

Subcutaneously-Administered Infliximab in the Management of Rheumatoid Arthritis: A Short Narrative Review of Current Clinical Evidence

Florenzo Iannone¹, Fabrizio Conti², Alberto Cauli³, Alberto Farina⁴, Roberto Caporali⁵

¹Rheumatology Unit, Department of Emergency and Organ Transplantation, Università Degli Studi Di Bari Aldo Moro, Bari, Italy; ²Rheumatology Unit, Department of Clinical, Internal, Anesthetic and Cardiovascular Sciences, Sapienza Università di Roma, Rome, Italy; ³Rheumatology Unit, Department of Medical Sciences and Public Health, AOU and University of Cagliari, Monserrato, Italy; ⁴Medical Affairs Department, Celltrion Healthcare Italy srl, Milan, Italy; ⁵Department of Clinical Sciences and Community Health, Research Centre for Adult and Pediatric Rheumatic Diseases, University of Milan, Milan, Italy

Correspondence: Florenzo Iannone, Rheumatology Unit, Department of Emergency and Organ Transplantation, Università Degli Studi Di Bari Aldo Moro, 11, Piazza Giulio Cesare, Bari (BA), 70124, Italy, Tel +39 080 5592775, Fax +39 080 5478802, Email florenzo.iannone@uniba.it

Abstract: The first subcutaneous (SC) formulation of infliximab CT-P13 has been authorized for the treatment of rheumatoid arthritis (RA) in Europe in 2019. Later, in 2020, approved indications were extended also to ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease (CD) and ulcerative colitis (UC). The present review provides summary of the key features of SC infliximab, with particular focus on pharmacokinetic profile, clinical development program in comparison with the intravenous (IV) formulation, and the latest evidence in the literature. We conclude that SC infliximab represents a new and promising approach in the treatment of patients with RA, offering an optimized clinical profile and a more practical option in comparison to the IV formulation. Nevertheless, SC formulation can improve the use of national health systems resources (e.g., through the time of healthcare workers not having to supervise infusions) and facilitate social distancing measures during the COVID-19 pandemic, as the patient can self-inject the medicine at home without going to the hospital. The limitations of the SC infliximab are mainly due to the limited experience of use in clinical practice and the absence of long-term drug retention data.

Keywords: rheumatoid arthritis, TNF inhibitors, infliximab, subcutaneous, intravenous, SC, IV, RA

Introduction

Rheumatoid arthritis (RA) is an immune mediated inflammatory disease affecting around 20 million people worldwide.¹ Symptoms are usually represented by joint pain, swelling and stiffness, which can lead to joint damage and irreversible disability.²⁻⁵ RA patients, compared to general population, show higher rates of disability, and frequently have a reduced work productivity, as well as health-related quality of life (HRQoL).⁶⁻⁸ The wide spread of the disease and the burden of its symptoms make RA a relevant global public health issue.

Medical treatment, including drug therapy, is a well-established option in the management of RA, having its primary goal in sustained clinical remission of patients. Low disease activity can be considered an alternative target, in particular for patients with a long duration of illness.^{9,10} European League Against Rheumatism (EULAR) recommends starting treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) early after diagnosis of RA. In case treatment target is not achieved with initial treatment with a csDMARD and poor prognostic factors are present, it is recommended to add a biologic DMARD (bDMARD) or a targeted synthetic DMARD (tsDMARDs).⁹

bDMARDs include different classes depending on their mechanism of action. Among them, tumor necrosis factor (TNF) inhibitors were the first to enter clinical practice in the late 1990s and early 2000s, but still represent an effective and widely used option to switch disease activity off and halt structural joint damage. Currently authorized TNF inhibitors for the treatment of RA include adalimumab, certolizumab pegol, etanercept, golimumab, infliximab. This class was also the first to receive approval in Europe for a biosimilar medicine: infliximab in 2013.¹¹ In the same class,

biosimilars of etanercept and adalimumab have been authorized since 2016 and 2017, respectively.^{12,13} Overall, TNF inhibitors biosimilars contributed to make the use of this class more sustainable for national health systems and broaden access to therapy: in Italy, since their introduction in clinical practice in 2015, to 2020, the overall expenditure has reduced from 648M € to 347M €, and the number of Defined Daily Doses (DDD) administered per 1000 inhabitants per day has grown from 1.0 to 1.36.^{14,15}

Until the approval of the first subcutaneous (SC) formulation of infliximab in 2019, this drug was exclusively administered by intravenous (IV) infusion – although a clinical study on a different SC formulation is reported in the literature but never entered clinical practice¹⁶ – while all other drugs in the class are only administered by SC injection. The development of an SC formulation of infliximab – administered at home and at a fixed dose – was designed to overcome on the one hand some general limitations related to IV formulations, for example the need to administer the drug in hospital, under the supervision of healthcare professionals and with the need also for the patient to spend time to receive the therapy, and on the other hand limitations related to infliximab itself, such as the need to adapt the dose and frequency of administration.

The IV formulation of CT-P13 (Remsima®, Celltrion Healthcare Co., Ltd., Incheon, Korea), an infliximab biosimilar, was authorized in European Union (EU) for the treatment RA in adult in 2013, and later in the United States in 2016.^{17,18} CT-P13 SC (Remsima® SC, Celltrion Healthcare Co., Ltd., Incheon, Korea) is currently the only SC formulation of infliximab available on the market. CT-P13 SC received EU approval for RA in 2019, and all other indications of IV infliximab, excluding pediatric indications, in 2020.^{19,20} The authorized dose of CT-P13 SC for the maintenance treatment of RA is 120 mg every 2 weeks (Q2W), after induction with two standard IV infliximab dose-loading administrations. More recently, straight initiation of SC treatment without IV loading was approved. In this case, the treatment should be started with a 120 mg SC injection every week for the first month (week 1, 2, 3, 4) and then the maintenance therapy with CT-P13 SC Q2W is started from week 6.²¹

The aim of this short narrative review is to summarize the main clinical evidence supporting the use of the SC formulation of infliximab in RA, with a discussion on strengths and limitations.

Current Clinical Evidence

Clinical Development Program of SC CT-P13

In order to obtain EMA approval and get all authorized indications in adult patients of IV infliximab as a line extension application of CT-P13, the clinical development program of CT-P13 SC was composed of two single-dose studies in healthy subjects (named CT-P13 1.5 and 1.9), one randomized controlled trial (RCT) SC vs. IV CT-P13 in RA patients (named CT-P13 3.5, NCT03147248) and one RCT SC vs. IV CT-P13 in with Crohn's disease (CD) and ulcerative colitis (UC) patients (named CT-P13 1.6, NCT02883452).

On the other side of the Atlantic Ocean, the US FDA has required the marketing authorization holder (MAH) to register the drug as an innovative medicine supported by further clinical trials. SC CT-P13 is given at a different dose, frequency, and route of administration in comparison with originator infliximab (Remicade, Janssen Biotech, Inc., Horsham, PA, USA), so CT-P13 SC could not be approved as a biosimilar. Therefore, in addition to the clinical trial program to register the medicine in the EU, most recently, in 2019 and 2020 respectively, MAH initiated two phase III placebo-controlled RCTs in CD and UC setting (NCT03945019 and NCT04205643), respectively.

Pharmacokinetic Profile

The proposed posology of 120 mg Q2W was identified on the basis of population pharmacokinetic (PK) and PK-PD modelling (PD: pharmacodynamics), with two main objectives in agreement with scientific advice from the European Medicines Agency: first, to exceed the trough serum concentration (C_{trough}) threshold equal to 1 µg/mL in RA and 5 µg/mL for the remaining indications; second, to produce a steady state AUC (area under the concentration-time curve) over 8 weeks ($AUC_{8\text{weeks,ss}}$) which could mimic as much as possible the values measured after administration of an infusion of 3 mg/kg or 5 mg/kg infliximab in RA and in the remaining indications, respectively.¹⁹ C_{trough} is generally considered an important efficacy index for infliximab

treatment.^{22–24} The maintenance of adequate concentrations over time can be considered a driver of the adjustment of the dosage and frequency of IV infliximab administration that often occurs in clinical practice.

Exploratory PK and efficacy/safety data were collected in small open-label studies CT-P13 3.5 Part 1 (RA patients; CT-P13 SC 90 mg/120 mg/180 mg Q2W) and CT-P13 1.6 Part 1 (CD patients; CT-P13 SC 120 mg/180 mg/240 mg Q2W).¹⁹ Subsequently, population PK modelling was conducted to find CT-P13 SC posology that would achieve the aforementioned PK endpoints for C_{trough} and AUC. The selected CT-P13 SC dosing regimen was then used in confirmatory studies CT-P13 3.5 Part 2 and CT-P13 1.6 Part 2.¹⁹

Single Dose Pharmacokinetics

Study CT-P13 1.5 evaluated PK of single injection of 120 mg, 180 mg and 240 mg CT-P13 SC, in comparison with a single IV infusion of 3 mg/kg and 5 mg/kg CT-P13 IV in healthy volunteers (6–10 subjects in each group). The overall mean bioavailability of CT-P13 SC in comparison with the IV formulation was 60.56%, with 90% confidence interval (CI) ranging from 51.93% to 70.63%.¹⁹

Steady State Pharmacokinetics

Part 1 (phase I) of study CT-P13 3.5 included patients with RA and aimed to identify the optimal dose to be used in part 2 (phase III) of the study.¹⁹ All patients received induction with CT-P13 IV 3 mg/kg at baseline and 2 weeks after. Overall, at week 6, 48 patients were randomized to receive IV CT-P13, 3 mg/kg every 8 weeks, or SC CT-P13 90 mg or 120 mg or 180 mg every 2 weeks. Steady state was considered to have been achieved between weeks 22 and 30, during which the primary PK measures were performed. SC cohorts $AUC_{8weeks,ss}$ was around 1.5-fold to 3.4-fold higher than the value observed in IV cohort. In all SC groups, C_{trough} values were much higher than the target C_{trough} ($>1 \mu\text{g/mL}$). Mean values of AUC, C_{trough} and maximum serum or plasma concentration (C_{max}) have been shown to be proportional to the administered dose. Similarly, part 1 (phase I) of study CT-P13 1.6, included patients with CD and aimed to identify the optimal dose to be used in part 2 (still phase I) of the study. All patients received induction with CT-P13 IV 5 mg/kg at baseline and 2 weeks after. Overall, at week 6, 44 patients were randomized to receive IV CT-P13, 5 mg/kg every 8 weeks, or SC CT-P13 120 mg or 180 mg or 240 mg every 2 weeks. In all SC groups, the C_{trough} was about 10 times higher than in IV group during the entire study, with values above $15 \mu\text{g/mL}$ and 1.1 – $1.9 \mu\text{g/mL}$, respectively. Also steady state AUC ($AUC_{8weeks,ss}$) was 1.3-fold to 2.0-fold higher in the SC groups vs. IV group.¹⁹

Effect of Weight on Predicted Exposure

The clearance and the volume of distribution of CT-P13 SC increase with increasing body weight. Therefore, considering that CT-P13 SC posology is fixed and it is not possible to optimize the dose based on body weight or other factors, the exposure to the drug for patients with high body weight is lower than for those with low weight.¹⁹

A PK model evaluated the impact of body weight by examining values of 50 to 150 kg (at 10 kg intervals) on maintenance therapy with infliximab at a dose of 120 mg sc every two weeks or 3 mg/kg IV every 8 weeks. The predicted trough concentration was 7 to 17 times higher in subjects treated with SC formulation than in IV (Figure 1).¹⁹ Similarly, infliximab exposure during steady state was evaluated compared to subjects treated with the IV formulation at the 5 mg/kg dose. Neutralizing antibodies status, known to be correlated with drug trough level and to be associated with potential treatment failure,²⁵ was assumed negative. Results reported in Figure 2 shows that CT-P13 SC $C_{trough,ss}$ was 2.6–10.6-fold higher than $C_{trough,ss}$ of IV formulation. Although a reduction of the difference was observed in heavier subjects, median concentration remained consistently $>1 \mu\text{g/mL}$.²⁰

The $AUC_{8weeks,ss}$ simulated value in the overall population was similar for SC and IV administrations (geometric mean ratio 0.97; 90% CI 0.96–0.98). AUC decreased with increased body mass and subjects treated with CT-P13 SC with high body mass showed reduced AUC.¹⁹

Clinical Trial in Rheumatoid Arthritis (3.5 Study)

Part I

Part 1 of study CT-P13 3.5 was designed as a randomized, open-label, parallel groups, multicenter, trial with the aim of evaluating PK, PD, efficacy and safety between SC and IV CT-P13 in co-administration with methotrexate (MTX) and

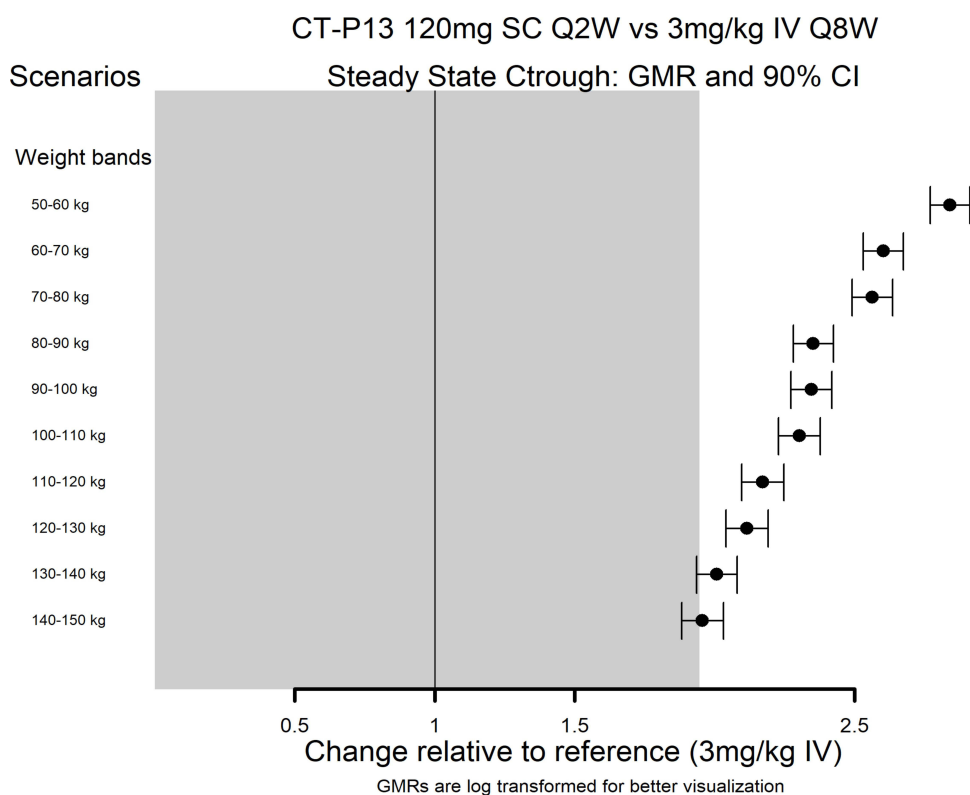


Figure 1 Simulation of blood concentrations in comparison vs. IV infliximab 3 mg/kg expressed as trough concentration, or C_{trough} , broken down by body weight bands. Summary Forest Plots of log transformed C_{trough} GMRs (90% CIs) for the Simulated CT-P13 SC 120 mg Q2W Maintenance Dosing Regimen vs. CT-P13 IV 3 mg/kg Q8W Maintenance Reference Treatment by weight bands.

Notes: CT-P13 IV 3 mg/kg Q8W is the reference treatment and CT-P13 SC 120 mg Q2W is the test treatment. Grey shaded area represents the 90% prediction interval in the reference treatment, and black points with horizontal bar represent the 90% CI. Reproduced from European Medicines Agency. Assessment report on extension(s) of marketing authorisation: remsima. Available from: https://www.ema.europa.eu/en/documents/variation-report/rem-sima-h-c-2576-x-0062-epar-assessment-report-variation_en.pdf.¹⁹

Abbreviations: CI, confidence interval; GMR, geometric mean ratio; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous.

folic acid in adult patients, with RA diagnosis according to the 2010 American College of Rheumatology (ACR)/EULAR classification criteria.¹⁹ The primary objective was to identify the most suitable dose of CT-P13 SC to be used later in part 2 of the study. To do that, the steady state AUC was measured between Week 22 and Week 30. All patients underwent the loading phase which involved administering two IV infusions of CT-P13 at weeks 0 and 2. At weeks 6, patients were randomized to receive SC or IV formulation of CT-P13. The subsequent maintenance phase involved administering additional doses of the drug assigned during randomization for up to one year (54 weeks). In particular, IV group received 7 IV infusions starting from week 6, every 8 weeks, at a dose of 3 mg/kg. 3 different SC groups (90 mg, 120 mg, 180 mg) received SC injections starting at week 6, every two weeks.¹⁹

Forty-eight patients were randomized in a 1: 1: 1: 1 ratio to 4 cohorts. Mean drug concentration levels before the following administration remained consistent from Week 14 onwards suggesting the achievement of the steady state. The steady state AUC normalized to 8-week time period between Week 22 and 30 ($AUC_{8weeks,ss}$) of SC groups was about 1.5–3.4 times higher than in IV group. Mean C_{trough} levels were considerably higher than the target concentration of 1 $\mu\text{g/mL}$ in every SC group (IV group 1: 0.80 ± 1.63 ; SC group 90 mg: 8.62 ± 6.83 ; SC group 120 mg: 13.64 ± 5.27 ; SC group 180 mg: 24.89 ± 8.58 $\mu\text{g/mL}$). Efficacy results, in terms of DAS28 (CRP) score reduction from baseline and relative number of patients achieving ACR clinical response, and safety profile were similar between IV and SC cohorts up to 54 weeks.¹⁹

According to PK and efficacy results, the dosing regimen of 120 mg SC administered every two weeks was selected for adoption in the following part 2 of the study.

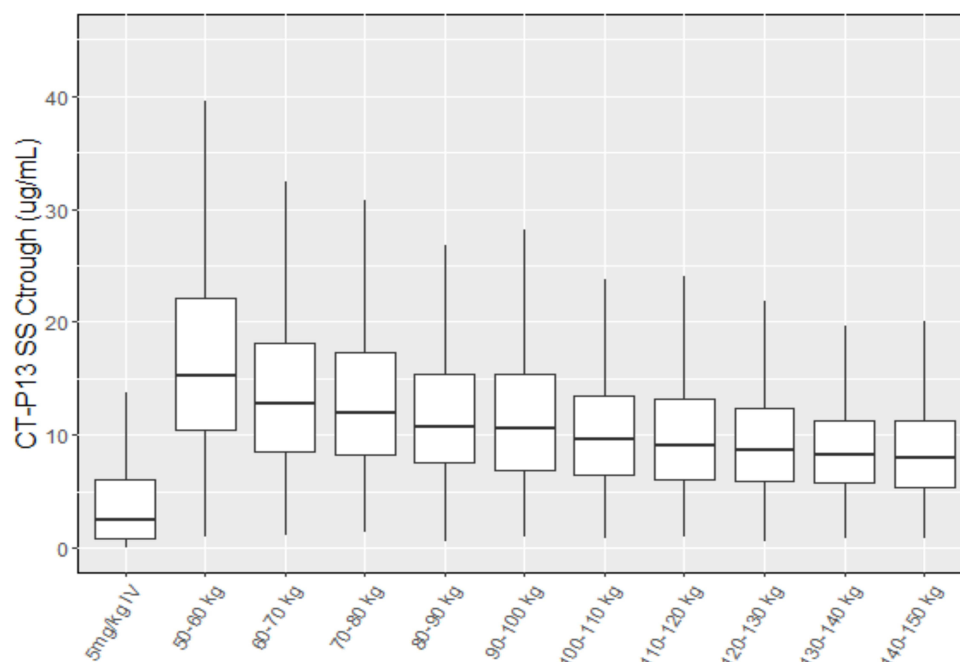


Figure 2 Simulation of blood concentrations in comparison vs. IV infliximab 5 mg/kg expressed as trough concentration, or C_{trough} , broken down by body weight bands. Boxplot of $C_{trough,ss}$ Obtained Following 120 mg Q2W SC and 5 mg/kg Q8W IV Maintenance Dosing Regimens for NAB- subjects.

Note: Reproduced from European Medicines Agency. Assessment report on extension(s) of marketing authorisation: remsima. Available from: https://www.ema.europa.eu/en/documents/variation-report/rem-sima-h-c-2576-ii-0082-epar-assessment-report-variation_en.pdf.²⁰

Abbreviations: $C_{trough,ss}$, trough serum concentration at steady state; IV, intravenous infusion; SC, subcutaneous injection; Q2W, every two weeks; Q8W, every eight weeks; NAB, negative neutralizing antibody; Simulation B, based on population PK model with (anti-drug antibodies) ADA titer and NAB status.

Part 2

Part 2 of CT-P13 3.5 study is a pivotal randomized, active-controlled, double-dummy, parallel groups trial,²⁶ with the aim to demonstrate therapeutic non-inferiority of the SC formulation of CT-P13, compared to the IV one, in terms of clinical efficacy in adult patients with active RA, diagnosed according to the 2010 ACR/EULAR classification criteria. Patients received MTX and folic acid during all study. Subjects with a history of treatment with any bDMARDs for RA and/or any TNF inhibitors for any other diseases were excluded. Study design is shown in Figure 3. The primary endpoint of non-inferiority was calculated at week

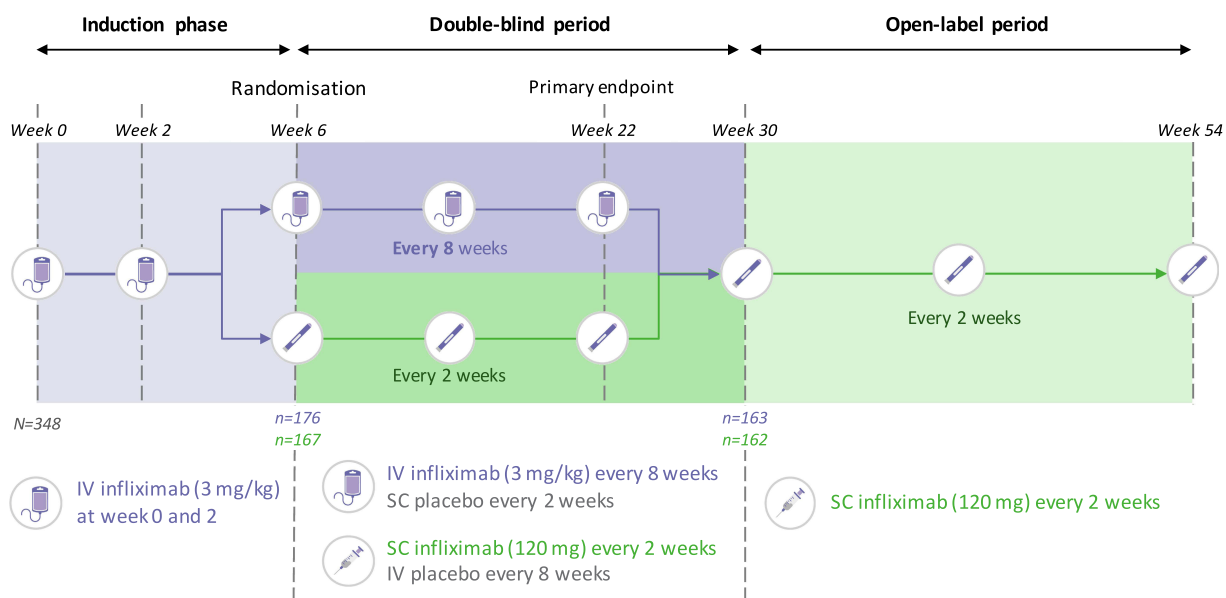


Figure 3 Design of part 2 of study CT-P13 3.5, a randomized, active-controlled, double-dummy, parallel groups, non-inferiority trial. The primary endpoint was measured during the double-blind and double-dummy phase at week 22, after which all patients switched to open-label SC formulation.

22 and corresponded to the mean reduction of DAS28 (CRP) score from baseline, with a predetermined margin of non-inferiority of 0.6 points. All patients underwent the loading phase with the administration of two IV infusions of CT-P13 at weeks 0 and 2. At week 6, according to the double-dummy design, patients were randomized to receive CT-P13 SC 120mg (and IV placebo) or 3mg/kg CT-P13 IV (and SC placebo). The study reverted to open at week 30 including administration of the only SC formulation and continued through week 54. Among the 357 subjects entered in the loading phase, 343 were randomized to SC (n=167) or IV (n=176) CT-P13 at week 6. DAS28-CRP at week 22 was 2.21 (0.22) in the CTP-13 SC arm and 1.94 (0.21) in CT-P13 IV, with a difference between the 2 arms of 0.27 (95%CI:0.02, 0.52). Thus, the primary endpoint of non-inferiority was met as the lower bound of the 95% CI was higher than the pre-specified non-inferiority margin of -0.6, also satisfying a margin of statistical superiority, since the same bound was above 0 (Figure 4). However, this may represent a modest superiority from a clinical point of view. Secondary efficacy measures, including mean change from baseline in DAS28 individual component, DAS28-CRP, DAS28-ESR, ACR response (individual component, ACR20, ACR50, ACR70 and hybrid ACR score), EULAR response rate, Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI), suggested slightly improved efficacy of CTP13 SC vs. IV at week 30. A similar trend in efficacy outcomes was observed in the two groups after switching to open-label SC formulation at week 30 through week 54. The study found no relevant differences in the safety profile between the two study groups, and a lower proportion of patients developing anti-drug antibodies (ADAs) and neutralizing antibody (Nabs) in the SC group.²⁶

Comparison vs. Adalimumab and Etanercept and vs. IV Infliximab

A systematic review and meta-analysis compared the efficacy and the safety of CT-P13 SC with IV infliximab, adalimumab, and etanercept, including their biosimilars, in moderate-to-severe RA patients.²⁷ The study included 13 parallel-group RCTs, published from January 2009 to August 2019 and 5400 subjects overall. Because of the modest number of recently published RCTs of adalimumab and etanercept in RA it was not possible to analyze the two interventions separately, which therefore have been analyzed together. Golimumab and certolizumab were not included due their low relative use in RA. The comparison vs. IV infliximab showed higher (with non-overlapping 95% CIs) efficacy rates in favor of CT-P13 SC at week 30 and 54 for most outcomes, including mean DAS28-CRP score reduction from baseline; DAS28-CRP remission rates; mean DAS28-ESR score change from baseline; DAS28-ESR remission rate at 54 weeks; proportion of patients achieving responses according to ACR20, ACR50, ACR70; proportion of patients achieving a EULAR-CRP good response; mean CDAI score change from baseline; CDAI remission rate at 54 weeks;

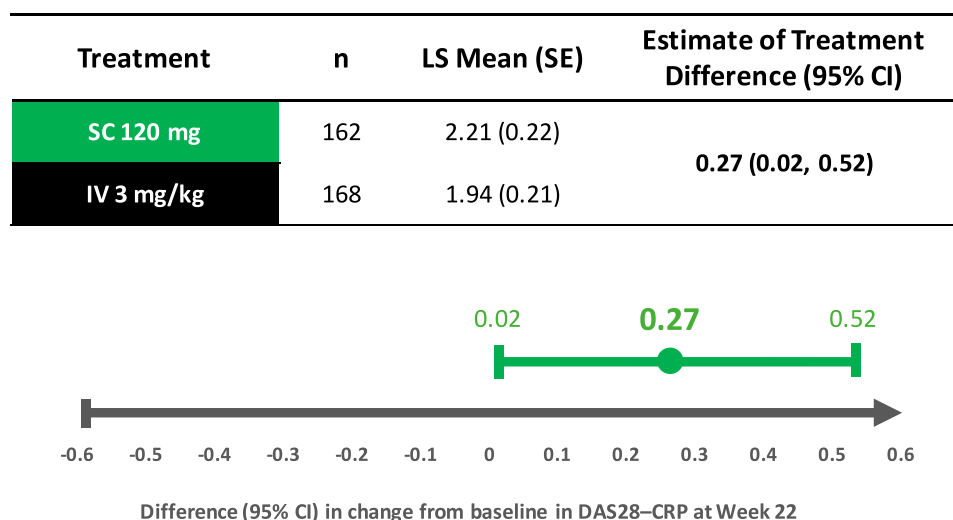


Figure 4 Primary endpoint results of part 2 of study CT-P13 3.5, analysis of change from baseline of DAS28 (CRP) at Week 22 (ANCOVA).

Notes: The treatment difference at Week 22 was estimated as 0.27 with corresponding lower limit of 95% CI of 0.02, which was greater than the pre-specified NI margin (-0.6) indicating NI of CT-P13 SC compared to CT-P13 IV. The estimate of treatment difference also reached the statistical superiority criterion (difference > 0). Country, Week 2 serum CRP concentration (≤ 0.6 mg/dL versus > 0.6 mg/dL) and Week 6 body weight (≤ 100 kg versus > 100 kg) were considered as covariates.

Abbreviations: CI, confidence interval; LS, least squares; SE, standard error.

mean SDAI score change from baseline; SDAI remission rate; Boolean clinical remission rate; ACR/EULAR remission rate. The comparison vs. adalimumab/etanercept showed higher (with non-overlapping 95% CIs) efficacy rate for CT-P13 SC vs. adalimumab/etanercept at 54 weeks for most outcomes: mean DAS28-CRP and DAS28-ESR change from baseline; proportion of patients achieving ACR50 and ACR70 responses; mean CDAI score change from baseline; mean SDAI score change from baseline; Boolean clinical remission rate.²⁷

Comparison vs. Reference IV Infliximab

Since the clinical development program of CT-P13 SC was conducted in head-to-head comparison vs. CT-P13 IV, there is lack of direct comparison vs. reference IV infliximab. A network meta-regression used individual patient data from two pivotal trials in patients with RA to fill this gap: the above-mentioned CT-P13 3.5 study (CT-P13 SC vs. CT-P13 IV), and CT-P13 3.1 study (CT-P13 IV vs. reference infliximab IV).²⁸ This meta-regression compared CT-P13 SC with: CT-P13 IV, reference infliximab IV, pooled data including both reference infliximab and CT-P13 IV. 3.1 and 3.5 studies had CT-P13 IV intervention or reference arm, respectively, therefore it was possible to indirectly compare CT-P13 SC with originator infliximab IV or with pooled data for originator infliximab IV and CT-P13 IV. Overall, 840 and 751 patients were evaluated at week 30 and 54, respectively. The results for all comparisons showed statistically significant differences in reduction from baseline in DAS28-CRP, CDAI, SDAI scores at 30 and 54 weeks in favor of CT-P13 SC. From week 30 to 54, the difference between SC and pooled IV group increased and remained statistically significant for changes in DAS28-CRP, CDAI and SDAI at week 54. The probability of achieving a good response according to EULAR-CRP and low disease activity according to DAS28-CRP, CDAI and SDAI were more than two times higher for CT-P13 SC compared with all IV treatment groups.²⁸

Discussion

The SC formulation of infliximab CT-P13 represents a promising approach in the treatment of RA, with an efficacy/safety/immunogenicity profile similar or even improved compared to the IV formulation of infliximab. In particular, the PK profile is more stable and the minimum pre-administration concentrations (C_{trough}) are higher in patients treated with SC in comparison to those treated with IV formulation, and we hypothesize that this potentially allows to avoid resorting to frequent dosage adjustments, in terms of dose per kg or frequency of dosing, which often occurs in normal clinical practice with IV infliximab. According to these characteristics, SC infliximab satisfies the definition of “biobetter” medicine:

Biobetter is a modified version of a specific approved biologic that enhances clinical outcomes (e.g., improved efficacy) and/or drug pharmacology. (e.g., pharmacokinetics and/or pharmacodynamics).²⁹

The SC administration may potentially offer convenience for the healthcare system, optimizing the organizational impact due to the preparation and administration of the IV infusion, allowing resources to be used more efficiently, and reducing direct costs associated with the infusion, which in Italy were quantified at around 156 euros for a standard infusion of 2 hours.³⁰

For patients and their caregivers, SC administration can offer benefits over their daily activities by reducing the frequency of days spent in the hospital to receive infusions. Indeed, the total median time including travel, administration and monitoring to receive an infliximab infusion was estimated at 6.5 hours. On the other hand, we believe that IV administration of infliximab cannot be totally replaced by SC, as a proportion of patients may require surveillance by healthcare professionals in hospital due to poor compliance, clinical reasons, or by preference.

Furthermore, in the current scenario of the COVID-19 pandemic, the availability of a new SC formulation allows to implement social distancing measures and potentially avoid some hospital admissions.

In RA, the TNF inhibitors class represents the most established treatment option, with infliximab being the first drug to be approved in Europe, and still used as first line therapy.³¹ Among TNF inhibitors, adalimumab and etanercept generally represent the most frequently used bDMARDs, due to their clinical profile, availability of SC formulation, and more recently thanks to the introduction of biosimilars, which has allowed a significant reduction in cost of therapy.

In this context, the SC formulation of infliximab may represent a new option, with a potentially better efficacy and safety profile than that of adalimumab and etanercept, as recently reported by a systematic review and meta-analysis by Caporali et al.²⁷ As previously discussed, an advantage for CT-P13 SC over adalimumab/etanercept was observed for

most of clinical endpoints analyzed, including the proportion of patients achieving DAS28 remission (CRP/ESR criteria), EULAR good response (CRP/ESR criteria), ACR20, CDAI remission; CDAI LDA, SDAI remission, any SAE, and discontinuation due to AEs. However, these results should be interpreted with caution, as results from other meta-analyses indicate a substantially similar efficacy profile of the different TNF inhibitors in the treatment of RA.³²

On the other hand, the SC formulation of infliximab has some limitations which we believe to be due mainly to the still limited experience of use in clinical practice. Especially, switch data from IV infliximab administered at doses \geq 5 mg/kg or frequency less than 8 weeks are still absent. This represents a limitation for clinical decision making, although the PK profile of infliximab SC seems reassuring, since the maintenance of stable and high plasma concentrations over time. Further limitations are linked to the absence of real-life data, especially on the long-term adherence and retention to the treatment. While, in the short term, two recent experiences from UK in patients affected with CD or UC have provided encouraging evidence on the feasibility of switching from patients currently in maintenance with IV infliximab, with almost all patients (around 98%) continuing treatment 3 months after the switch, with 3 months C_{trough} often higher than before switching, and with remarkable satisfaction towards the SC formulation.^{33,34}

Conclusions

Our brief review of current clinical evidence suggests a promising role of SC infliximab in the management of RA. SC versus IV administration of infliximab results in an optimized pharmacokinetic profile, as seen by more stable blood concentrations and higher C_{trough} . The SC formulation represents a new option in the treatment of RA, offering a similar or improved efficacy, safety and immunogenicity profile in comparison to the IV formulation, and results from a systematic review and meta-analysis indicate efficacy and safety advantages over adalimumab/etanercept. The limitations of the SC formulation are mainly due to the still limited experience of use in clinical practice, therefore further real-life studies are needed to further clarify its place in treatment strategies.

Disclosure

AF is an employee of Celltrion Healthcare Italy srl. Professor Fabrizio Conti reports personal fees from Lilly, personal fees from BMS, personal fees from Galapagos, personal fees from AbbVie, personal fees from Pfizer, outside the submitted work. Professor Roberto Caporali reports personal fees from pfizer, personal fees from AbbVie, personal fees from amgen, personal fees from celltrion, personal fees from BMS, personal fees from Lilly, personal fees from MSD, personal fees from Fresenius-Kabi, personal fees from Galapagos, during the conduct of the study. The other authors report no conflicts of interest in this work.

References

1. Safiri S, Kolahi AA, Hoy D, et al. Global, regional and national burden of rheumatoid arthritis 1990–2017: a systematic analysis of the global burden of disease study 2017. *Ann Rheum Dis*. 2019;78(11):1463–1471. doi:10.1136/annrheumdis-2019-215920
2. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. *Nat Rev Dis Primers*. 2018;4:18002.
3. Centers for Disease Control and Prevention. Rheumatoid Arthritis (RA). [cited 2021, January 29]. Available from: <https://www.cdc.gov/arthritis/basics/rheumatoid-arthritis.html>. Accessed May 4, 2022.
4. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388(10055):2023–2038. doi:10.1016/S0140-6736(16)30173-8
5. Sparks JA. Rheumatoid arthritis. *Ann Intern Med*. 2019;170(1):ITC1–ITC16. doi:10.7326/AITC201901010
6. Sokka T, Krishnan E, Häkkinen A, et al. Functional disability in rheumatoid arthritis patients compared with a community population in Finland. *Arthritis Rheum*. 2003;48(1):59–63. doi:10.1002/art.10731
7. West E, Jonsson SW. Health-related quality of life in rheumatoid arthritis in Northern Sweden: a comparison between patients with early RA, patients with medium-term disease and controls, using SF-36. *Clin Rheumatol*. 2005;24(2):117–122. doi:10.1007/s10067-004-0976-6
8. Puolakka K, Kautiainen H, Mottonen T, et al. Predictors of productivity loss in early rheumatoid arthritis: a 5 year follow up study. *Ann Rheum Dis*. 2005;64:130–133. doi:10.1136/ard.2003.019034
9. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79:685–699. doi:10.1136/annrheumdis-2019-216655
10. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis*. 2016;75(1):3–15. doi:10.1136/annrheumdis-2015-207524
11. European public assessment report Remsima. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/remsim>. Accessed August 27, 2021.
12. European public assessment report Benepali. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/benepali>. Accessed August 27, 2021.

13. European public assessment report Amgevita. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/amgevita>. Accessed August 27, 2021.
14. Italian Medicines Agency (AIFA). The use of drugs in Italy National Report, Year 2015 (OSMED report). Available from: <https://www.aifa.gov.it/uso-dei-farmaci-in-italia>. Accessed August 27, 2021.
15. Italian Medicines Agency (AIFA). The use of drugs in Italy National Report, Year 2020 (OSMED report). Available from: <https://www.aifa.gov.it/uso-dei-farmaci-in-italia>. Accessed August 27, 2021.
16. Westhovens R, Houssiau F, Joly J, et al. A phase I study assessing the safety, clinical response, and pharmacokinetics of an experimental infliximab formulation for subcutaneous or intramuscular administration in patients with rheumatoid arthritis. *J Rheumatol*. 2006;33:847–853.
17. European Medicines Agency. Remsima summary of product characteristics. [cited 2021 January 29]. Available from: https://www.ema.europa.eu/en/documents/product-information/rem-sima-epar-product-information_en.pdf. Accessed May 4, 2022.
18. US Food and Drug Administration. Highlights of prescribing information, inflectra (infliximab-dyyb). [cited 2021 January 29]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125544s0081bl.pdf. Accessed May 4, 2022.
19. European Medicines Agency. Assessment report on extension(s) of marketing authorisation: remsima. Available from: https://www.ema.europa.eu/en/documents/variation-report/rem-sima-h-c-2576-x-0062-epar-assessment-report-variation_en.pdf. Accessed August 30, 2021.
20. European Medicines Agency. Assessment report on extension(s) of marketing authorisation: remsima. Available from: https://www.ema.europa.eu/en/documents/variation-report/rem-sima-h-c-2576-ii-0082-epar-assessment-report-variation_en.pdf. Accessed August 30, 2021.
21. Remsima Product Information. 30/04/2021 Remsima - EMEA/H/C/002576 - II/0095. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/rem-sima>. Accessed August 30, 2021.
22. Takeuchi T, Miyasaka N, Inoue K, et al. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. *Mod Rheumatol*. 2009;19(5):478–487. doi:10.3109/s10165-009-0195-8
23. Mulleman D, Lin, DCM, et al. Trough infliximab concentrations predict efficacy and sustained control of disease activity in rheumatoid arthritis. *Ther Drug Monit*. 2010;32(2):232–236. doi:10.1097/FTD.0b013e3181cc6fef
24. Wolbink GJ, Voskuyl AE, Lems WF, et al. Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2005;64(5):704–707. doi:10.1136/ard.2004.030452
25. Perdriger A. Infliximab in the treatment of rheumatoid arthritis. *Biologics*. 2009;3:183–191. doi:10.2147/btt.2009.3099
26. Westhovens R, Wiland P, Zawadzki M, et al. Efficacy, pharmacokinetics and safety of subcutaneous versus intravenous CT-P13 in rheumatoid arthritis: a randomized phase I/III trial. *Rheumatology*. 2021;60(5):2277–2287. doi:10.1093/rheumatology/keaa580
27. Caporali R, Allanore Y, Alten R, et al. Efficacy and safety of subcutaneous infliximab versus Adalimumab, etanercept and intravenous infliximab in patients with rheumatoid arthritis: a systematic literature review and meta-analysis. *Expert Rev Clin Immunol*. 2021;17(1):85–99. doi:10.1080/1744666X.2020.1858803
28. Combe B, Allanore Y, Alten R, et al. Comparative efficacy of subcutaneous (CT-P13) and intravenous infliximab in adult patients with rheumatoid arthritis: a network meta-regression of individual patient data from two randomised trials. *Arthritis Res Ther*. 2021;23(1):119. doi:10.1186/s13075-021-02487-x
29. D'Amico F, Solitano V, Aletaha D, et al. Biobetters in patients with immune-mediated inflammatory disorders: an international Delphi consensus. *Autoimmun Rev*. 2021;20(7):102849. doi:10.1016/j.autrev.2021.102849
30. Mazzuoli S, Tricarico D, Demma F, et al. Accelerated infliximab infusion: safety, factors predicting adverse events, patients' satisfaction and cost analysis. a cohort study in IBD patients. *PLoS One*. 2016;11(11):e0166443. doi:10.1371/journal.pone.0166443
31. Sánchez-Piedra C, Sueiro-Delgado D, García-González J, et al. Changes in the use patterns of bDMARDs in patients with rheumatic diseases over the past 13 years. *Sci Rep*. 2021;11(1):15051. doi:10.1038/s41598-021-94504-x
32. Graudal N, Kaas-Hansen BS, Guski L, et al. Different original and biosimilar tnf inhibitors similarly reduce joint destruction in rheumatoid arthritis—a network meta-analysis of 36 randomized controlled trials. *Int J Mol Sci*. 2019;20(18):4350. doi:10.3390/ijms20184350
33. Verma AM, Patel A, Subramanian S, et al. From intravenous to subcutaneous infliximab in patients with inflammatory bowel disease: a pandemic-driven initiative. *Lancet Gastroenterol Hepatol*. 2021;6(2):88–89. doi:10.1016/S2468-1253(20)30392-7
34. McGoran J, Wilson A, McErlain S, et al. Initiation of subcutaneous infliximab (Remsima) therapy for the treatment of inflammatory bowel disease during the COVID-19 pandemic. *Frontline Gastroenterol*. 2021;13(1):89–90. doi:10.1136/flgastro-2020-101760