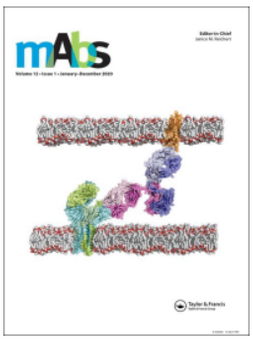

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REVIEW

Innovative approaches to biologic development on the trail of CT-P13: biosimilars, value-added medicines, and biobetters

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ABSTRACT

The biosimilar concept is now well established. Clinical data accumulated pre- and post-approval have supported biosimilar uptake, in turn stimulating competition in the biologics market and increasing patient access to biologics. Following technological advances, other innovative biologics, such as "biobetters" or "value-added medicines," are now reaching the market. These innovative biologics differ from the reference product by offering additional clinical or non-clinical benefits. We discuss these innovative biologics with reference to CT-P13, initially available as an intravenous (IV) biosimilar of reference infliximab. A subcutaneous (SC) formulation, CT-P13 SC, has now been developed. Relative to CT-P13 IV, CT-P13 SC offers clinical benefits in terms of pharmacokinetics, with comparable efficacy, safety, and immunogenicity, as well as increased convenience for patients and reduced demands on healthcare system resources. As was once the case for biosimilars, nomenclature and regulatory pathways for innovative biologics require clarification to support their uptake and ultimately benefit patients.

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Introduction

Advancing technologies have enabled further innovations in biologic development, resulting in medicines that offer benefits beyond those offered by reference biologics, or their biosimilars. However, a lack of consensus on nomenclature and regulatory approaches toward these innovative biologics threatens their successful uptake, now that increasing numbers of these medicines are reaching the market. In addition, requirements for clinical and pharmacoeconomic evaluation must also be carefully considered and met by developers, to ensure physician and patient confidence in these innovative medicines. We examine some of these issues, by drawing on experiences with biosimilars and focusing on innovative biologics such biobetters and value-added medicines (VAMs), with particular reference to the subcutaneous (SC) formulation of the infliximab biosimilar CT-P13 (CT-P13 SC).

Many biologics are available for the treatment of patients with immune-mediated inflammatory diseases (IMIDs), with SC treatment options being developed in addition to intravenous (IV) medications (Supplementary Figure 1). For the first tumor necrosis factor (TNF) inhibitor, infliximab, initial approval was gained in 1998 from the United States (US) Food and Drug Administration (FDA), for the treatment of Crohn's disease (CD).[1] Infliximab indications approved by the FDA and European Medicines Agency (EMA) now encompass rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis, CD, and ulcerative colitis (UC) in adults, as well as CD and UC in pediatric patients.[2,3]

Several biosimilars of TNF inhibitors are now available (Supplementary Table 1). CT-P13 was the first infliximab biosimilar to receive regulatory approval for all indications of the reference product (RP).[4–6] This followed the demonstration of

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Table 1. Overview of clinical trials of subcutaneous CT-P13.

	Phase I CT-P13 SC 1.5 study	Phase I CT-P13 SC 1.6 study		Phase I/III CT-P13 SC 3.5 study		Phase I CT-P13 SC 1.9 study
Study	Pilot	Part 1 (dose-finding)	Part 2 (NI test)	Part 1 (dose-finding)	Part 2 (NI test)	PK
Population	Healthy subjects	CD	UC, CD	RA		Healthy subjects
Primary endpoint	Safety	Dose-finding (up to W30)	PK (W22)	Dose-finding (up to W30)	Efficacy (W22)	PK (up to W12)
Test, reference	CT-P13 SC (PFS), CT-P13 IV	CT-P13 SC (PFS), CT-P13 IV	CT-P13 SC (PFS), CT-P13 IV	CT-P13 SC (PFS), CT-P13 IV	CT-P13 SC (PFS), CT-P13 IV	CT-P13 SC (PFS), CT-P13 SC (AI)
Study duration (total including follow-up)	8 weeks (total 12 weeks)	54 weeks (total 62 weeks)	54 weeks (total 62 weeks)	54 weeks (total 62 weeks)	54 weeks (total 62 weeks)	8 weeks (total 12 weeks)
Presentations or publications	UEGW 2017[13]	DDW 2018 (Part 1 W30);[14] ECCO 2019 (Part 1 W54)[15]	UEGW 2019 (Part 2 W30);[16] ECCO 2020 (Part 2 W54)[17]	EULAR 2018 (Part 1 W30);[18] EULAR 2019 (Part 1 W54)[19]	EULAR 2019 (Part 2 W30);[20] ACR 2019 (Part 2 W54);[21] Westhovens et al.[22]	ECCO 2019[23]

ACR, American College of Rheumatology; AI, autoinjector; CD, Crohn's disease; DDW, Digestive Disease Week®; ECCO, European Crohn's and Colitis Organisation; EULAR, European League Against Rheumatism; IV, intravenous; NI, non-inferiority; PFS, prefilled syringe; PK, pharmacokinetics; RA, rheumatoid arthritis; SC, subcutaneous; UC, ulcerative colitis; UEGW, United European Gastroenterology Week; W, Week.

equivalence to infliximab RP in terms of efficacy in the Phase III PLANETRA study,[7] and in terms of pharmacokinetics (PK) in the Phase I PLANETAS study.[8] Randomized controlled trials of CT-P13 in over 1,200 patients have provided evidence of biosimilarity and switchability consistently, while a risk management plan encompassing more than 5,000 patients has been implemented to monitor the efficacy and safety of CT-P13 data globally (Supplementary Table 2). The advent of biosimilars has facilitated substantial cost savings for health-care systems, with market competition stimulated by the reduced costs of biosimilars relative to RPs, enabling greater patient access to biologic therapy,[9] although uptake has varied globally.

While biosimilars are biologics that have no clinically meaningful differences from their RP,[10] advances in biologic development have led to innovative medicines that offer improvements for patients versus the RP. "VAMs" and "biobetters" (or "biosuperiors") are terms that have been used to describe such products, although these terms are not consistently defined or used, and definitions may overlap. The first biobetter to receive FDA approval, in 1996, was a fast-acting insulin analogue, insulin lispro, produced by altering the amino acid sequence at two positions.[11,12] Subsequently, multiple strategies, often involving molecular engineering, have been used in biobetter development, while varied approaches, including drug repositioning and reformulation, have been taken to develop VAMs. Innovation has recently been achieved for infliximab with the development of CT-P13 SC (Table 1[13–23]), with changes in both the formulation and administration route relative to the IV-administered CT-P13 (CT-P13 IV). CT-P13 SC has been approved by the EMA for the treatment of RA, AS, CD, UC, PsA, and psoriasis, and is the first SC-administered infliximab to receive regulatory approval in any territory.[4,24,25]

Defining innovative biologics

Biosimilars are biologic medicines that have an identical primary molecular structure and comparable quality characteristics and non-clinical profile to their RP, a biologic licensed by the relevant authority.[10,26] Biosimilars have no clinically meaningful differences in safety, purity, and potency from the RP, although minor differences are likely due to the complexity of biologics and differences in manufacturing processes.[10,26] Regulatory pathways for biosimilars are now well established, with 59 biosimilars currently authorized via the EMA centralized procedure (as of November 24, 2020)[27] and 28 biosimilars licensed by the US FDA (as of July 7, 2020).[28]

Due to technology advances, the development of improved versions of approved biologics, rather than biosimilars, has become possible. A biobetter is a recombinant protein drug that is in the same class as an existing biopharmaceutical and targets the same epitope but has been modified to gain specific attributes. Relevant modifications may include: a new drug delivery method or modifications to provide clinically relevant improvement(s) versus the existing biological product (such as improved efficacy, safety or tolerability, or reduced immunogenicity).[29,30] For example, the type II, glycoengineered anti-CD20 monoclonal antibody obinutuzumab is a rituximab biobetter, with a different mechanism of action compared with its type I RP.[31–33] Biobetters can also be easier to administer, or may have an improved dosing regimen (e.g., due to a longer serum half-life).[34,35]

VAMs have been defined by Medicines for Europe as "medicines based on known molecules that address healthcare needs and deliver relevant improvement for patients, healthcare professionals (HCPs) and/or payers."[36] Relevant improvements might be related to the efficacy or safety profile, administration method or ease of use, or could result from new indications or patient populations being targeted.[36] Strategies of repositioning, reformulation, or combination (with other drugs, devices, or services), collectively referred to as drug repurposing, may enable a medicine to deliver added value.[36] However, definitions and/or classifications of repositioning and reformulation vary, and not all changes will provide added value.[37] Repositioning may involve identifying a new indication for a drug that is anatomically and/or therapeutically distinct from the original indication, or a different pharmacological target in a similar indication.[37] However, "repositioning" has also been used to describe new uses in similar indications, or drugs newly launched in major (rather than emerging) pharmaceutical markets.[37] Reformulation might include changes to the release profile, pharmaceutical form, or route of

administration of a drug, or changes to excipients with no impact on PK parameters.[37] This definition excludes changes to the chemical structure of the drug itself, or development of a new product without altering the formulation (such as a change in dose), although these scenarios have also been described as "reformulation."[37] Drug repurposing generally involves off-patent molecules[38,39] but can occur for discontinued drugs or molecules that have never been commercialized.[37] VAMs are beginning to emerge in the biologic arena as medicines come off patent.[39]

Regulatory approaches to innovative biologics

The biosimilar regulatory landscape

Biosimilar regulatory pathways are now well established, supported by guidance documents issued by regulatory authorities such as the EMA (Supplementary Figure 2). Biosimilar development programs aim to establish "biosimilarity" based on a stepwise "totality of evidence" approach (Supplementary Figure 3).[10,26] Extensive, varied testing methods are used to demonstrate that physicochemical and biological attributes of the candidate biosimilar and RP are proven identical or comparable.[10,40] For example, non-clinical data supporting FDA approval of CT-P13 demonstrated that the biosimilar was highly similar to its RP.[41] In addition, non-clinical studies of CT-P13 demonstrated similarity in human tissue binding, off-target toxicity, and PK/toxicokinetic profiles to the European Union (EU)-sourced RP.[42] Clinical trials must then establish similarity of the candidate biosimilar to the RP in terms of PK and efficacy; pharmacodynamic, immunogenicity, and safety profiles must also be comparable.[10,43] FDA approval of CT-P13 followed the demonstration that CT-P13 and the EU-sourced RP were highly similar in terms of PK, immunogenicity, safety, and efficacy across studies in patients with RA and AS,[7,8] as well as the three-way comparability of PK and safety between CT-P13, EU-sourced reference infliximab, and US-sourced reference infliximab.[44] The requirements of biosimilar clinical studies contrast with those for new drug development, for which the main goal is to demonstrate clinical efficacy in each indication (Supplementary Figure 3). As such, data requirements for the approval of biosimilars and new biologics differ (Supplementary Figure 4). Following regulatory approval, a risk management plan and pharmacovigilance system (for the EMA) or a risk evaluation and mitigation strategy (for the FDA) may need to be established.[40,45] Real-world data have been accumulating for biosimilars,[46–50] supporting increased confidence in these innovative medicines and their ongoing clinical use.

During clinical development of biosimilar monoclonal antibodies, the potential impacts of anti-drug antibodies (ADAs) on PK, efficacy, and safety[51,52] mean that immunogenicity assessment is crucial.[10,53] However, the performance of immunogenicity assays poses a challenge for inter-study comparability,[54,55] with reported proportions of infliximab ADA-positive patients varying widely (0–65.3%).[56] FDA guidance notes that biosimilar efficacy studies may not be required if the results of PK/pharmacodynamic and clinical immunogenicity studies provide adequate evidence for biosimilarity.[10]

Local biosimilar regulatory guidance applies for each jurisdiction globally, although there may be similarities between regulators due to shared scientific perspectives and collaboration.[57] Regulatory approaches can vary, such as regarding requirements for submission of *in vivo* data,[58] or the use of local versions of the RP for biosimilarity assessment.[57] For example, the EMA allows RPs for clinical trials to be produced outside EU, while the FDA requires that at least one clinical PK study is conducted using the US-licensed version of the RP.[10,26] Studies evaluating a biosimilar in patients of a particular ethnicity are also required by some regulatory agencies, such as in Japan:[59] to support approval of CT-P13, bridging and extension studies were required in Japanese patients (Supplementary Table 2). Robust biosimilar development plans should include strategies to ensure alignment with the approaches of different regulatory agencies to minimize any inefficiencies or delays, including taking advantage of opportunities for discussion with the agencies.[60–62] However, proposals to further optimize regulatory pathways have been made, involving greater alignment between agencies and re-evaluation of biosimilar regulatory approval requirements.[63] One suggestion is that perhaps Phase III comparative efficacy studies should no longer be required: the decisive factor in biosimilar regulatory decisions, to date, appears to have been high similarity in terms of analytical characterization and human PK studies, rather than the outcome of efficacy trials.[63] In addition, large pre-approval clinical studies may not be needed in the future as advancing analytical technologies allow more discriminatory evidence to be collected alongside comparative PK and postmarketing monitoring.[64]

Design of biosimilar efficacy studies: establishing equivalence margins

Biosimilar efficacy trials must be carefully designed. Studies should be conducted in populations that allow the greatest sensitivity for the detection of potential differences between the candidate biosimilar and its RP.[10,43] Equivalence, rather than non-inferiority, study designs allow demonstration that the candidate biosimilar is neither inferior nor superior to its RP.[10,43] Prespecified equivalence margins must be determined, reflecting acceptable variations in efficacy with reference to existing data for the RP: this is used to determine target study population size.[65,66] Typically, equivalence margins are symmetrical and two-sided; the 95% confidence interval (CI) for the difference in the relevant endpoint between biosimilar and RP should be fully contained within the equivalence margin to support the conclusion of equivalence.

There is currently no standard method to define the prespecified equivalence margin. To support CT-P13 approval, EMA guidelines were consulted[67,68] and a systematic literature review (unpublished) was conducted to inform determination of the equivalence margin for the pivotal PLANETRA study of CT-P13 in patients with RA.[7] Treatment differences in 20% improvement in American College of Rheumatology criteria (ACR20) response rates for patients with RA (receiving concomitant methotrexate) treated with reference infliximab versus placebo ranged from 17.6% to 37.8% (Supplementary Table 3). Among other considerations, these response rates informed the 15% equivalence margin used in the PLANETRA study.[7] Subsequently, equivalence of efficacy for CT-P13 and reference infliximab was concluded: the

95% CI for the difference in ACR20 response rates at Week 30 was −6% to 10%, contained within the prespecified −15% to 15% equivalence margin.[7]

The regulatory landscape for VAMs and biobetters

No standardized guidance is available from major regulatory agencies regarding the approval pathways for innovative biologic drugs. Varied regulatory pathways have been taken to gain approval for repurposed drugs.[69] For example, obinutuzumab received a positive opinion from the EMA through the centralized procedure with an orphan medicinal product designation for untreated chronic lymphocytic leukemia (CLL),[32] while FDA approval was received via a Biologics License Application (BLA) with Breakthrough Therapy designation.[70] In addition, the SC formulation of rituximab received EU marketing authorization following extension applications for the new route of administration,[71] while FDA approval was via BLA.[72]

The EMA hybrid medicines pathway evaluates applications for "a generic medicine that is based on a reference medicine but has a different strength, a different route of administration or a slightly different indication from the reference medicine" that rely on data for both the reference and new products.[73] In the US, applications under the 505(b)(2) pathway sometimes concern changes to approved drugs (for example, changes to dosage, strength, route of administration, or formulation) where the applicant relies on information from published literature or previous FDA findings.[74] Until March 23, 2020, the 505(b)(2) pathway was also open to follow-on versions of biologics approved viaa New Drug Application – the regulatory process for biologic approval before the Biologics Price Competition and Innovation Act was adopted.[75–77] After this date, biologics differing from approved products are unlikely to be considered under the biosimilar approval pathway by the FDA and will likely require a full BLA.[75] While several recombinant protein therapeutics have been approved under the 505(b)(2) pathway in the past, some have been licensed as biosimilars in the EU,[77] which could suggest that they do not offer clinically meaningful benefits for patients compared with their respective RPs.

Future regulatory pathways might vary, depending on the regulatory agency's perspective on the biobetter and VAM concepts, and might depend on the nature of differentiation from the RP (e.g., clinical outcomes vs. patient convenience). Importantly, the clinically relevant differences between biobetters and RPs mean that indication extrapolation, as permitted for biosimilars,[10,43] does not apply.[30] However, we suggest that indication extrapolation might be appropriate for VAMs, depending on the nature of the benefit they provide. Regardless of the availability of regulatory guidance documents, discussions with leading regulatory agencies and strategic alignment with the requirements of each agency can facilitate appropriate development decisions and help to avoid delays.

Despite uncertainty and the lack of dedicated, expedited regulatory pathways, opportunities may remain for developers to streamline development of biobetters and VAMs, particularly as placebo-controlled trials are not warranted. Existing knowledge of the drug target can reduce research and development costs, while prior development of related drugs can assist biomarker selection, boosting efficiency.[78–80] In addition, safety monitoring is likely to focus on adverse events already known to be related to the established target pathway.[78] However, it is essential that sufficient, novel, head-to-head clinical data are available to support comparison between the innovative biologic and RP for determination of added value.

Innovative biologic development: CT-P13 SC case study

Non-clinical and clinical development of CT-P13 SC

Both the formulation and administration route of CT-P13 SC are altered relative to CT-P13 IV. The EMA Summary of Product Characteristics indicates that several excipients differ between CT-P13 IV and CT-P13 SC, and states that CT-P13 SC was well tolerated in rabbits at the actual concentration to be used in humans in preclinical safety evaluations.[4] Reflecting the need for extensive non-clinical characterization of innovative biologics, more than 20 physicochemical and 40 functional and biological tests (unpublished) were employed during the development of CT-P13 SC.[41]

The clinical development program for CT-P13 SC (Table 1) used CT-P13 IV as the RP. The CT-P13 SC 1.5 dose escalation study was conducted in healthy volunteers to establish the safety of CT-P13 SC; cohorts received one of the three doses, beginning with the lowest dose, with subsequent cohorts initiated based on the absence of dose-limiting toxicities.[13] Across all CT-P13 SC and CT-P13 IV cohorts, bioavailability was 60.56% (95% CI: 51.93–70.63).[81] The dose-linearity in PK profiles following a single CT-P13 SC injection[13] paved the way for clinical studies in patient populations. The Phase I CT-P13 SC 1.6 study was conducted in patients with inflammatory bowel disease (IBD): Part 1 was a dose-finding study, conducted in patients with CD,[15] and Part 2 evaluated non-inferiority in terms of PK in patients with CD or UC.[16] The Phase I/III CT-P13 SC 3.5 study, conducted in patients with RA, comprised two Parts: Part 1 was dose-finding study,[19] while Part 2 established non-inferiority of CT-P13 SC versus CT-P13 IV in terms of efficacy and evaluated a single switch from CT-P13 IV to CT-P13 SC (Supplementary Figure 5 shows the study design).[22] While the aforementioned studies administered CT-P13 SC via prefilled syringe, administration of CT-P13 SC via autoinjector was assessed as an alternative in the Phase I CT-P13 SC 1.9 study in healthy volunteers.[23]

In Part 1 of the CT-P13 SC 3.5 study, efficacy profiles were similar for CT-P13 SC and CT-P13 IV arms up to Week 54.[19] In Part 2, non-inferiority between treatments was concluded for the primary efficacy endpoint, change from baseline to Week 22 in Disease Activity Score in 28 joints (DAS28)-(C-reactive protein [CRP]), since the lower limit of the 95% CI for the estimate of treatment difference (0.27 [95% CI: 0.02–0.52]) exceeded the prespecified non-inferiority margin of −0.6.[22] In addition, ACR response rates were similar between treatment arms up to Week 22.[22] Efficacy up to Week 54 was similar between treatment arms in terms of mean DAS28 (CRP) scores, even after the CT-P13 IV group switched to CT-P13 SC at Week 30.[22] In terms of PK, mean serum concentrations consistently exceeded the threshold target–therapeutic concentration in Part 1[19] and Part 2.[22] Drug

exposure was well maintained, with trough serum concentrations higher and more constant with CT-P13 SC versus CT-P13 IV:[19,22] this high consistency in drug exposure could enhance treatment options for patients.[19] In addition, overall safety profiles were comparable between arms for both study parts.[19,22] In Part 2, the majority of localized injection site reactions, infusion-related reactions (recorded for CT-P13 IV only), and systemic injection reactions were grade 1–2 in intensity.[22]

Detecting immunogenicity provides valuable information about treatment efficacy, since development of ADAs can contribute to suboptimal drug concentrations and lack or loss of response,[50,56,82] although the impact of low levels of ADAs on drug retention needs to be confirmed.[83] It is also important to consider that different types of ADAs can have different clinical consequences: while neutralizing ADAs prevent target binding, non-neutralizing ADAs forming immune complexes may also lead to changes in clearance, as well as immune complex–mediated hypersensitivity reactions.[84] A range of methods can be used to detect ADAs, with varying sensitivities and free drug tolerances, including electrochemiluminescent (ECL) immunoassay, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, and homogeneous mobility shift assay.[85] Clinical studies for CT-P13 used a high-sensitivity ECL-based affinity capture elution assay to detect ADAs, offering improved sensitivity and drug tolerance compared with the ELISA method used in clinical studies for the RP.[85]

Immunogenicity rates for IV- and SC-administered biologics vary on a case-by-case basis: the immunogenicity rate for the IV route was higher than that for the SC route for abatacept,[86,87] while contradictory findings were observed for golimumab,[88–90] rituximab,[91–94] tocilizumab,[95,96] trastuzumab,[97,98] and vedolizumab.[99–101] The potential for increased immunogenicity with SC- versus IV-administered biologics has been suggested, due to factors including proximity to antigen-presenting Langerhans cells,[102,103] with particular concerns for infliximab ascribed to its chimeric nature.[104] For the recently approved SC infliximab, its immunogenicity appeared lower compared with its IV formulation at Week 22 in RA patients (CT-P13 SC: 50.3%; CT-P13 IV: 61.5%).[22] However, features other than administration route and biologic structure influence immunogenicity, including formulation, protein concentration, dose and administration device, patient population, genotype (as recently demonstrated for infliximab[105,106]), immunosuppressive effects of the drug, and concomitant medications.[102,107] Administration intervals, which impact drug serum concentrations, can also influence immunogenicity.[107] As well as differences between IV and SC administration, a Phase I study comparing SC and intramuscular (IM) administration of an experimental infliximab formulation identified lower immunogenicity and greater efficacy with SC versus IM administration[108] – a finding considered in the development of CT-P13 SC.

The proportion of ADA-positive patients was similar between the CT-P13 SC and CT-P13 IV arms in Part 2 of the CT-P13 SC 3.5 study (51.9% and 62.1%, respectively, at Week 30, prior to patients in the CT-P13 IV arm switching to CT-P13 SC).[22] As discussed, factors including the change in formulation and administration intervals might contribute to any such differences in immunogenicity. Alternatively, the higher pre-dose drug concentrations maintained with CT-P13 SC versus CT-P13 IV[19,22] could lead to differences in immunogenicity. Antibody responses are impacted by the antigen dose, with both very low and high doses able to induce immune tolerance (Supplementary Figure 6). In high-zone tolerance, high concentrations of a soluble protein induce long-lasting, specific immune tolerance,[109,110] while lower concentrations stimulate antibody responses, exemplified by the association between low serum infliximab levels early in treatment and subsequent detection of ADAs.[50,111,112] In the case of CT-P13, one hypothesis is that the higher trough concentrations achieved following SC administration (Figure 1[113]) remain within the high-zone tolerance range, and thereby offset the potentially more immunogenic nature of the SC route. Another possibility is that high concentrations of unbound CT-P13, achieved through frequent SC administration, might restrict the development of ADAs otherwise elicited by target–therapeutic antibody immune complexes.[109]

Regulatory approval of CT-P13 SC and future plans

CT-P13 SC recently received regulatory approval in the EU, initially for the treatment of patients with RA, sought through an expanded authorization for the new formulation as a line extension.[24,114] Subsequently, regulatory approval for CT-P13 SC has been extended to the adult indications approved for CT-P13 IV, encompassing IBD, AS, PsA, and psoriasis,[4] following marketing authorization granted by the European Commission in July 2020.[25] For regulatory approval of CT-P13 SC via an extension application,[115] additional dose-finding, dose-limiting toxicity, and device studies were conducted (Table 1), following on from the assessments supporting biosimilar approval of CT-P13 IV. When FDA approval is sought for CT-P13 SC, it is likely that new drug evaluation pathways will be followed.[24] In line with the conclusions of a review of regulatory perspectives toward biobetters,[30] discussions with the FDA indicated that a pivotal study in each requested indication would be required for CT-P13 SC approval, rather than the biosimilar regulatory pathway being followed.[24]

Pharmacoeconomic considerations for innovative biologics

Adoption of biosimilars in place of RPs has enabled healthcare systems to achieve substantial cost savings, with biosimilar price discounts relative to RPs stimulating market competition.[9] Prior to the introduction of CT-P13, budget impact analyses suggested that its uptake in six European countries could deliver net savings of €15.3 million or €20.8 million (depending on whether switching from the RP was permitted) over 3 years; these savings could be reinvested to finance the treatment of an additional 1,200–1,800 patients.[116] In practice, the United Kingdom has saved £99,400,000 by switching to infliximab biosimilars for the treatment of patients with RA and IBD during the 2017/18 financial year (Supplementary Table 4). In addition, decreases in average European list prices have improved patient access to biologics.[9] For example, following the introduction of infliximab biosimilars in Norway in 2013, the costs of infliximab

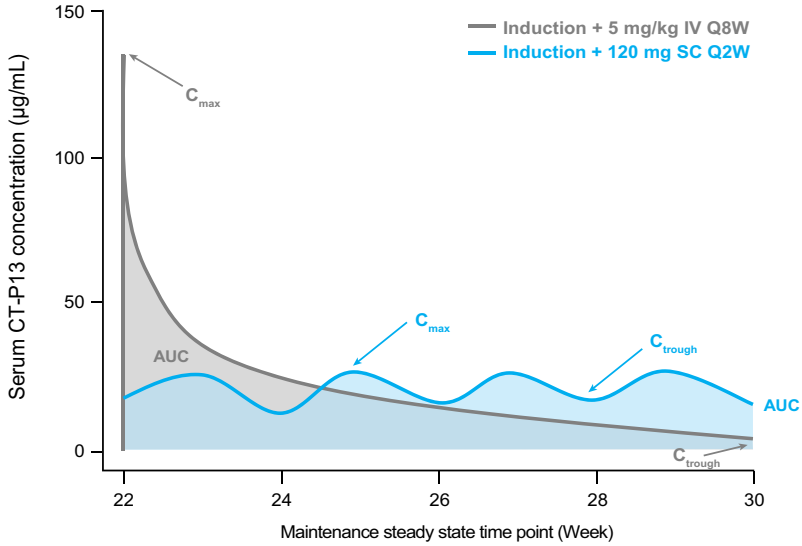

Figure 1. Generalized simulated serum concentration–time profile for CT-P13 following administration via IV or SC routes. Adapted with permission from Schreiber et al.[113] AUC, area under the concentration–time curve; C_{max}, maximum serum concentration; C_{trough}, trough serum concentration; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous.

therapy decreased by almost half, while the number of patients receiving infliximab biosimilars increased substantially (Supplementary Figure 7). However, the biosimilar landscape varies between countries, linked to differences in biosimilar policies and reimbursement systems.[117] Differences in biosimilar discount rate relative to RPs may also influence biosimilar uptake: for example, analysis of IMS data to the second quarter of 2017 showed that discount rates exceeding 50% for CT-P13 versus the infliximab RP were linked with CT-P13 market shares approaching 100% (across all indications) in Bulgaria (from 2014) and Norway (from 2015), contrasting with discount rates and market shares both below 50% in Spain and France.

Beyond the benefits of cost savings from biosimilar uptake enabling additional patients to be treated, improved cost-effectiveness may allow biologic treatment to be extended to other patient groups or earlier in the course of disease.[117] This implies that cost-effectiveness analyses conducted for RPs should be revisited following biosimilar availability.[117] Analyses should use net prices to accurately assess value;[118] however, limited access to pricing information, as well as variations between countries and treatment settings, can lead to biased cost-effectiveness estimates. In addition, national variations challenge extrapolation of analyses between countries;[117] methodologies should be appropriate for the setting, considering the resources of the healthcare system.[119] Cost savings from biosimilar uptake could also support patient access to other treatments or be reinvested in healthcare systems (such as through employing additional HCPs).[49,117] Furthermore, competition between biosimilars and RPs may encourage further innovation by developers,[117] leading to the development of biobetters or VAMs.

VAMs and biobetters may provide several benefits for healthcare systems (Supplementary Table 5). Irrational use of medicines – including poor adherence, off-label use, prescribing inefficiency, and medicine wastage – places a significant cost burden on healthcare systems.[120,121] Medicines offering increased convenience for patients might improve adherence, while drug repositioning/reformulation and packaging optimization could limit off-label use and medicine wastage, respectively.[120] Ready-to-use formulations could also reduce the medicine handling burden for HCPs.[120] Alongside benefits for patients, changes in drug administration route, such as from IV to SC, might generate cost savings for healthcare systems as in-hospital treatment time and resources are reduced.[122–125] The increased availability of treatment options offering benefits over RPs could impact price setting for other innovative medicines being launched for that indication, reducing their budget impact.[120] Furthermore, while therapeutic advantages mean that biobetters may attract a price premium, this might be offset by other factors such as reduced dosing frequency.[30]

Potential budget savings could be used to provide personalized patient care, which may lead to further cost savings. Therapeutic drug monitoring, encompassing measurement of ADAs and drug PK parameters, could be used to optimize therapy for individual patients with IMIDs.[126,127] Dashboards guiding personalized dosing could help this approach to deliver clinical benefits,[128] as recently demonstrated in patients with IBD.[129] Biomarker monitoring, such as for fecal calprotectin in patients with IBD, can also provide useful insights into disease and therapeutic status.[130] The objective information gained from these techniques could be used to inform treatment decisions, ultimately improving patient care.

Delivering the benefits of innovative biologics to patients

Potential benefits of VAMs and biobetters for patients

Innovative approaches to medicine development can deliver a multitude of benefits for patients, by addressing unmet needs and offering alternatives to existing treatments. For example, the biobetter obinutuzumab demonstrated superior efficacy

compared with rituximab in the treatment of CLL,[131,132] with efficacy also identified in rituximab-refractory patients.[133] The development of innovative medicines may also encourage investigation of their use in novel indications in which existing products are not approved. In addition, combination products could offer improved convenience and ease of medicine delivery,[38] while further benefits may be achieved by replacing RPs with biobetters or VAMs in existing combination therapies.

Reformulated medicines could allow dosing to be tailored to individual patients, alongside optimizing PK and improvements in efficacy, safety, and patient convenience and experience.[38,120] For CT-P13 SC, immunogenicity and PK have previously been discussed. In addition, the altered administration route for CT-P13 SC could offer patients increased flexibility and convenience: two factors contributing to patient preferences for SC- versus IV-administered anti-TNFs, alongside reduced hospital attendance and increased ease of use (Supplementary Table 5). The choice of autoinjector and prefilled syringe administration devices for CT-P13 SC could also increase treatment options for patients. In patients with UC receiving golimumab and patients with RA receiving methotrexate, patient satisfaction was high with autoinjector administration and ease of use was greater with autoinjector versus prefilled syringe administration,[134,135] indicating the attractiveness of this approach. SC administration also offers the benefit of being less invasive than IV administration, although pain-free administration of larger fluid volumes and minimizing injection site reactions represent challenges of the SC route (Supplementary Table 5).

In the future, availability of both CT-P13 IV and CT-P13 SC could facilitate personalization of therapy. To date, CT-P13 SC maintenance treatment has been evaluated in the context of CT-P13 IV induction treatment. This treatment strategy is reflected in the current EU prescribing information, as CT-P13 SC treatment should be initiated as maintenance therapy following induction with CT-P13 IV.[4] For ustekinumab, a pilot study recently evaluated induction therapy with the SC (rather than IV) formulation in patients with CD, establishing comparability of PK and acceptability of the approach.[136]

Supporting the uptake of innovative biologics through patient empowerment: dissemination of evidence and education

Dissemination of evidence and education is important to support the uptake of therapeutics developed through innovative approaches, with accumulating evidence positively influencing patient, HCP, and payer perceptions (Supplementary Figure 8). For biosimilars, patient understanding of the rationale for their development has been crucial to support successful biologic treatment initiation with, or switching to, biosimilars. Concerns surrounding the safety and efficacy of biosimilars had to be addressed,[137] with real-world data helping to improve physician confidence toward biosimilar use in indications approved by extrapolation, such as IBD.[138–140] In addition, nocebo effects resulting from negative patient perceptions have been observed in studies of patients with IMIDs switching from RPs to biosimilars.[141] Such nocebo effects pose a risk to biosimilar uptake, treatment adherence and potential cost savings.[141] However, strategies for minimizing the risk of patients with IMIDs experiencing nocebo effects have been widely discussed, including providing tailored educational initiatives for patients and HCPs (to address knowledge gaps and misconceptions).[139,142] Medical society position papers and recommendations can also deliver valuable guidance and advocacy for the use of biosimilars.[138,139] Furthermore, the importance of patient–HCP relationships in avoiding nocebo effects has been noted in the context of IMIDs, with positive framing, open communication, and shared decision-making often beneficial.[137,139,142] Nurses may play a particularly important role in addressing concerns for patients with IBD, for example, due to their frequent interaction with patients.[137,139,140] Similar educational approaches, targeting both patients and HCPs, may be important to support the introduction of VAMs and biobetters, as the concepts become established. For biosimilars, differences in regulatory requirements between countries were highlighted as a barrier to acceptance by healthcare systems, HCPs, and patients, and regulatory alignment is recommended.[143] This too might be an important consideration for biobetters and VAMs.

Benefits and challenges of innovative biologics: the developers' perspective

Developers must be cost competitive throughout the process of research, development, manufacturing, and distribution of innovative biologics, while maintaining product quality, sustainable supply, and proper pharmacovigilance systems. Balancing this investment, pricing and market access policies that support long-term market sustainability and healthy competition should be encouraged, as discussed for biosimilars.[144] In the context of multiple competitors, additional innovation could enable a product to be competitive in the biologics market: this in turn might determine the future success of a biologic developer.

Targeting unmet clinical needs is fundamental to successful development of biobetters and VAMs[120,145,146] – a factor shown to support price premiums in an analysis of repurposed drugs.[147] Consultation with patient groups and HCPs may help to ensure that development appropriately addresses such needs.[120] Once an unmet need has been identified, the size of the potential market must be quantified to ensure the viability of product development.[146]

Drug repositioning or reformulation could offer cost-effective and reduced-risk routes for drug development.[37] Repositioned drugs may be eligible for patent protection, if sufficient evidence is available and the novelty and inventiveness of the new use can be demonstrated,[148] while composition of matter patent protection may be available for medicines incorporating new formulations, delivery mechanisms, or combinations of active pharmaceutical ingredients.[149] Biobetters that offer advantages over RPs and any biosimilars may be patentable, and will benefit from data and market exclusivity rights.[30] Once licensed, medicines with FDA approval under the 505(b)(2) pathway could benefit from 3- or 5-year exclusivity (depending on new clinical data or chemical entities),[74] while per the EMA, an additional year of data exclusivity and/or market protection might be granted for

repositioned drugs (although for market protection, only if the new indication is registered within 8 years of initial approval).[148] In contrast, the EMA incorporates any changes in strength, pharmaceutical form, and route of administration under the "global marketing authorization" concept, meaning that data and marketing protections are determined solely by the initial authorization.[150] Regardless of patent protection for the new medicine, patents for the RP should not delay product launches for biobetters (unlike the situation for biosimilars), while increased differentiation from the RP could reduce the risk of patent litigation.[30]

In terms of pricing, biosimilars have been offered at discounts of up to 90% compared with RP list prices,[9] while biosimilar competition has exacerbated price erosion for RPs and biosimilars.[9,151,152] However, differentiation from RPs may allow biobetters to command higher prices[153] and be less susceptible to price erosion than biosimilars, subject to the assessment of added value by payers. In addition, biobetters offering significant advantages over the RP could also impact the market share for biosimilars.[12] In this way, companies with biologic–biosimilar pipelines may use biobetter development as a defense strategy.[78] For CT-P13 SC, the SC administration route provides differentiation from all IV-administered anti-TNFs, which could result in its market impact extending beyond reference and biosimilar infliximab.

For biobetters, therapeutic advantages could potentially allow increased cost-effectiveness versus RPs or biosimilars, if these are not outweighed by increased prices. When determining pricing strategies, developers should consider the price range of existing products with the same mechanism of action, while considering the clinical profile and additional value of the innovative product, as should payers (discussed below). However, undisclosed discounts for competitor products, associated with tendering, might present a barrier to such evaluation. Meta-analysis, meta-regression, and budget impact analyses could be used to help set the price range for innovative products. Importantly, developers should consider how manufacturing and formulation choices affect drug administration costs, as this impacts cost-effectiveness.[154]

Developers must also be mindful of the requirements and challenges presented by health technology assessment (HTA) procedures. Pricing and reimbursement issues have been identified as key hurdles to the development of VAMs[120] and explored in a white paper.[155] A significant challenge is ensuring that the benefits of VAMs are recognized in HTAs, and that the level of evidence required is aligned with the level of reward from HTA bodies and payers.[120] This issue is particularly relevant for VAMs benefiting patient-reported outcomes or patient preferences, in part due to HTA reliance on data from randomized controlled trials (vs. real-world data) and impact on quality-adjusted life-years, which often poorly capture these effects.[120,155] Differences in HTA approach between countries adds complexity, and some perspectives used can miss benefits for society or healthcare systems as a whole.[120,155] Pricing policies presenting challenges for developers also include positioning based on active substance alone, or a lack of flexibility in pricing over time (as additional evidence emerges) or between indications.[38,120] For drug repositioning, a lack of pricing incentives for innovation surrounding established products means that developers are substantially more likely to pursue drug repositioning early or at a mid-stage in the product life cycle, rather than after RP patent expiration.[69,148]

The poorly defined regulatory landscape for biobetters and biologic VAMs, discussed previously, also poses challenges and risks for developers. Compared with abbreviated biosimilar approval pathways, development can be more time-consuming and costly. However, drug repositioning could substantially reduce clinical development time and the risk of drug failure due to safety issues.[148] Another important consideration is that biobetters may not show clinical improvements versus the RP in all indications; linked to this is the lack of indication extrapolation possible for biobetters, while this is a possibility for biosimilars.[30] This uncertainty should be considered during development of any biobetter candidate, as differences in benefit between indications could impact the potential market for the biobetter.

Developers have a key role in supporting stakeholders to promote confidence in the uptake of innovative biologics. Proper management of supply chains to avoid product shortages will be crucial to build trust in these medicines, with the importance of reliable supply chains previously discussed for biosimilars.[156] Pharmaceutical companies must construct clinical databases to capture outcomes and long-term drug performance beyond the information required for regulatory approval, as discussed for biosimilars,[157] and in line with pharmacovigilance requirements that regulatory authorities may have.[40,45] In the biosimilar arena, evidence has been accumulating from real-world studies,[49,158] clinical study extension phases,[158] and recently, a Phase III non-inferiority study in patients with CD.[159] The extension phases of the PLANETRA and PLANETAS studies reported efficacy analyses in different patient subgroups and analysis populations, and implemented alternative statistical techniques for handling missing data.[160,161] Taken together, this evidence may have helped to alleviate concerns about indication extrapolation and switching from the RP in the case of CT-P13 treatment of IBD.[158,162] Indeed, members of the European Crohn's and Colitis Organisation had significantly greater confidence in biosimilars in 2015 than 2013, 2 years after CT-P13 became available in the EU.[162] Shifts in the positions of medical societies have also reflected the changing evidence base.[140,163] To facilitate effective communication with relevant stakeholders, developers should consider strategies such as translation into local languages or providing lay summaries of data.[139]

Conclusions

The introduction of biologic therapies led to a paradigm shift in the treatment of many IMIDs, with the subsequent availability of biosimilars facilitating reductions in treatment costs without compromising efficacy or safety. Ensuing cost savings provide opportunities to treat additional patients, to expand eligibility criteria (such as to patients earlier in the disease course), or to reinvest in the healthcare system (which could provide additional services for patients or increase capacity). Regulators formulated dedicated biosimilar review pathways, expediting their assessment, approval and availability for

patients. In light of advancing technologies and innovative approaches, biologics with differences from the RP – offering improvements for patients, including in terms of convenience and acceptability – are being produced, which could allow developers to be competitive in a crowded biosimilars market. However, these innovative biologics face obstacles, particularly related to nomenclature, regulatory pathways, and pharmacoeconomic assessment. Terms such as "VAM" and "biobetter" have been used to describe such products, although a lack of consensus on their definitions might cause confusion regarding the differences and potential benefits that an innovative biologic may offer versus the original biologic. A lack of clear guidance and alignment between regulatory agencies in terms of requirements for the approval of VAMs or biobetters poses further challenges for developers and could hinder HCP and patient confidence in these medicines. As for biosimilars, pharmacoeconomic evaluations may need to be revisited and approaches tailored to ensure that the benefits of VAMs or biobetters for patients are recognized. Timely regulatory and healthcare policy decisions would expedite achieving the benefits of innovative medicines, including cost savings for healthcare systems, to their full potential. Thus, there is a pressing need to streamline and align regulatory decision-making processes across different regions. Ultimately, collaboration between healthcare systems, HCPs, and manufacturers is key to improving patient access to innovative medicines (Supplementary Figure 9). Long-term efficacy, safety, and immunogenicity data, including evaluation of drug retention rates, will be required to support the uptake of VAMs and biobetters, as for biosimilars.

In the case of CT-P13, an SC formulation has been developed, offering a change in administration route versus CT-P13 IV and the infliximab RP. Clinical studies have demonstrated that CT-P13 SC offers benefits in terms of PK profile compared with CT-P13 IV, with higher and more stable trough serum concentrations maintained, alongside comparable efficacy and overall safety profiles. Despite the perceived increased immunogenicity of the SC administration route, the dosing schedule evaluated to date for CT-P13 SC has elicited similar immunogenicity as CT-P13 IV treatment; high-zone tolerance provides one potential explanation for these observations. Experience with CT-P13 SC evaluation by the EMA and FDA has highlighted differences in their approaches to assessing this type of innovative biologic. The FDA has perceived CT-P13 SC as a new drug, requiring pivotal clinical trials in each indication, while the EMA required a "hybrid" dataset including clinical studies additional to those needed for the biosimilar approval pathway.

The novel formulation and change in administration route of CT-P13 SC may provide potential benefits for patients in terms of PK profile and convenience versus CT-P13 IV. Given the lack of consensus surrounding the nomenclature for innovative biologics, these features mean that it could be appropriate to describe CT-P13 SC as either a biologic VAM or a biobetter. Ultimately, regardless of the terminology used, innovative biologics like CT-P13 SC should be able to deliver additional benefits for patients compared with RPs, within the resource constraints of health care systems.

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Abbreviations

ACR	American College of Rheumatology
ACR20	20% improvement in American College of Rheumatology criteria
ADA	anti-drug antibody
AI	autoinjector
AS	ankylosing spondylitis
AUC	area under the concentration–time curve
BLA	Biologics License Application
CD	Crohn's disease
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum serum concentration
CRP	C-reactive protein
C_{trough}	trough serum concentration
DAS28	Disease Activity Score in 28 joints
DDW	Digestive Disease Week®
ECCO	European Crohn's and Colitis Organisation
ECL	electrochemiluminescent
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
HCP	healthcare professional
HTA	health technology assessment
IBD	inflammatory bowel disease
IM	intramuscular
IMID	immune-mediated inflammatory disease
IV	intravenous
NI	non-inferiority
PFS	prefilled syringe
PK	pharmacokinetic(s)
Q2W	every 2 weeks
Q8W	every 8 weeks
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RP	reference product
SC	subcutaneous
TNF	tumor necrosis factor
UC	ulcerative colitis
UEGW	United European Gastroenterology Week
US	United States
VAM	value-added medicine
W	Week

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