their response during the first year of therapy maintenance (secondary non-responders) (Rutgeerts P, 2005; Hanauer SB, 2002; Chaudhari U, 2001). This results in reduced quality of life and risk of irreversible organ damage and disability. Immune responses may arise months or years after starting the treatment; consequently, they may only be detected when wider cohorts of patients are exposed for long time to a biological medicine, including different batches of the biological products or their biosimilars. (Syversen SW, 2021a; Syversen SW, 2021b).

5.1.1. The clinical value of mAb therapeutic monitoring
The clinical value of drug monitoring is to support informed decisions for the management of non-responders, helping clinicians optimize dosage regimens or switching new therapeutic strategies, reducing unnecessary interventions.

The concept of TDM is not new in pharmacology and is applied to several medicines including immunosuppressants, antibiotics, antiepileptics, antidepressants, digoxin and methotrexate. In the era of personalised (or precision) medicine, TDM is also gaining popularity for biological medicines in order to tailor therapies to a single patient, in particular for guiding an effective regimen that could address poor responsiveness to the disease or after the onset of toxic effects (Di Paolo A, 2021). In particular, proactive TDM, an individualised treatment strategy in which drug doses and timing of administered doses are adjusted based on scheduled measurements of serum drug levels, has been adopted by some clinicians (Grossberg LB, 2017).

As previously discussed, in the case of monoclonal antibodies, the measurement of serum concentrations should be coupled by the measurement of the corresponding ADA; this approach is called therapeutic drug and immunogenicity monitoring (TDIM).

Given the high cost of biological medicines, such as mAb, TDIM can lead to a better use of these drugs with a significant impact on health budgets (Beeg 2020).

The efficacy of TDIM for improving patients’ outcomes and reducing costs has been mainly investigated in patients with inflammatory bowel diseases, treated with the anti-TNFα monoclonal antibodies IFX and ADMB. This is also due to the longer time these biologicals have been on the
market, allowing for more data to be obtained than for other anti-TNF monoclonal antibodies. Many studies showed positive correlations between IFX concentrations and the outcomes of therapy, or on the incidence of immunogenicity on long-term drug efficacy (Beeg M, 2019; Syversen SW 2021a; Syversen SW 2021b). Moreover, the results of two randomised clinical trials, with a relatively large sample size and rigorous design, were reported in 2021. These studies investigated the effect of TDIM versus standard therapy for remission induction (Syversen SW 2021a) or for sustained disease control without disease worsening (Syversen SW 2021b), in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn’s disease, or psoriasis undergoing treatment with infliximab. No effect of TDIM was observed on the induction of disease remission (i.e., on the primary treatment failure during the induction period) while a significant and clinically relevant effect was observed in sustaining disease control during maintenance therapy, reducing secondary loss of response (26% for TDIM vs 44% for the standard approach).

5.1.2. Analytical methods applied to TDIM
Different bioanalytical assays are being used for TDIM, including enzyme-linked immunosorbent assays (ELISA) (Maser EA, 2003; Baert F, 2003; Hanauer SB, 2006; Ternant D, 2006; Vande Casteele N, 2012), radioimmunoassays (Radstake TR, 2009), electrochemiluminescent immunoassay (Yoo DH, 2013), reporter gene assay (Steenholdt C, 2013), homogeneous mobility shift assays (Wang SL, 2012), with ELISA being the most popular. The variety of methods and thresholds applied (Steenholdt C, 2013; Steenholdt C, 2016; Silva-Ferreira F2016) and the limited or contradictory (Borren NZ, 2021) evidence of the superiority of TDIM over empiric decisions call for further research (Ricciuto A, 2018).

As part of the PhD programme, I relied on the recent demonstration of the usefulness of SPR technology when applied for the measurement of serum concentrations of the anti-TNFα infliximab and anti-infliximab antibodies (Beeg M, 2019).

SPR is a widely used technology to study in real time the interaction between two unlabeled molecules, one immobilized on a sensor chip, the other flowing through a microfluidic system over the chip surface. According to these features, SPR allows direct detection and measurement of serum antibodies in a very short experimental time (few minutes); consequently, avoiding the long incubation/separation/washing/detection steps of classic ELISA tests. This results in a reduced
complexity and variability and, notably, in a more reliable measurement of low-affinity patient’s anti-drug antibodies. Indeed, even though ELISA is the most common technique used to detect the production of anti-drug antibodies, the multiple incubations and washing steps affect the detection of low affinity antibodies and reduce the accuracy and precision of the measurements. Beeg et al., 2019 characterized and validated a novel analytical assay (Figure 5) to measure serum concentrations of IFX and the corresponding ADA, based on SPR. In this novel assay the patient’s serum flows over parallel surfaces of the same sensor chip coated with TNFα and IFX, allowing specific binding of the serum IFX and ADA, respectively (Beeg M, 2019). This binding results in immediate and concentration-dependent SPR signals, from which IFX and ADA concentrations are determined simultaneously on calibration curves.

Figure 5: Surface plasmon resonance illustration courtesy of Dr. Marco Gobbi and Dr. Marteen Beeg

The assay performances were also rigorously characterized and validated, following the accepted guidelines for bioanalytical methods, as regards, for example, precision, accuracy and matrix effects. In particular, accuracy was determined by expressing the calculated concentration as a percentage of the nominal concentration and, according to EMA guidelines, has to be within 15% of the nominal value for each concentration (±20% for the LLOQ as an exception). Precision, was expressed by the CV (%), and must not exceed 15% for all concentrations (20% for the LLOQ). For
the validation of the SPR, matrix effects were also checked, spiking different concentrations of IFX or ATI in the serum from six different subjects. Most importantly, the analysis of the plasma of a limited number of patients treated with IFX (fifteen) suggested the possibility that ELISA could miss the presence of ADA in some patients (Beeg M, 2019).

5.2. Hypothesis and objectives
The hypothesis underlying the laboratory part of this PhD research project is that the measurement of TNF inhibitors and ADA in the blood (proactive TDIM) can support informed decisions for a more rational management of biological therapies. The results should help improve the appropriateness and personalisation of care, with important advantages for both patients and the NHS.

The possibility that ELISA, i.e. the most common technique used in clinical practice for TDIM, could not provide reliable results as regards the presence of ADA might have important consequences for the correct interpretation of the clinical outcome and/or for the appropriate clinical decisions. Moreover, the poor reliability of the ELISA tests might also have resulted in conflicting results observed in previous studies assessing TDIM efficacy.

The following section reports the study I participated in, assisted by laboratory supervisor, to compare ELISA and SPR on a larger number of patients treated with IFX, to test the hypothesis that SPR could allow to detect ADA in patients otherwise considered ADA-negative by ELISA. In addition, SPR should allow the characterization of patient’s ADA in terms of its binding parameters and their neutralizing properties. This should be useful for clarifying the kinetic reasons for the different detection of ADA with the two methods.

5.3. Materials and Methods
IFX trough levels and ADA serum concentrations were measured with a commercial ELISA and by SPR. The concentrations of IFX and ADA in each serum sample were determined by SPR in triplicate, with ex-novo preparation of samples and calibration curves, by two separate researchers with different experience (MB, EA).

In particular, IFX and ADA were measured with CE-marked ELISA kits distributed by R-Biopharm AG (Germany), according to manufacturer’s guidelines. With this kit (RIDASCREEN®IFX), plasma IFX is captured by TNFα applied to the surface of the well and, after a washing step, detected by a highly
specific anti-IFX monoclonal antibody (MA-IFX6B7) conjugated with horseradish peroxidase. For these analyses plasma samples were diluted 100 times. ADA were measured by RIDASCREEN® anti-IFX, with plasma samples diluted 200-fold. In this case, ADA were captured by IFX applied to the surface of the wells and, after a washing step, recognized by biotin-conjugated IFX which was eventually detected by peroxidase-conjugated streptavidin. The manufacturer recommends measuring ADA when IFX concentrations in the serum sample are below 1 μg/ml. To expand the population, and to investigate the assay’s performance in patients with higher drug concentrations, ADA concentrations were measured in all serum samples with IFX below 3 μg/ml.

With regard of the SPR, TNFα, IFX (Inflectra, as indicated), and IgG (control) were immobilized using amine-coupling chemistry on parallel strips of the same sensor chip (GLC, BioRad), according to manufacturer’s recommendation. The calibration curves of IFX and ADA were obtained with the IFX biosimilar CT-P13 (Hospira S.r.l., Naples, Italy) and the commercial anti-IFX antibody HCA-216 (Bio-Rad Laboratories, Segrate, Italy). After rotation of the fluidic system, analyte solutions were injected in parallel surfaces, so that they flowed on all the immobilized ligands, creating a multi-spot interaction array (Figure 6).
Before injection, human sera containing either IFX or ADA were subjected to acidic pre-treatment. Firstly, the samples were diluted 1:20 in 100 mM acetic acid pH 3 and incubated for 15 min at room temperature. Subsequently, the samples were diluted 1:1.5 in 0.5 M phosphate buffer pH 7.4, to a 30-fold overall sample dilution. The running buffer of the SPR instrument was 10 mM phosphate buffer containing 150 mM NaCl and 0.005% Tween 20 (PBST pH 7.4). Diluted patients’ sera or calibration standards flowed over immobilized ligands for three min at a rate of 30 µL/min. Dissociation was measured in the following 7-11 minutes. All of these assays were performed at 25 °C. The sensorgrams (time course of the SPR signal in RU) were normalized to a base-line value of 0. The signals observed in the surfaces immobilizing the ligands were corrected by subtracting the nonspecific response observed in the reference surface (“empty” surface for immobilized TNFα, and IgG for immobilized IFX). When indicated, the sensorgrams were fitted using the ProteOn analysis software to obtain the kon and koff and the equilibrium dissociation constant (K_D).

The calibration curves included six-point calibrators in the range of 0.25-8 µg/mL control serum for IFX or 5-40 µg/mL control serum for the commercial anti-IFX antibody. Two separate runs with
calibrators were carried out, one at the beginning and one at the end of each analytical session. Responses, expressed as the RU at the end of the dissociation phase, were plotted against the corresponding analyte concentration and the data were fitted using weighted \((1/x^2)\) linear regression. All calibration curves analyzed during method validation showed determination coefficients \((r^2)\) over 0.99; the accuracy of the back-calculated concentrations was always within the acceptance limits \((\pm 15\% \text{ of the nominal value})\).

ADA were expressed as μg Equivalents/mL, to illustrate that the ADA used for the calibration curves are different from those produced by the patients.

5.3.1. Cohort of patients
We analyzed the serum samples from 76 patients in maintenance therapy with IFX (Remsima®, Celltrion; Inflectra®, Pfizer) for IBD, either Crohn’s disease or ulcerative colitis, at the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico (Milan, Italy) between April 2018 and July 2019. Inclusion criteria were adult age and the beginning of IFX therapy at least 8 weeks before serum sampling.

The study was approved by the Ethical Committee of the Fondazione IRCCS “Cà Granda” (n. 1310/2019). All patients provided informed consent and medical information about patients were retrospectively extracted from medical records. Because of the study’s retrospective nature and the lack of routine clinical score recording, clinical activity was based on the judgment of the treating physicians, as documented in the patients’ charts.

Blood samples were taken just before the infusion of a maintenance dose, to obtain drug trough levels, and sera were immediately obtained and stored at −80° until analysis.

Biochemical and endoscopic activity were concomitantly assessed through CRP and colonoscopy reports, respectively, considering CRP obtained two months before or after the date of sampling for TDIM, and for endoscopic activity reports obtained six months before or after.

5.4. Results
Table 6 reports the main clinical characteristics of the 76 patients included in the sample.

Table 6. Characteristics of the 76 patients (Beeg M, 2021)

<table>
<thead>
<tr>
<th>Sex</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, no. (%)</td>
<td>50 (65.8%)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>26 (34.2%)</td>
</tr>
<tr>
<td>Mean age at diagnosis (yr, SD)</td>
<td>29.1 ± 12.7</td>
</tr>
</tbody>
</table>
Mean duration of IFX therapy (mo, SD) | 37.3 ± 30.1
---|---
IBD type, no. (%) | 53 (69.7%) 23 (30.3%)
  - Crohn’s disease | 53 (69.7%)
  - Ulcerative colitis | 23 (30.3%)
Crohn’s disease location, no. (%) | 12 (22.6%) 31 (58.5%) 10 (18.9%) 3 (5.7%) 20 (37.7%)
  - ileum | 12 (22.6%)
  - ileo-colon | 31 (58.5%)
  - colon | 10 (18.9%)
  - upper | 3 (5.7%)
  - perianal disease | 20 (37.7%) 3 (5.7%)
Ulcerative colitis location, no. (%) | 0 (0.0%) 13 (56.5%) 10 (43.5%)
  - Proctitis | 0 (0.0%)
  - Left sided colitis | 13 (56.5%)
  - Extensive | 10 (43.5%)
Extraintestinal manifestations, no. (%) | 7 (9.7%)
Concomitant IMM therapy, no. (%) | 19 (25.0%)
IFX therapy regimen, no. (%) | 51 (67.1%) 25 (32.9%)
  - Standard | 51 (67.1%)
  - Optimized | 25 (32.9%)

IMM = immunomodulator (azathioprine, methotrexate).
IFX standard regimen = 5mg/kg every 8 weeks, optimized regimen = 10 mg/kg and/or frequency shorter than 8 weeks.

The concentrations of IFX and ADA in each serum sample determined by SPR confirmed that SPR is highly reproducible and robust (Figure 1a in the Appendix 3).

IFX was detectable in the sera of 57 and 56 patients by SPR and ELISA, respectively. The values with the two methods showed a very good correlation (Figure 7) with a Pearson coefficient of 0.90 (p<0.001). After removal of the patients with out-of-scale values, the slope was not significantly different from 1, highlighting the quantitative correspondence.
Figure 7. Correspondence between serum concentrations of IFX determined by SPR and ELISA. The graph reports the values in 58 patients, i.e. those in which IFX levels were measurable by at least one method. These data were analyzed using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla California USA). The Pearson correlation coefficient was 0.90 (p < 0.001). The linear regression of the points, after removal of those out-of-scale for ELISA, showed an intercept of 0.32 (not different from 0) and a slope of 1.03 (not significantly different from 1) (Beeg M, 2021). The correlation between ELISA and the SPR seems to be excellent up to approximately 10 ng/ml, but ELISA saturates at higher doses of IFX. In light of that the SPR assay would be more beneficial than ELISA.

The Figure 8 shows the numbers of patients with IFX serum levels within the assumed therapeutic range (3-7 μg/mL) (21), and the numbers of with too low or too high levels, as identified with the two methods.

Figure 8: Levels of IFX in μg/mL, detected by ELISA or SPR. Nd indicates levels below the LOD (0.25 μg/mL), and 3-7 (μg/mL) indicates the therapeutic range (Beeg M, 2021).
The comparison with the ELISA assay allowed to highlight good correspondence between the serum IFX concentrations measured with SPR and those measured by ELISA; although they were not exactly superimposable (Figure 1b in the Appendix 3) (Maser EA 2006; Vande Casteele N, 2015)

However, only two patients among those with IFX detectable by both methods had differences that may induce the clinician to modify therapy: one patient (#67) had in-range values by ELISA (2.05 μg/mL) but high values by SPR (8.85 μg/mL); and one patient (#70) had too low SPR values (1.52 μg/mL) and in-range ELISA values (4.65 μg/mL).

The IFX serum levels showed wide inter-individual variability in the patients tested. In the whole set of data, only 22 patients (29%) had IFX in the therapeutic range, independently of the analytical method. Similar proportions of patients (24-28%, depending on the method) had IFX levels exceeding the therapeutic range while quite a high proportion (43-47%) had too low values. Approximately 25% of patients had undetectable IFX by both methods.

Fourteen patients were ADA-positive with both ELISA and SPR; however, the ADA concentrations were strikingly different. Our hypothesis is that ELISA may markedly underestimate ADA concentrations due to the different affinity between patients’ ADA.

The ELISA we used is a drug-sensitive assay that detected ADA only in serum from 36 patients with low IFX (< 3 μg/mL). ADA were detectable in 14 of these (18% of total, Figure 9A), all with undetectable IFX. In contrast, no ADA were found in the 16 patients with detectable IFX. Six patients had no IFX or ADA.

For all the 76 patients analyzed by SPR, ADA were detectable in 28 (37%) (Figure 5B). All the patients with undetectable IFX (19) had ADA, whose levels varied widely (1.4-85 μg Eq/mL). ADA were also clearly detected in 9 patients with detectable IFX, six of them with IFX>3 μg/mL (red in Fig 9B). These data confirm that ADA detection by SPR is “drug-tolerant” (i.e., the ability of the SPR to detect ADA in the presence of a defined concentration of drug).

This is a well-known limitation of ELISA that prevents the measurement of ADA in the presence of IFX.
Figure 9. Levels of anti-IFX antibodies (ADA) and IFX, measured by: A) ELISA in the plasma of 36 patients (i.e. those with IFX<3 μg/mL) and B) SPR (76 patients). ADA are expressed as μg Equivalents/mL, to indicate that the ADA used for the calibration curves are different from those produced by the patients (Beeg M, 2021).

On the other hand, the detection of IFX binding to immobilised TNFa in ADA-positive samples could be due to either too-low ADA concentration, or the presence of not-neutralizing ADA. Consequently, we examined the neutralizing properties of the ADA detected by SPR. All the ADA-positive serum samples were spiked with 8 ug/mL IFX, and the SPR binding signal to immobilised TNFa was compared to the SPR binding signal observed with 8 ug/mL IFX in the absence of ADA. Thus, neutralizing antibodies will reduce the IFX-dependent binding signal whereas non-neutralizing ones will not. The data suggest that most of the ADA detected in the IFX-negative samples were neutralising, as expected, whereas the ADA in IFX-positive samples (9 patients, red in Figure 4B) appeared to be not-neutralising.

All the patients’ sera showing ADA with ELISA (n=14) also showed ADA with SPR. We identified 8 patients’ sera ADA-positive by SPR and ADA-negative by ELISA.

To clarify this difference, we looked more in detail at the sensorgrams obtained when injecting the serum samples containing the different patients’ ADA over immobilised IFX. SPR can follow the association and dissociation phases in real time, estimating the underlying rate constants, and this is a further value of this method. In particular, we focused on the dissociation rate constant (koff), expressed in s⁻¹, by fitting the sensorgram in the dissociation phase (the association rate constant, kon, cannot be estimated in this case because it also depends on the ADA concentration which is not known).
The patients’ ADAs detectable only by SPR, but not ELISA, had a significantly (p<0.001) faster dissociation rate constant (2.1x10⁻³ s⁻¹, 95% CI 1.7-2.3 x10⁻³) than the ADAs detectable by both SPR and ELISA (0.9x10⁻³ s⁻¹, 95% CI 0.7-1.2 x10⁻³) (Figure 10A). Figure 10B shows simulated sensorograms as a visual and practical representation of the impact of the detected koff on the dissociation phase. Within a time-frame of 20 min, the ADA with a koff of 2.1x10⁻³ s⁻¹ (the mean koff of the ADAs detectable by SPR but not ELISA) almost completely dissociated from immobilized IFX in 20 min, whereas those with a koff of 0.9x10⁻³ s⁻¹ dissociated only 65%.

**Figure 10:** Left panel shows the dissociation rate constants (koff, in s⁻¹) determined by SPR for the patients’ ADA; each point represents a single patient. Only some of these patients’ ADA were detectable by ELISA (blue), and these had significantly slower koff than the ADA not detectable by ELISA (red) (p<0.001 Student’s T test). The koff value of the commercial anti-IFX antibody used for the calibration curve is shown for comparison (green).

Right panel shows the sensorgrams simulating the SPR binding signals of three different ADA, with identical concentration (1x10⁻⁸ M) and kon (1x10⁵ M⁻¹s⁻¹) but different koff, corresponding to the mean values shown in the upper panel.

### 5.5. Discussion
Therapeutic drug and immunogenicity monitoring represent a valid method to individualise treatment strategy and maximize efficacy, safety, and cost-effectiveness of biological drugs and in particular anti-TNF therapy (Bloem K, 2017; Papamichael K, 2019; Medina F, 2017; Ma C, 2019; Ricciuto A, 2018). This is particularly important when switching patients from originators to considerably less expensive biosimilars and when there are concerns with their effectiveness in practice. The envisaged availability and convenience of TDIM may help ascertain the cause for any decrease in effectiveness with switching, and avoid automatic switching back to the more expensive
originator in patients with a loss of response, approximately 25 to 30% of patients (Qiu Y, 2017). Recently, a RCT conducted among 20 Norwegian hospitals showed that proactive TDIM during maintenance therapy with infliximab (the originator or a biosimilar product) was more likely to lead to sustained disease control in patients with immune-mediated inflammatory diseases (Syversen SW, 2021; Wallace ZS, 2021). However, proactive monitoring is currently not routinely offered to patients treated with biological medicines across countries. Despite the promising results of the Norwegian trial, other studies assessing the clinical utility of TDIM over empirical decisions have reported conflicting results (Ricciuto A, 2018; Qiu Y, 2017; Syversen SW, 2021; Wallace ZS, 2021; Borren NZ, 2021). The variety of analytical methods and thresholds may be one of the key reasons for these contradictions. In fact, various immunoassay approaches have been used to detect and quantify ADA (Beeg M, 2021), but a unified and validated approach is still lacking. Comparison of different techniques did actually highlight different results in terms of both IFX and ADA titers (Allocati E, 2022).

Through the SPR-based assays, it is possible to propose a more reliable therapeutic drug monitoring-based algorithm approach, providing new information with potential clinical relevance. I and others confirmed the reproducibility and the reliability of the SPR assay for TDIM. Indeed, the SPR allows simultaneous measurement of IFX and the corresponding ADA within one injection cycle; dozens of consecutive injections can be carried out on the same chip thanks to the highly efficient procedure for surface regeneration; and a cycle of injection of serum samples and chip regeneration takes approximately 20 min (Beeg M, 2021).

Moreover, the possibility offered by SPR to detect ADA in patients otherwise considered ADA-negative by ELISA could have important implications for clinicians and also for a more reliable interpretation of the clinical trials designed to evaluate the efficacy of TDIM.

This might be the case for

i) Patients with active disease who showed no IFX by either method. According to ELISA results (no ADA present), physicians could envisage the need to increase the IFX dose, but this would be deleterious if ADA are actually present (as for the SPR result).

ii) Patients were in remission despite low or undetectable levels of IFX, and in these cases too ELISA did not detect ADA whereas SPR did. These patients may benefit from stopping treatment because
presumably their clinical remission is not linked to the drug, and SPR results could support this decision so as to avoid the potential side effects associated with ADA.

iii) Patients with more than adequate IFX levels (≥6 ug/mL) and no disease activity. Indeed, SPR but not ELISA, detected ADA in the serum of five patients with this characteristics, in this case the information provided by SPR - but not ELISA - could suggest adding an immunomodulator to prevent ADA adverse effects (Beeg M, 2021).

While some clinical guidance recommends TDIM when patients loss response to treatment (reactive monitoring) (Steenholdt C, 2013; NICE, 2016), it has not widely been adopted and currently not typically reimbursed by national health services across Europe, as seen for example in Italy. If the usefulness of TDIM to support clinical decisions, and thereby improving patients’ outcomes and the rational use of biologic agents, can be confirmed, possibly with more reliable analytical methods, it may become a key tool for the management of the increasing number of patients undergoing switching between originators and biosimilars as well as between biosimilars (Allocati E, 2022).

During my PhD project, I had the opportunity to visit different centres of NHS Scotland in Edinburgh and Glasgow. I met different healthcare professionals, pharmacists, rheumatologists, NHS Scotland healthcare personnel and University Professors at Strathclyde Institute of Pharmacy and Biomedical Sciences. In the context of broader discussion about potential measures to enhance the use of biosimilars given envisaged savings without compromising care, we also discussed the issue of TD(I)M.

In Scotland, indeed, there is a strong interest in TDIM of biological medicines (both originators and their biosimilars). However this approach is not commonly adopted. Gastroenterologists sporadically use TDM to measure through levels of drugs patients treated with infliximab to drive decision making and improve patient care.

The experience presented by the rheumatologists in collaboration with Strathclyde University concerned the patient level studies using administrative databases in Scotland.

The interlinked Scottish datasets that include data from ambulatory and hospital care, prescribing and dispensing, activities and outcome could be easily complemented with information derived from routine TDIM.
An attempt to collect data on TDM of rheumatology patients treated with infliximab was undertaken using ELISA as analytical method. The length of the analysis and logistical constraints as sample shipping, discouraged both physicians and patients; for instance, the need to recall patients if they need therapy adjustment is a concern because these patients are routinely reassessed every 6 months. A quicker method such as SPR may reduce the time to complete the analysis allowing more rapid decisions, and ideally, point of care delivery system, once validated for the major biologics/biosimilars would appear particularly useful.

Routine patient monitoring may also have a positive impact on discontinuation or adverse events from biosimilars where these are caused by patients’ negative perception of biosimilars or any change in therapy, the so-called nocebo effect. In particular, the emergence of side effects after switching and their resolution after reverting to the formulation previously prescribed (originator or another biosimilar) may have been a result of the nocebo effect (Gorovits B, 2018; Feuerstein JD, 2017; Gomollón F, 2017).

Patient information remains essential to strengthen their relationship with the doctor and to accept biosimilars, including switching between biosimilars, and TDIM can help in this respect along with general patient information (Allocati E, 2022).
CHAPTER 6: Education and training of health professionals/liaison with health authorities

6.1. Introduction

Despite accumulating medical literature that supports biosimilar use, and the growing recognition of their role and value, as presented in the previous chapters, some obstacles to a more widespread adoption remains. Indeed, one of the major barriers to biosimilar prescription is continued concerns with their efficacy and safety.

The different uptake in different countries, as well as across different diseases (rheumatology, gastroenterology and dermatology among others) may reflect gaps in patients’ and clinicians’ knowledge and understanding of the risks and benefits with biosimilars. There are reasons why physicians remain reluctant to prescribe biosimilars or switch their patients to a biosimilar can vary.

The systematic review by Leonard et al. evaluated healthcare providers’ knowledge, perceptions, and prescribing behaviours of biosimilar medicines with the aim to assess the need for clinician-directed biosimilar education. What transpired was that biosimilars were still largely considered second-line therapies since clinicians were still hesitant about biosimilar safety, efficacy, extrapolation and automatic substitution.

These uncertainties show the gap in biosimilar knowledge and understanding among clinicians, as well as a lack of biosimilar awareness. Indeed, the majority of the included studies highlighted that healthcare practitioners reported an incomplete or basic awareness of biosimilar medicines, with a higher level of familiarity among pharmacists than physicians (Leonard E, 2019).

Other studies consistently reported that prescribers have little knowledge of the manufacturing, approval requirements, or ongoing regulation of biologic and biosimilar products (Jimenez-Pichardo L, 2018; Leonard E, 2019; Hemmington A, 2017; Aladul MI, 2018). Moreover, physician specialists generally have positive attitudes towards the prescription of biosimilars to naïve patient, but they seem to be less confident about the extrapolation of indications and switching patients from an originator biologic to a biosimilar (Leonard E, 2019; Hemmington A, 2017; Aladul MI, 2018).

Another important concern on the use of biosimilars, especially in chronic conditions, where patients may be required to switch from the reference products to biosimilar medicines, is represented by concerns with immunogenicity. Incorrectly, both physicians and patients fear that switching automatically brings an increased risk of immunogenicity (Park W, 2016). However, there
appears little clinical evidence to support this occurring to date evidenced in particular by the NOR-SWITCH study as well as a number of other studies in patients switched between biosimilars (Jørgensen KK, 2017; Allocati E, 2022).

A lack of awareness, knowledge gaps, and misperceptions about biosimilars of healthcare providers may contribute to the development of the nocebo effect, i.e., a reduction in treatment benefits in patients switching from originator biologics to biosimilars, and in particular in patients with autoimmune diseases (Rezk MF, 2017; Pouillon L, 2018). The nocebo effect is the phenomenon that occurs when a patient's negative perception of a therapy causes a treatment to have a worse outcome than would otherwise be expected (Rezk MF, 2018; Colloca L, 2019). Consequently, to minimize or avoid this effect, and improve treatment outcomes, there is a need to address clinical and contextual aspects as patients’ lack of positive information, the provision of negative information, negative patient–clinician communication and interaction during treatment, and patients’ emotional burden during treatment.

In the recent years, educational initiatives have been launched by regulatory authorities such as the EMA and FDA to help close gaps in patients’ and healthcare professionals’ awareness and knowledge of biosimilars and their clinical use (EMA healthcare professionals, 2016; EU commission event, 2018; FDA biosimilar educational material). At the same time, professional medical societies such as the European Society for Medical Oncology (Tabernero et al., 2016) and the American Society of Clinical Oncology (Lyman et al., 2018) have published literature on biosimilars and their clinical implementation, strongly emphasizing the importance of education and open patient–clinician dialogue as a mean of ensuring biosimilar acceptance. An international task force on rheumatologic diseases issued recommendations that will likely reduce potential nocebo effects, addressing the misconception that the lower price of biosimilars denotes lower quality than bio-originators, and emphasizing the importance of patient healthcare provider consultation in therapeutic decision-making (Kay et al., 2018).

International and national initiatives do have an important role in creating an overall scientific and cultural environment promoting the use of biosimilars. However, local specificities in prescription trajectories and habits require tailored programs for the education of healthcare professionals, which can be combined with other activities including benchmarking, prescribing targets and financial incentives to enhance biosimilar use. For these reasons, two local health authorities of the Tuscany region (ASL Toscana Centro, ASL Toscana Nord-Ovest), commissioned the Mario Negri...
Institute to undertake an educational program to improve the appropriateness of prescribing and reduce public expenditure. Biologics and biosimilars were identified as a key area for this initiative, and the following sections report a description of this initiative.

The Tuscany region already ranks among the best Italian regions in the provision of healthcare services (LEA griglie monitoraggio, 2017). Indeed, in the last few years, a strong effort has been put in place by the regional government to reform the governance of drugs and help control related expenditures (Fantini MP, 2016). Moreover, Tuscany is considered one of the first movers in the implementation of policies fostering increased biosimilar penetration (AIFA. monitoraggio consumi e spesa biosimilari). However, there is still room for improvement given increasing pressure on available resources.

6.2. Methods
The project started with a preparation phase dedicated to defining the training objectives and modalities. A working group composed of the Mario Negri researchers, with myself as a key member, and governance managers of the two health authorities, met in several online meetings to set up a training course. The aim of the training course was to promoting the appropriateness of biologic medicines and their biosimilars as part of initiatives to reduce pharmaceutical expenditure.

The group identified three clinical areas where biological and biosimilar medicines are commonly used on a number of different diseases. These areas were: rheumatology, gastroenterology and dermatology.

The training courses also sought to provide different health professionals with the knowledge regarding biosimilar medicines including the research and development path as well as the scientific and regulatory requirements underlying their marketing authorisation. The Mario Negri team gave the participants information about the context of the supply of biosimilar drugs in Italy, appropriateness and therapeutic monitoring.

I developed key metrics of prescription performance together with the governance managers of the two health authorities. These indicators were developed on the bases of prescription databases, medical exemptions (i.e., codes used to identify a group of conditions) and specialty of the prescriber.
Specifically, the indicators were aimed to measure:

- Active principle and medicinal product dosage unit for biological medicines with biosimilars (adalimumab, infliximab, etanercept, rituximab);
- Active principle and medicinal product dosage unit for biological medicines without biosimilars (tocilizumab; sarilumab, anakinra, ustekinumab, secukinumab, ixekizumab; guselkumab; vedolizumab; golimumab; certolizumab pegol; brodalumab; risankizumab; tildrakizumab);
- Active principle and medicinal product dosage unit for small molecules licensed for the target conditions (abatacept, baricitinib, tofacitinib; apremilast);
- Number of patients already treated for the disease who start a biological medicine (naïve);
- Number of patients already under biological treatment who switch (from originator to biosimilar OR from biosimilar to originator OR biosimilar to another active principle including small molecule).

These indicators were used as starting point for the course content and planned as potential monitoring indicators to assess the impact of the educational program.

4.2.1. Participants

161 health professionals working in the context of the two local health authorities were invited by the responsible of the continuing educational office (U.O.C. formazione). Although the majority of biologic medicines are prescribed by specialists and the indicators concerned mainly the biologics used in rheumatology, gastroenterology and dermatology, it was deemed important to involve also general practitioners and other healthcare professionals including hospital pharmacists. Multidisciplinary and a common understanding of complex issues are fundamental for adequate patient care and health service organisation.

4.2.2. Content and organisation

The course programme was finalized with the support of representatives of the three main clinical fields addressed by the program, i.e. rheumatology, gastroenterology and dermatology. They proposed three clinical cases to support the discussion and interactions among participants.
The course was organized in two modules of three hours each held over two days. The modules were carried out online due to the pandemic restriction. Table 5 reports the content of the two sessions and the speakers responsible for each part.

**Table 5: program of first and second day course**

<table>
<thead>
<tr>
<th>Topics 1st day</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of biological and biosimilar medicines, authorisation and regulatory aspects at both European and national levels, switch and automatic substitution.</td>
<td>Eleonora Allocati and Rita Banzi (Mario Negri)</td>
</tr>
<tr>
<td>Results presentation about the analysis of the selected indicators in regard of biological and biosimilar prescription in both ASL.</td>
<td>Pharmacist of the local health authority</td>
</tr>
<tr>
<td>Guided discussion</td>
<td>Rita Banzi and Eleonora Allocati (Mario Negri)</td>
</tr>
<tr>
<td>Clinical case presentation and discussion</td>
<td>Specialists of the Healthcare units</td>
</tr>
<tr>
<td>Conclusions ad operative indication</td>
<td>Rita Banzi and Eleonora Allocati (Mario Negri)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topics 2nd day</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frame of the problem of prescriptive appropriateness of biological and biosimilar drugs. Introduction of the therapeutic monitoring of biological and biosimilar drugs as a tool in support of prescriptive appropriateness.</td>
<td>Rita Banzi and Marco Gobbi (Mario Negri)</td>
</tr>
<tr>
<td>Interdisciplinary working group</td>
<td>Working group(s) facilitators Eleonora Allocati and Rita Banzi and local health unit representatives</td>
</tr>
<tr>
<td>Proposal presentation (oral and written) of standardized procedure, shared and integrated for the assessment of prescriptive appropriateness Plenary discussion</td>
<td></td>
</tr>
<tr>
<td>Conclusions</td>
<td>Rita Banzi Mario Negri representative</td>
</tr>
</tbody>
</table>

During the first module, after the presentation of the objectives of the course, an overview of the definitions of biologic and biosimilar drugs, their authorisation and regulatory aspects at both European and national levels, with particular reference to switch and substitution, was provided. One pharmacist, representing one of the two ASLs presented the analysis of the indicators of biological and biosimilar prescription in both ASLs. Following this, specialty physicians presented...
the three clinical cases concerning patients under biological treatment (rheumatology, gastroenterology and dermatology),

The second module discussed the issue of the appropriateness of biological and biosimilar medicines. As an example of a possible tool to support prescribing appropriateness (Chapter 5), the therapeutic monitoring of drugs and in particular of biological and biosimilar drugs, was introduced. Following this, participants were involved in group activities in three breakout sessions centered on the clinical cases presented during the first day. These three groups were firstly divided by medical specialties (rheumatology, gastroenterology and dermatology) and then other specialties and the pharmacists were added. After discussion, each working group developed a written proposal. This proposal was presented by a member of each group in a plenary session organised after the breakout sessions. In the first part of the presentation, each group described all the aspects they assumed relevant for the decision of prescribing a biological medicine both for naïve patients or patients already under biological treatment in terms of their posology, product technical information, presence/absence of specific guidelines, personal experiences, diagnostic and monitoring techniques, toxicity profile, patients characteristics, adverse events, costs, and patients opinion, and explaining their choices.

In the second part of the presentation, the healthcare professionals suggested which elements they considered important for a standardized prescribing procedure and for the evaluation of the appropriateness of prescriptions. In particular, they had to answer key information in support of the clinicians as well as the possible collaboration with hospital pharmacists and general practitioners.

6.3. Results
The education program was replicated in four sessions between September and November 2021. Thirty to 40 participants attended each complete course (Table 6). There was an interesting case-mix of medical specialisations: not only gastroenterologists, dermatologists and rheumatologists but also oncologists, internal medicine physicians and general practitioners participated. This heterogeneity may be explained by the relevance of the topic of biological and biosimilars.
### Table 6: participants for each edition

<table>
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<tbody>
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<td>Gastroenterologist</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Rheumatologists</td>
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<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Dermatologists</td>
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<td>4</td>
<td>4</td>
</tr>
<tr>
<td>General practitioners</td>
<td>8</td>
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<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Pharmacists</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Other medical specialties</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>31</strong></td>
<td><strong>32</strong></td>
<td><strong>32</strong></td>
<td><strong>40</strong></td>
</tr>
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</table>

The findings from the documents on standardized procedures, shared and integrated for the assessment of prescribing appropriateness prepared by the working groups can be qualitatively summarised as follows:

Physicians and other healthcare professionals may have some difficulties to understand the biosimilar authorisation pathway, but still understood the studies assessing the effectiveness and safety of these medicines. Indeed, the majority of the attendees were confident in prescribing biosimilars in naïve patients, with some restraint in switching to a biosimilars or switching from one biosimilar to another.

An important aspect that emerged from the discussion was the lack of comparative evidence between medicines belonging to different classes. For instance, biologics with expired patent for which biosimilars are available vs newer agents still covered by patents, as in the case of dermatology where there is a lack of comparative evidence between the anti-TNF adalimumab and the anti-IL-17 secukinumab (Sbidian E, 2020). Clinical guidelines were cited as a possible tool to support decisions but they were often considered too generic to account for the complexity of decision-making at the patient-level.

All the participants were in favour of a better integration of the experience gained by the different specialities and a more proactive interaction with general practitioners. While not directly involved in the prescribing of biological medicines – with the exception of insulins and erythropoietins -
general practitioners could play an important role in providing information regarding patients, the management of adverse events and co-medications. The majority of the physicians reported concerns about the mechanism of procurement of biological and biosimilar medicines. Purchase (procurement) deals between the local health authorities and pharmaceutical companies occur every four years and they are usually based on tenders. This determines which biosimilars will be available in the engaged hospital. Due to this, there could be the possibility that the prescribed biosimilar in the first four years of treatment cannot be prescribed in the second four years of treatment because of the absence of the drug itself. First of all, the tenders apply to all medicines that are purchased by the hospital, not only biosimilar medicines, and this purchase method is the same all over Italy. Secondly, the hospital regulators seem to favour switching biological medicines with the same active principle more than the physicians, overcoming doubts around the practice of switching. Educating the healthcare professionals on the clinical effectiveness and safety of multiple switches using recently published consolidated evidence may be get past this specific concern.

The local health authorities planned to analyse at regular times the monitoring indicators to assess the impact of the educational program. This analysis is still ongoing and the results are not available at the time of the thesis writing.

6.4. Discussion
Through this educational programme, I together with others in Mario Negri (RB and MG) provided health professionals with basic knowledge regarding biological and biosimilar medicines including the research and development paths and scientific and regulatory requirements underlying their marketing authorisation. We (EA, RB, and MG) also provided healthcare professionals with information regarding the supply of biosimilars in Italy, their appropriateness, and the importance of the therapeutic monitoring as a valid method to individualize treatment strategy and maximize efficacy, safety, and cost-effectiveness of biological drugs therapy.

Not surprisingly, the course revealed a general positive attitude on biological medicines and biosimilars. However, despite the general positive attitude on biosimilars that came up during these four editions, other relevant considerations need to be taken.

Through this course, I tried to understand in depth physician behaviour and insights regarding their adoption of biological medicines in general and biosimilars in particular, in order that we can provide
better and more specific educational initiatives on this topic in the future. Indeed, knowledge of healthcare provider’s opinions about biosimilars is important to target future interventions to improve their use.

One of the first steps toward the use of biosimilars in clinical practice should be to make sure all stakeholders, and especially physicians, are well informed on the different treatment options. For this, educational activities could represent a valid support for the implementation of biosimilars in a healthcare system.

During my visit at NHS Scotland, pharmacists and other key personnel explained how they tackled the issue of biosimilar acceptance in their context. While the uptake was slower with infliximab, the first approved biosimilar, it became faster with the newer biosimilars such as adalimumab, etanercept and rituximab. The growing body of evidence supporting the use of biosimilars, i.e., their similar effectiveness and safety as well as savings, increased their use and the number of patients whom were able to receive biologics within a fixed budget. The increase of biosimilar uptake has been made possible thanks to a strong communication and interaction between clinical pharmacists, physicians, nurses and patients. For instance the majority of patients who were switched to biosimilar did not re-switch back to the originator. Moreover, the acceptance of biosimilars was one of the main drivers of the discount of adalimumab originator (Moorkens E 2021).

An interesting approach was the communication to patients. Whenever a new biosimilar was going to enter the market, educational and training materials such as leaflets, billboards, were prepared and disseminated in the hospitals. Patients, who were intended to switch from the originator to biosimilar, were also contacted by the nurses and trained about the new biosimilar.

Both pharmacists and other key personnel discussed the resistances against the use of biosimilars administrated subdermally, especially when involving new devices. This was the case of insulin analogues that were marketed with new devices different from the ones used for the administration of the originator. The suboptimal adherence to treatment was fixed by homecare assistance on how to use new devices. The service was free of charge for the patient but paid by the hospital. The main obstacle is the sustainability of these services.
Overall, I understood that in Scotland there is a close communication between patients and pharmacists that appear much more developed than the current situation in Italy. Healthcare professionals working together to help maximise the care for patients within available budgets.
CHAPTER 7: General Discussion
With this thesis, I tackled several important issues on the use of biological and biosimilar medicines. The central theme was the appropriate use of these medicines and the assessment of tools and measures to better access and use high quality and affordable medicines. The programme adopted a multidisciplinary approach, combining regulatory and literature analyses with experimental projects and educational activities. This is a key element as medicine development, licensing, and correct use in practice are strictly related and require the integrated efforts of different stakeholders.

The analysis of the approval of biosimilars in Europe, in Chapter 3, depicts a complex but homogenous scenario. The requirement for showing similarity in terms of clinical efficacy and safety provides a robust demonstration of comparable clinical outcomes but lays a burden on biosimilar manufacturers and may delay the introduction of the drugs.

Overall, the data I retrieved from our systematic reviews, as reported in Chapter 4, highlights that switching from an originator to its biosimilars in chronic conditions as well as in type 1 diabetes mellitus and type 2 diabetes mellitus, seems not to be associated with major efficacy, safety, or immunogenicity issues. Similar conclusions can be drawn about the safety and efficacy of switching from one biosimilar to another of the same medicinal biologic medicine and multiple switches.

In line with the hypothesis of the laboratory part of my PhD research project, I demonstrated that the measurement of TNF inhibitors and ADA in the blood (proactive TDIM) can support informed decisions for a more rational management of biological therapies. The results, reported in Chapter 5, confirm that TDM is a valuable aid to improve the appropriateness and personalisation of care.

Through the educational programme for health professional in the Tuscany region (Chapter 6), I gathered information on physician attitude and behaviour, as well as insights in their clinical-decision making to adopt biological medicines in general and biosimilars in particular. The course highlighted the need for better and more specific educational initiatives on this topic and greater collaboration among health care professionals in the future. Indeed, knowledge of healthcare provider’s opinions about biosimilars is important to target future interventions to improve their use.
Figure 11: the introduction of biological medicines and their biosimilars, and to optimize their clinical use, lessons learned

This figure represents a sort of system map that describes the lessons learned through the analysis of the biosimilars’ path from their regulatory framework, their marketing authorization and introduction, to their use into the market.

The sections below together with the Figure 11, report the main lessons that can be learned from the analyses presented in this thesis.

7.1. The European regulatory framework: consistent and structured but possible changes may increase competitiveness

The robust regulatory standards for biosimilars in Europe and other countries has led to the licensing of high-quality biosimilars, equivalent to their reference products in terms of efficacy and safety. Our analysis of the current regulatory process and approval of biosimilars in Europe, highlighted that almost all biosimilars were authorised on clinical evidence demonstrating comparable efficacy and safety for biosimilars and the reference products.

Since the implementation of the legal framework for biosimilars in Europe almost two decades ago, extensive experience has been gained with the development, approval and use of increasingly complex biosimilars. The initial approach to biosimilars was cautious and conservative to protect patients’ safety.
Generally, an improved understanding of the biosimilar concept, highly similar but not identical, would help to support a possible revision of the regulatory requirements for developing and licensing of biosimilars. The comparability exercise envisages a stepwise approach possibly including analytical and animal studies, and clinical PK/PD/immunogenicity studies and, depending upon the level of similarity demonstrated, initially analytical and animal studies, and clinical PK/PD/immunogenicity studies may be performed.

Despite analytical and PK assessment are among the strongest elements applied to establish biosimilarity, the generation of clinical evidence from comparative clinical effectiveness studies may be required by regulatory agencies as the final step to establish biosimilarity (Chapter 1). In addition, given the high variability both at the product and patient level, the clinical equivalence documented in comparative effectiveness trials may be poorly informative at an individual level. The development of sensitive and reliable analytical techniques to detect differences between the biosimilar and the originator product, may offer a more adequate tool to support the appropriate use of biologics.

Comparative efficacy trials may not be needed as far as sufficient analytical data, produced through physicochemical and functional assays, and PK data allow a robust conclusion of biosimilarity. This can be done without jeopardizing the generation of evidence supporting biosimilarity, thus fulfilling the European regulatory standards. Importantly, it may instead reduce the time to biosimilars entering the market.

Earlier access to biosimilars can lead to more competition and price reductions, lowering the economic burden on healthcare systems and allowing more and more patients access to biological treatments. Savings derived from the adoption of biosimilars may be invested to cover the procurement of other innovative and effective medicines.

Moreover, an immunogenicity risk assessment that considers product- and patient-related risk factors and includes data derived from comparative PK studies may inform on the need for additional safety studies. These latter would not be necessary for medicines where the immunogenicity risk is deemed low, such as insulin analogues, and can be addressed with PK studies.

As mentioned below, measures to monitor the clinical use of these complex medicines after their licensing would be needed to generate real world evidence helpful to tailor treatment decisions.
7.2. Current evidence on switching studies and the need of new policies

The availability of a greater number of biosimilars and their role to decrease the pharmaceutical expenditure have increased the possibility to switch between the originator and its biosimilars as well as to switch among biosimilars of the same active principle. More than fifteen years of clinical experience have been gained on the switching practice while biosimilars have been available into the market. Overall, there is overwhelming evidence to sustain the efficacy and safety of switching from originators to biosimilars.

Through the systematic reviews I conducted during the PhD programme, I can confirm that switching does not affect the effectiveness and safety of treatments in chronic conditions (Chapter 4). The wealth of data that came up from our analyses, focusing on the case models of insulin analogues and anti-TNF, highlights that switching seems not to be associated with relevant differences in terms of safety, immunogenicity, and efficacy.

Unlike the amount of evidence evaluating the switching from originator to its biosimilar, the number of studies evaluating the switch among biosimilars is lower. This may depend by the absence of a real need for these studies, especially when other tools as the therapeutic drug monitoring, are available and effective. As mentioned before, once approved on the market biosimilars are expected to have the same benefit-risk profile as the originator in all disease indications, with a natural variability in response and immunogenicity that is typical of complex medicines.

On one hand, there is sufficient evidence to conclude on the robustness of the way biosimilars are developed and approved, and there should not be any doubt that biosimilars are interchangeable and the risk of immunogenicity after switching is no greater than switching between two batches of any biological medicine. On the other hand, newer approaches and technologies are made available to healthcare professionals to provide the safety of interchangeability.

In light of that, the lack of a common approach to interchangeability, including switching and substitution practices, at the European level may be among the causes of the scarce confidence in the switching practice.
As thoroughly discussed in the thesis, while the evaluation and approval of biosimilars are centralised under the responsibility of the EMA, decisions related to prescribing practices of approved medicines, including interchangeability, fall under the responsibility of the individual EU Member States. EMA has no official position and provides no recommendations on the interchangeability of biosimilars with their reference product. More doubts are created by the fact that regulatory information and guidance on interchangeability, and associated practices of switching and substitution, considerably varies across national medicines agencies in terms of availability, extent, and content.

There is a need to tackle these concerns through position papers or other joint documents at the regulatory level but also supporting healthcare professionals and patients on their appropriate use in clinical practice. In light of that, on the 19th of September 2022, the EMA in collaboration with the Heads of Medicines Agencies, has published a new statement on the scientific rationale supporting interchangeability (EMA interchangeability position). In particular, in the statement is highlighted that “once a biosimilar is approved in the EU it is interchangeable, which means the biosimilar can be used instead of its reference product (or vice versa) or one biosimilar can be replaced with another biosimilar of the same reference product”. While, the decision on which biological medicines are available for prescribing and whether automatic substitution is allowed at pharmacy level is still up to the Member States, this harmonised and clear position on interchangeability of the EMA represents the breakthrough for reducing any uncertainty that prescribers may have when deciding to prescribe biological medicines.

7.3. Therapeutic drug monitoring as a possible improvement in routine clinical practice and more

Despite the number of studies confirming the safety and efficacy biosimilars, the healthcare professionals’ and patients mistrust to a more widespread adoption, remain. Instead of building more clinical switching studies, a possible tool could be the therapeutic monitoring of biological and biosimilar drugs. The concept of TDM, is not new in pharmacology. It is applied to several medicines and is gaining popularity also for biological medicines. Through our prospective study, we proved that TDM can support informed decisions for a more rational management of biological therapies, improving the appropriateness and personalisation of care, wiping out any remaining doubt (Chapter 5).
Our main hypothesis was that the proactive measurement of TNF inhibitors and ADA in the blood (proactive TDIM) can support informed decisions for a more rational management of biological therapies. We are confident that TDM in clinical care will allow to improve the appropriateness and personalisation of care, with important advantages for the patients and the National Health Service.

Unfortunately, clinical trials on the clinical utility of TDIM for improving clinical outcomes compared with standard therapy, are few and mainly focused on anti-TNF (infliximab). The lack of full demonstration of the efficacy of TDIM may relate to a variety of factors, including study designs, the treatment phase (induction or maintenance therapy) and analytical procedures. Taking as model the NOR-DRUM A and B RCTs, further high-quality clinical trials should explore the effects of TDIM of different biologics and in different settings to fill this knowledge gaps.

The generation of robust evidence will have an impact on the revision of guidelines, which are now inconsistent regarding recommendations for TDM.

In addition to clinical trials, real-life evidence generated through the collection of prescriptions and clinical data in practice may improve clinical decision-making both at the individual patient and in general. The model here can be the Danish Registry for Biological Treatment in Rheumatology (DANBIO database) that has been designed to capture operational clinical data as part of routine clinical care. Without additional work for the clinician, it offers a clinically useful service with immediate access to well-presented longitudinal patient records, while at the same time providing a powerful research database. For patients and clinicians, registration has proved helpful rather than a hindrance (DANBIO registry). The registry formed the bases to build the first study of large-scale, non-medical switching in routine care with prospective data collection. These studies contributed with important knowledge of post-marketing effectiveness of non-medical switching (DANBIO registry; Ibfelt EH, 2016).

Focusing clinical research on TDIM and establish a clinical national and international registers has the potential to improve outcome in the individual patient, it can promote better quality of treatment in general, and data can be analysed and shared among healthcare’s, to answer important clinical research questions.
7.4. Education
The increased understanding of rational prescribing of medicines by physicians is enhanced by their greater awareness of the impact of their decisions on healthcare budgets without jeopardizing patient care. The adoption of biosimilars in clinical guidelines and guidelines on rational prescribing can create increased support for biosimilars. In addition, public and independent information and education regarding biosimilars among healthcare professionals remains essential to reduce the mistrust against biosimilar medicines thereby helping to address any misinformation regarding biosimilars among patients and the public.

7.5. Future perspectives
Concluding, with this thesis, I tried to answer to the overarching question of how to optimize the use of biological medicines and their biosimilars in the European health systems, with a focus on policy and research actions addressing medicines' development, their introduction on the market and correct use in practice. Altogether, the different strategies exploited in my project could support a clinical decision-making to achieve a more rational use of biological medicines. This would benefit both patient’s outcomes and health budgets. I highlighted the need to revise the regulatory framework to encourage earlier access to biosimilars, without lowering the evidence on biosimilars efficacy and safety. Comparative efficacy trials may not be needed as far as sufficient analytical data allowing robust conclusion of biosimilarity and fulfilling the European regulatory standards. Moreover, measures to monitor the clinical use of these complex medicines through TDIM, after their licensing represents a possible tool to generate real world evidence helpful to tailor treatment decisions. The introduction of TDIM in routine care may support decisions for a more rational prescription of biological therapies, improving the appropriateness and personalisation of care. Clinicians may be willing to support their clinical-decision making with objective data about medicine and antibodies levels, but there is a need to assess clinical utility of TDIM in clinical studies, before its broader implementation. At patient level, the increase of biosimilar uptake also rely on a strong communication and interaction between clinical pharmacists, physicians, nurses and patients. Indeed, education regarding biosimilars among healthcare professionals remains essential to reduce the mistrust against biosimilar medicines thereby helping to address any misinformation regarding biosimilars among patients and the public.
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Appendix 1 of Chapter 4 – insulins

1. Search strategies

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Embase search
28.04.20 N= 1144

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Cochrane library search
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#5 MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees

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#7 #3 OR #5

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#9 MeSH descriptor: [Diabetes Mellitus] this term only

#10 "type 1 diabetes mellitus"

#11 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees

#12 "type 2 diabetes mellitus"

#13 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees

#14 hyperglycaemia

#15 MeSH descriptor: [Hyperglycaemia] this term only

#16 "gestational diabetes"

#17 MeSH descriptor: [Diabetes, Gestational] this term only

#18 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19 "insulin glargine"

#20 "insulin detemir"

#21 "insulin degludec"

#22 "insulin long acting"

#23 MeSH descriptor: [Insulin, Long-Acting] explode all trees

#24 "insulin lispro"

#25 "insulin aspart"

#26 "insulin glulisine"

#27 "rapid acting insulin"
"short acting insulin"

MeSH descriptor: [Insulin, Short-Acting] this term only

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"isophane insulin"

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"nph insulin"

"intermediate insulin"

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"insulin analogue"

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"accession number" near EMBASE

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Appendix 2 of Chapter 4 – anti-TNFs

1. Search strategies

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Updated to 02.10.2020 N= 76
Updated to 04.02.2022 N= 189

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Updated on 06.03.2022 N= 0
Appendix 3 of Chapter 5

Figure 1a: Inter-assay reproducibility of the SPR assay.

The graphs show the results for each serum sample tested in triplicate, with ex-novo preparation of samples and calibration curves, by two separate researchers with different experience.

Figure 1b: Venn diagrams

Venn diagrams showing the numbers of patients detected by ELISA only (red), SPR only (green) or both ELISA and SPR (brown) for the different concentration ranges.