

**Remsima (infliximab biosimilar) for  
subcutaneous injection for managing Crohn's  
disease and ulcerative colitis**

**Evidence review**

Publication date February 2021

This evidence review sets out the best available evidence on Remsima, (infliximab biosimilar) for subcutaneous injection for managing Crohn's disease and ulcerative colitis. It should be read in conjunction with the [evidence summary](#), which gives the likely place in therapy and factors for decision making.

Commissioned by NHS England.

## **Disclaimer**

The content of this evidence review was up to date in February 2021. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [Medicines and Healthcare products Regulatory Agency](#) (MHRA) or [NICE](#) websites for up-to-date information.

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## Contents

Background .....	4
Product overview .....	4
Mode of action .....	4
Regulatory status .....	5
Dosing information .....	6
Objective .....	7
Review questions .....	7
Summary of included studies .....	7
Effectiveness and safety .....	7
Person-centred factors .....	10
Limitations of the evidence .....	11
Resource implications .....	12
References .....	12
Development of the evidence review .....	12
Process .....	12
Expert advisers .....	12
Terms used in this evidence review .....	13
Appendices .....	15
Appendix A: PICO table .....	15
Appendix B: Summary of included studies .....	16
Appendix C: Results tables .....	18
Appendix D: Literature search strategy .....	20

## Background

This evidence review considers Remsima, a biosimilar of infliximab, for subcutaneous injection (Celltrion Healthcare Hungary). Remsima (subcutaneous) received a marketing authorisation for managing rheumatoid arthritis in December 2019 and received a license extension for Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriasis in July 2020. This evidence review focuses on the license extension for Crohn's disease and ulcerative colitis only.

NICE has produced an [evidence summary on remsima \(subcutaneous\) for managing rheumatoid arthritis](#).

Infliximab is recommended as an option for treating moderately to severely active ulcerative colitis (see [NICE's technology appraisal guidance on infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy](#)) and severe active Crohn's disease (see [NICE's guideline on Crohn's disease: management](#)) in adults whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy, including steroids and immunosuppressive therapies.

Remsima (subcutaneous) is licensed in adults only. Remsima (subcutaneous) should be given as a planned course of treatment until treatment failure, or until 12 months after the start of treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the person, and their carer if appropriate.

No other infliximab products are licensed in the UK for subcutaneous administration for managing Crohn's disease and ulcerative colitis.

## Product overview

### Mode of action

Infliximab is a monoclonal antibody that inhibits the activity of tumour necrosis factor (TNF)-alpha, a pro-inflammatory mediator. It is referred to as a TNF-alpha inhibitor.

Infliximab treatment of Crohn's disease has also been associated with a reduction in C-reactive protein, an inflammatory biomarker.

Remsima for subcutaneous injection is a biosimilar of infliximab (see the [summary of product characteristics \[SPC\] for Remsima](#)). As a biosimilar medicine, Remsima is highly similar to another biological medicine (the 'reference medicine') that is licensed for use in Crohn's disease and ulcerative colitis. The reference medicine for Remsima is Remicade (infliximab).

The active substance of a biosimilar and its reference medicine is the same biological substance but, just like the reference medicine, the biosimilar has a degree of natural variability. Approved biosimilar medicines have proven that this variability and any differences between the biosimilar and its reference medicine do not affect safety or effectiveness. Further information is available in the [European Medicines Agency's \(EMA's\) overview of biosimilar medicines](#) and [NHS England's information on biosimilar medicines](#).

## **Regulatory status**

Remsima (subcutaneous) (Celltrion Healthcare Hungary) has a marketing authorisation for:

- Treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- Treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).
- Treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies.

For the full list of licensed indications see the [SPC for Remsima \(subcutaneous\)](#).

## **Dosing information**

Remsima (subcutaneous) is available as a solution for injection in a prefilled syringe and a prefilled pen formulation. Each 1 ml single dose prefilled syringe and prefilled pen contains 120 mg infliximab.

### **People currently on maintenance infliximab (intravenous) treatment**

When switching from maintenance intravenous infliximab treatment to subcutaneous infliximab, the subcutaneous formulation may be administered 8 weeks after the last administration of the intravenous infusions of infliximab (which is given every 8 weeks). The [SPC for Remsima \(subcutaneous\)](#) states that there is insufficient information regarding switching people with Crohn's disease having intravenous infusions of infliximab higher than 5 mg/kg every 8 weeks to Remsima (subcutaneous).

### **People with moderately to severely active Crohn's disease being started on infliximab**

Treatment with Remsima (subcutaneous) should be started as maintenance therapy 4 weeks after the last administration of 2 intravenous infusions of infliximab 5 mg/kg given 2 weeks apart.

The recommended dose for Remsima (subcutaneous) is 120 mg once every 2 weeks. If a patient with moderately to severely active Crohn's disease does not respond after 2 doses of intravenous infusions of infliximab, no additional treatment with infliximab should be given.

### **People with ulcerative colitis being started on infliximab**

Treatment with Remsima (subcutaneous) should be started as maintenance therapy 4 weeks after the last administration of 2 intravenous infusions of infliximab 5 mg/kg given 2 weeks apart.

The recommended dose for Remsima (subcutaneous) is 120 mg once every 2 weeks.

Follow the [SPC for Remsima \(subcutaneous\)](#) for all dosing information including dosing for people with fistulising active Crohn's disease.

## Objective

This evidence review aims to review the best available evidence on the effectiveness and safety of infliximab biosimilar Remsima (subcutaneous) compared with intravenous infliximab in people with Crohn's disease or ulcerative colitis.

## Review questions

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see [appendix A](#) for more information). The review questions for this evidence review are:

1. What is the effectiveness of the infliximab biosimilar Remsima (subcutaneous) compared with intravenous infliximab in adults with Crohn's disease or ulcerative colitis?
2. What is the safety of the infliximab biosimilar Remsima (subcutaneous) compared with intravenous infliximab in adults with Crohn's disease or ulcerative colitis?

## Summary of included studies

A literature search for infliximab biosimilar Remsima (subcutaneous) identified 177 references (see [appendix D](#) for full details). These references were screened using their titles and abstracts and 0 full text references were obtained and assessed for relevance.

One study, an open-label phase 1 randomised controlled trial, was identified from a license extension variation to the [European Public Assessment Report \(EPAR\) for Remsima](#) and is included in the evidence review.

A summary of the included study is shown in [appendix B](#).

## Effectiveness and safety

Full details of the results are in [appendix C](#).

The efficacy and safety of Remsima (subcutaneous) compared with Remsima (intravenous) in people with Crohn's disease and ulcerative colitis was assessed in

an unpublished open-label randomised, phase 1 trial (n=131). All participants received 2 doses of Remsima intravenously at weeks 0 and 2 before randomisation. Participants were then randomised. Participants were then randomised to either Remsima (intravenous) or Remsima (subcutaneous).

Remsima (subcutaneous) was given at week 6 and then every 2 weeks up to week 54 (people who weighed under 80 kg received 120 mg and people who were 80 kg or more received 240 mg). The licensed dose of Remsima (subcutaneous) is 120 mg every 2 weeks.

Remsima (intravenous) was given at weeks 6, 14 and 22 and then switched to Remsima (subcutaneous) at week 30, where it was given once every 2 weeks up to week 54.

Where possible, week 30 data are reported because this was when Remsima (subcutaneous) and Remsima (intravenous) were directly compared.

**Review question 1: What is the effectiveness of subcutaneous infliximab biosimilar Remsima (subcutaneous) compared with intravenous infliximab in adults with Crohn's disease or ulcerative colitis?**

**Reduction in disease severity and symptoms**

These results are taken from CT-P13 1.6 Part 2 in the [EPAR](#).

In people with active Crohn's disease, the efficacy of Remsima (subcutaneous) at week 30 appeared to be comparable to Remsima (intravenous) in terms of clinical remission (CDAI score of under 150 points) and clinical response (Crohn's disease activity index [CDAI]-70 response and CDAI-100 response):

- clinical remission (60.7% [17/28] and 56.0% [14/25] respectively)
- clinical response, CDAI-70 (67.9% [19/28] and 68.0% [17/25] respectively)
- clinical response, CDAI-100 (67.9% [19/28] and 64.0% [16/25] respectively).

No statistical analyses were reported.

Endoscopic remission (Simplified Endoscopic Activity Score for Crohn's Disease [SES-CD] score less than or equal to 2) was determined in a subgroup of



participants at week 22 who had colonoscopy. The proportion of people in endoscopic remission at week 22 was higher in the Remsima (subcutaneous) group than in the Remsima (intravenous) group (35.7% [5/14] and 14.3% [1/7] respectively). No statistical analysis reported.

In people with active ulcerative colitis, the efficacy of Remsima (subcutaneous) was generally comparable to Remsima (intravenous) in terms of clinical remission (total Mayo score), clinical response (total and partial Mayo score) and mucosal healing:

- clinical remission, total Mayo score, week 22 (44.7% [17/38] and 25.6% [10/39] respectively)
- clinical response, total Mayo score at week 22 (63.2% [24/38] and 43.6% [17/39] respectively)
- clinical response, partial Mayo score at week 30 (86.8% [33/38] and 74.4% [29/39] respectively)
- clinical remission, partial Mayo score at week 30 (68.4% [26/38] and 53.8% [21/39] respectively)
- mucosal healing at week 22 (47.4% [18/38] and 30.8% [12/39] respectively).

No statistical analyses were reported.

### **Time to loss of response**

No evidence was identified that investigated time to loss of response.

### **Review question 2: What is the safety of the infliximab biosimilar Remsima (subcutaneous) compared with intravenous infliximab in adults with Crohn's disease or ulcerative colitis?**

The safety profile of intravenous infliximab is well established. This section focuses on the safety of Remsima (subcutaneous) compared with Remsima (intravenous), not the safety of infliximab overall.

Between week 6 and week 30, treatment related localised injection site reactions were more frequent in the subcutaneous group (10/66, 15.2%) than in the intravenous group (1/65, 1.5%). This is possibly why there were more treatment-related adverse events overall in the subcutaneous group (22/66, 33.3%) than in the

intravenous group (15/65, 23.1%). During the entire maintenance phase, between week 6 and 54, the most frequently reported signs and symptoms of localised injection site reactions in all participants were injection site erythema. The majority of the participants recovered without any treatments. No serious localised injection site reactions were reported.

Between week 6 and week 30, the number of people who discontinued treatment because of a treatment related adverse event was 0/66 (0.0%) in the subcutaneous group compared with 3/65 (4.6%) in the intravenous group.

The EPAR concluded that the safety data for Remsima (subcutaneous) was considered adequate and supported the proposed extension of the license.

## **Person-centred factors**

Infliximab is usually given by intravenous infusion in a hospital setting, which poses potential logistical problems such as travel, time, expense, time off work and childcare. All of these could be a barrier to the uptake of intravenous infliximab or its ongoing use. Some homecare providers offer intravenous infliximab, but expert advisers have suggested that the uptake of this option is low.

The [NICE COVID-19 rapid guideline on gastrointestinal and liver conditions treated with drugs affecting the immune response](#) recommends that people should continue with existing courses of treatment to minimise the risk of a flare-up. But it also recommends thinking about whether any changes are needed to minimise face-to-face contact during the COVID-19 pandemic, including route of administration.

Remsima (subcutaneous) allows patients, or their family members or carers, to administer the treatment themselves at home if they have received training. However, injection site reactions and dexterity problems may reduce uptake and adherence may be a problem once treatment is initiated. The frequency of dosing is higher with Remsima (subcutaneous), which is administered every 2 weeks compared with Remsima (intravenous), which is every 8 weeks.

## Limitations of the evidence

The data in the license extension variation to the [European public assessment report \(EPAR\) for Remsima](#) have some limitations. Firstly, they come from a study that has not yet been published in a peer-reviewed journal. Secondly, the study was small, and the primary outcome was pharmacokinetic. Therefore, the study was not powered to detect differences in the secondary efficacy and safety outcomes. No comparative statistical analyses were conducted for the clinical effectiveness outcomes.

Another limitation of this study is that people weighing 80 kg or more received 240 mg of Remsima (subcutaneous) and people under 80 kg on 120 mg could have their dose increased to 240 mg. This differs from the licensed dose for the subcutaneous formulation, which is 120 mg for all weights without dose escalation. Therefore these findings may not be generalisable to all people receiving the licensed dose of 120 mg.

The study was open label and as such subject to potential bias. Some components of the outcome scores used are subjective, therefore are subject to bias in an open-label trial in which clinician and patient outcome reporting could be influenced by the treatment received.

Another limitation was that Remsima (subcutaneous) was only compared with Remsima (intravenous) and not with other biosimilars or Remicade, the infliximab intravenous reference product. However, the EPAR states that there is no regulatory requirement to repeat the demonstration of biosimilarity against the reference product once the marketing authorisation has been granted.

Colonoscopy was not performed on all participants. Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) was only assessed in people who had confirmed mucosal abnormalities at their previous assessment. Therefore only improvements are likely to be seen and any disease progression in people without abnormalities at previous assessment could be missed. The EPAR stated that, on request, the company provided convincing evidence that this approach did not produce skewed results but this evidence was not included in the EPAR.

Another limitation is that there are currently no data on the efficacy or safety of switching from intravenous to subcutaneous infliximab in people who are already established on intravenous infliximab, because all participants in the study were biologic-naive. There are also no long-term outcomes comparing Remsima (subcutaneous) with Remsima (intravenous) after 30 weeks. Although, participants in the study were followed-up for 54 weeks, participants in the Remsima (intravenous) group were switched to Remsima (subcutaneous) at week 30.

## Resource implications

The cost of prescribing Remsima (subcutaneous) for managing ulcerative colitis and Crohn's disease will vary by locality. Therefore it is not possible to show the overall resource impact.

A resource impact tool allows localities to use their own figures. See the [resource impact assessment](#) accompanying this evidence review for more information.

## References

No references

## Development of the evidence review

### Process

The [evidence summary: process guide](#) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

## Expert advisers

### Details of expert advisers and any declarations of interest

Name, job title/organisation	DOI
Dr Charmian Banks, Gastroenterologist & General Physician, Royal Surrey County Hospital NHS Trust	No direct interests
Dr Rachel Cooney, Consultant Physician & Gastroenterologist, University Hospitals Birmingham NHS Foundation Trust	Janssen IBD account manager development day Janssen advisory board

Name, job title/organisation	DOI
Dr Charles Murray, Consultant Gastroenterologist, Royal Free London NHS Foundation Trust and University College London Hospitals Foundation Trust	Private medical practice Joint venture investment HCA London Digestive Centre Speaking honoraria for Shire, Tillotts, MSD, Abbvie, Janssen and Biogen

## Terms used in this evidence review

### Biosimilar

A biosimilar medicine is a biological medicine that has been shown not to have any clinically meaningful differences from the originator medicine in terms of quality, safety and efficacy. Where NICE has already recommended the originator biological medicine, the same guidance will normally apply to a biosimilar of that originator.

### Clinical remission (Crohn's disease)

Clinical remission in Crohn's disease was defined as an absolute Crohn's disease activity index (CDAI) score of under 150 points.

### Clinical remission (ulcerative colitis)

A total Mayo score of 2 points or less with no individual subscore exceeding 1 point, or partial Mayo score of 1 point or less and mucosal healing (defined as absolute endoscopic subscore of 0 or 1 from Mayo Scoring System).

### Clinical response (Crohn's disease)

CDAI-70 response defined as a decrease in CDAI by at least 70 points and CDAI-100 response defined as a decrease of at least 100 points from baseline.

### Clinical response (ulcerative colitis)

A decrease from baseline in total Mayo score of at least 3 points and at least 30% from baseline or a decrease from baseline in partial Mayo score of at least 2 points, with an accompanying decrease from baseline in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1.

### Endoscopic response

A decrease in 50% or more of overall Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) score from the baseline value and endoscopic remission defined as an absolute SES-CD score of 2 points or less.

# Appendices

## Appendix A: PICO table

### PICO table

Criteria	Details
P – Population and indication	Adults with moderate to severe Crohn’s disease or fistulising active Crohn’s disease who have not responded to conventional therapy or who are intolerant or have contraindications to such therapies. Adults with moderate to severe ulcerative colitis who have not responded to conventional therapy or who are intolerant or have contraindications to such therapies.
I – Intervention	Infliximab biosimilar Remsima (subcutaneous)
C – Comparator(s)	Intravenous infliximab
O – Outcomes	Reduction in disease severity Reduction in symptoms of Crohn’s disease or ulcerative colitis Time to loss of response Adverse effects Immunogenicity
Inclusion criteria	-
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials
Language	English
Patients	Human studies only
Age	Adults 18 years and over
Date limits	None
Exclusion criteria	-
Publication type	Pre-prints before peer review, letters, conference abstracts or studies that have not been published in full
Study design	Non-comparative and observational studies

## Appendix B: Summary of included study

### Summary of included study

Study	Number of participants	Population	Intervention	Comparison	Outcomes
CT-P13 1.6 Part 2 Open label phase 1 randomised controlled trial results taken from the <a href="#">EPAR</a>	n=131 (Crohn's disease n=53, ulcerative colitis n=78 [54 weeks])	Adults aged 18 to 75 years inclusive, with active Crohn's disease or ulcerative colitis of at least 3 months' duration <b>Active Crohn's disease:</b> <ul style="list-style-type: none"> <li>• CDAI score 220 to 450 points</li> <li>• unresponsive to, intolerant to, or had medical contraindications for corticosteroids and/or an immunosuppressant</li> <li>• at least one of: C-reactive protein concentration over 0.5 mg/dl, fecal calprotectin over 100 micrograms/g, SES-CD of at least 6 points for ileal-colonic Crohn's disease or at least 4 points including ulcer score from at least 1 segment for ileal or colonic Crohn's disease</li> </ul> <b>Active ulcerative colitis:</b> <ul style="list-style-type: none"> <li>• total Mayo score 6 to 12 points with endoscopic subscore of at least 2 at screening</li> <li>• unresponsive to, intolerant, or contraindications for conventional therapies</li> </ul> <b>Baseline disease activity:</b> Baseline CDAI scores 296.4 and 294.8 and total Mayo scores 7.9 and 8.3 in the	Remsima (subcutaneous) (n=66) All participants had Remsima (intravenous) at weeks 0 and 2, before randomisation Subcutaneous 120 mg or 240 mg (dose based on body weight) at week 6 and then every 2 weeks up to week 54. Participants weighing less than 80kg were given 120 mg and participants weighing 80 kg or more were given 240 mg (in total 29% of study population weighed 80 kg or more at week 6).	Remsima (intravenous) (n=65) All participants had Remsima (intravenous) at weeks 0 and 2, before randomisation Intravenous 5 mg/kg: further 3 doses at week 6, 14 and 22 Switched to Remsima (subcutaneous) at week 30 with dose based on body weight (same weight based dosage as intervention group). Given every 2 weeks up to week 54	Adverse events <b>Crohn's disease</b> <ul style="list-style-type: none"> <li>• clinical remission</li> <li>• CDAI-70 response</li> <li>• CDAI-100 response</li> <li>• endoscopic response</li> <li>• endoscopic remission</li> </ul> <b>Ulcerative colitis</b> <ul style="list-style-type: none"> <li>• clinical remission</li> <li>• clinical response</li> <li>• mucosal healing</li> </ul>



Study	Number of participants	Population	Intervention	Comparison	Outcomes
		subcutaneous and intravenous groups respectively.			

Abbreviations: CDAI, Crohn's disease activity index; SES-CD, Simplified Endoscopic Activity Score for Crohn's disease

## Appendix C: Results tables

### Results table for CT-P13 1.6 Part 2

Results taken from European Public Assessment Report. CT-P13 was a non-inferiority study with a pharmacokinetic primary outcome so all the efficacy and safety outcomes below were secondary outcomes.

Outcome	Intervention Remsima (subcutaneous)	Comparator Remsima (intravenous)	Analysis
<b>Efficacy outcomes</b>	<b>n=66</b>	<b>n=64</b>	-
<b>Crohn's disease</b>	<b>n=28</b>	<b>n=25</b>	-
Clinical remission, CDAI under 150 (week 30)	17/28 (60.7%; 40.6% to 78.5%)	14/25 (56.0%; 95% CI 34.9% to 75.6%)	No analysis
CDAI-70 response (week 30)	19/28 (67.9%; 95% CI 47.7% to 84.1%)	17/25 (68.0%; 95% CI 46.5% to 85.1%)	No analysis
CDAI-100 response (week 30)	19/28 (67.9%; 95% CI 47.7% to 84.1%)	16/25 (64.0%; 42.5% to 82.0%)	No analysis
Change from baseline SES-CD (mean [SD], week 22)	n=15 -8.9 (7.59); 95% CI -13.07 to -4.67	n=7 -4.4 (4.76); 95% CI -8.83 to -0.03	No analysis
Endoscopic remission, SES-CD (week 22)	5/14 (35.7%; 95% CI 12.8% to 64.9%)	1/7 (14.3%; 95% CI 0.4% to 57.9%)	No analysis
<b>Ulcerative colitis</b>	<b>n=38</b>	<b>n=39</b>	-
Clinical response, total Mayo score (week 22)	24/38 (63.2%; 95% CI 46.0% to 78.2%)	17/39 (43.6%; 95% CI 27.8% to 60.4%)	No analysis
Clinical response, partial Mayo score (week 30)	33/38 (86.8%; 95% CI 71.9% to 95.6%)	29/39 (74.4%; 95% CI 57.9% to 87.0%)	No analysis
Clinical remission, total Mayo score (week 22)	17/38 (44.7%; 95% CI 28.6% to 61.7%)	10/39 (25.6%; 95% CI 13.0% to 42.1%)	No analysis
Clinical remission, partial Mayo score (week 30)	26/38 (68.4%; 95% CI 51.4% to 82.5%)	21/39 (53.8%; 95% CI 37.2% to 69.9%)	No analysis
Mucosal healing (week 22)	18/38 (47.4%; 95% CI 31.0% to 64.2%)	12/39 (30.8%; 95% CI 17.0% to 47.6%)	No analysis
<b>Safety outcomes</b>	<b>n=66</b>	<b>n=65</b>	-
People with at least 1 treatment related adverse event (week 6 to week 30)	22/66 (33.3%)	15/65 (23.1%)	No analysis
People with at least 1 treatment related serious adverse event (week 6 to week 30)	0/66 (0.0%)	1/65 (1.5%)	No analysis
Localised treatment related injection site reactions (week 6 to week 30)	10/66 (15.2%)	1/65 (1.5%)	No analysis
Treatment related infusion reactions,	1/66 (1.5%)	2/65 (3.1%)	No analysis

<b>Outcome</b>	<b>Intervention Remsima (subcutaneous)</b>	<b>Comparator Remsima (intravenous)</b>	<b>Analysis</b>
systemic injection reaction, or delayed hypersensitivity (week 6 to week 30)			
Treatment related adverse events leading to treatment discontinuation (week 6 to week 30)	0/66 (0.0%)	3/65 (4.6%)	No analysis

Abbreviations: CDAI, Crohn's disease activity index; CI, confidence interval; SD, standard deviation; SES-CD, Simplified Endoscopic Activity Score for Crohn's disease

Clinical remission in Crohn's disease was defined as an absolute Crohn's disease activity index (CDAI) score of under 150 points.

Clinical remission in ulcerative colitis was defined as a total Mayo score of 2 points or less with no individual subscore exceeding 1 point, or partial Mayo score of 1 point or less and mucosal healing (defined as absolute endoscopic subscore of 0 or 1 from Mayo Scoring System).

CDAI-70 response defined as a decrease in CDAI by at least 70 points and CDAI-100 response defined as a decrease of at least 100 points from baseline.

Clinical response in ulcerative colitis was defined as a decrease from baseline in total Mayo score of at least 3 points and at least 30% from baseline or a decrease from baseline in partial Mayo score of at least 2 points, with an accompanying decrease from baseline in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1.

Endoscopic remission defined as an absolute Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) of 2 points or less.

Mucosal healing was assessed by endoscopic subscore of the Mayo Scoring System (MSS), which evaluated the degree of endoscopic rectal inflammation based on a 4-point scale according to flexible proctosigmoidoscopy findings.

## Appendix D: Literature search strategy

### Database search strategies

#### **Database: Medline**

Platform: Ovid

Version: Ovid MEDLINE(R) <1946 to November 05, 2020>

Search date: 06/11/2020

Number of results retrieved: 105

Search strategy:

- 
- 1 (Crohn\* adj1 disease).ti,ab. (39954)
  - 2 Crohn Disease/ (39213)
  - 3 "ulcerative colitis".ti,ab. (34223)
  - 4 Colitis, Ulcerative/ (34824)
  - 5 Proctocolitis/ (812)
  - 6 proctocolitis.ti,ab. (387)
  - 7 Colorectitis.ti,ab. (9)
  - 8 Inflammatory bowel diseases/ (22957)
  - 9 (Inflammatory bowel disease\* or Inflammatory bowel disorder\* or IBD).ti,ab. (44115)
  - 10 or/1-9 (102067)
  - 11 (subcutaneous or sc).ti,ab. (177464)
  - 12 Injections, Subcutaneous/ (32856)
  - 13 11 or 12 (194381)
  - 14 Infliximab/ (10363)
  - 15 infliximab\*.ti,ab. (10442)
  - 16 14 or 15 (13093)
  - 17 Biosimilar Pharmaceuticals/ (2113)
  - 18 biosimilar\*.ti,ab. (2612)
  - 19 17 or 18 (2833)
  - 20 16 and 19 (454)
  - 21 13 and 20 (4)
  - 22 (remsima or CT-P13 or CTP13 or inflectra).ti,ab. (208)
  - 23 21 or 22 (211)
  - 24 10 and 23 (122)
  - 25 limit 24 to english language (119)
  - 26 limit 25 to (letter or historical article or comment or editorial or news or case reports) (14)
  - 27 25 not 26 (105)

#### **Database: Medline in-process**

Platform: Ovid

Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to November 05, 2020>

Search date: 06/11/2020

Number of results retrieved: 33

Search strategy:

- 
- 1 (Crohn\* adj1 disease).ti,ab. (5012)

- 2 Crohn Disease/ (0)
- 3 "ulcerative colitis".ti,ab. (4260)
- 4 Colitis, Ulcerative/ (0)
- 5 Proctocolitis/ (0)
- 6 proctocolitis.ti,ab. (44)
- 7 Colorectitis.ti,ab. (1)
- 8 Inflammatory bowel diseases/ (0)
- 9 (Inflammatory bowel disease\* or Inflammatory bowel disorder\* or IBD).ti,ab. (7367)
- 10 or/1-9 (12191)
- 11 (subcutaneous or sc).ti,ab. (21211)
- 12 Injections, Subcutaneous/ (0)
- 13 11 or 12 (21211)
- 14 Infliximab/ (0)
- 15 infliximab\*.ti,ab. (1563)
- 16 14 or 15 (1563)
- 17 Biosimilar Pharmaceuticals/ (0)
- 18 biosimilar\*.ti,ab. (791)
- 19 17 or 18 (791)
- 20 16 and 19 (123)
- 21 13 and 20 (4)
- 22 (remsima or CT-P13 or CTP13 or inflectra).ti,ab. (49)
- 23 21 or 22 (52)
- 24 10 and 23 (35)
- 25 limit 24 to english language (35)
- 26 limit 25 to (letter or historical article or comment or editorial or news or case reports) (2)
- 27 25 not 26 (33)

**Database: Medline epub ahead of print**

Platform: Ovid

Version: Ovid MEDLINE(R) Epub Ahead of Print <November 05, 2020>

Search date: 06/11/2020

Number of results retrieved: 7

Search strategy:

- 
- 1 (Crohn\* adj1 disease).ti,ab. (785)
  - 2 Crohn Disease/ (0)
  - 3 "ulcerative colitis".ti,ab. (669)
  - 4 Colitis, Ulcerative/ (0)
  - 5 Proctocolitis/ (0)
  - 6 proctocolitis.ti,ab. (5)
  - 7 Colorectitis.ti,ab. (0)
  - 8 Inflammatory bowel diseases/ (0)
  - 9 (Inflammatory bowel disease\* or Inflammatory bowel disorder\* or IBD).ti,ab. (1272)
  - 10 or/1-9 (1984)
  - 11 (subcutaneous or sc).ti,ab. (2493)
  - 12 Injections, Subcutaneous/ (0)
  - 13 11 or 12 (2493)

- 14 Infliximab/ (0)
- 15 infliximab\*.ti,ab. (297)
- 16 14 or 15 (297)
- 17 Biosimilar Pharmaceuticals/ (0)
- 18 biosimilar\*.ti,ab. (161)
- 19 17 or 18 (161)
- 20 16 and 19 (36)
- 21 13 and 20 (2)
- 22 (remsima or CT-P13 or CTP13 or inflectra).ti,ab. (9)
- 23 21 or 22 (10)
- 24 10 and 23 (7)
- 25 limit 24 to english language (7)
- 26 limit 25 to (letter or historical article or comment or editorial or news or case reports) (0)
- 27 25 not 26 (7)

**Database: Medline daily update**

Platform: Ovid

Version: Ovid MEDLINE(R) Daily Update <November 05, 2020>

Search date: 06/11/2020

Number of results retrieved: 0

Search strategy

- 
- 1 (Crohn\* adj1 disease).ti,ab. (33)
  - 2 Crohn Disease/ (30)
  - 3 "ulcerative colitis".ti,ab. (27)
  - 4 Colitis, Ulcerative/ (23)
  - 5 Proctocolitis/ (0)
  - 6 proctocolitis.ti,ab. (0)
  - 7 Colorectitis.ti,ab. (0)
  - 8 Inflammatory bowel diseases/ (49)
  - 9 (Inflammatory bowel disease\* or Inflammatory bowel disorder\* or IBD).ti,ab. (70)
  - 10 or/1-9 (112)
  - 11 (subcutaneous or sc).ti,ab. (113)
  - 12 Injections, Subcutaneous/ (12)
  - 13 11 or 12 (121)
  - 14 Infliximab/ (10)
  - 15 infliximab\*.ti,ab. (10)
  - 16 14 or 15 (12)
  - 17 Biosimilar Pharmaceuticals/ (5)
  - 18 biosimilar\*.ti,ab. (7)
  - 19 17 or 18 (7)
  - 20 16 and 19 (1)
  - 21 13 and 20 (0)
  - 22 (remsima or CT-P13 or CTP13 or inflectra).ti,ab. (0)
  - 23 21 or 22 (0)
  - 24 10 and 23 (0)
  - 25 limit 24 to english language (0)
  - 26 limit 25 to (letter or historical article or comment or editorial or news or case reports) (0)

27 25 not 26 (0)

**Database: Embase**

Platform: Ovid

Version: Embase <1974 to 2020 Week 44>

Search date: 06/11/2020

Number of results retrieved: 147

Search strategy:

- 
- 1 (Crohn\* adj1 disease).ti,ab. (76605)
  - 2 Crohn disease/ (90963)
  - 3 "ulcerative colitis".ti,ab. (61889)
  - 4 ulcerative colitis/ (74179)
  - 5 proctocolitis/ (903)
  - 6 proctocolitis.ti,ab. (620)
  - 7 coloproctitis.ti,ab. (3)
  - 8 inflammatory bowel disease/ (34701)
  - 9 (Inflammatory bowel disease\* or Inflammatory bowel disorder\* or IBD).ti,ab. (93009)
  - 10 or/1-9 (189914)
  - 11 (subcutaneous or sc).ti,ab. (281504)
  - 12 infliximab/ (51512)
  - 13 infliximab\*.ti,ab. (26469)
  - 14 12 or 13 (52435)
  - 15 biosimilar agent/ (4793)
  - 16 biosimilar\*.ti,ab. (7308)
  - 17 15 or 16 (8300)
  - 18 14 and 17 (2031)
  - 19 11 and 18 (39)
  - 20 (remsima or CT-P13 or CTP13 or inflectra).ti,ab. (717)
  - 21 19 or 20 (736)
  - 22 10 and 21 (463)
  - 23 limit 22 to english language (456)
  - 24 23 not (letter or editorial).pt. (443)
  - 25 24 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (160)
  - 26 nonhuman/ not (human/ and nonhuman/) (4728974)
  - 27 25 not 26 (160)
  - 28 elsevier.cr. (26433300)
  - 29 27 and 28 (147)

**Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL**

Platform: Wiley

Version:

CDSR – Issue 11 of 12, November 2020

CENTRAL – Issue 11 of 12, November 2020

Search date: 06/11/2020

Number of results retrieved: CDSR 0 ; CENTRAL 13.

#1 (Crohn\* NEAR/1 disease):ti,ab 4272  
 #2 [mh ^"crohn disease"] 1588  
 #3 "ulcerative colitis":ti,ab 4447  
 #4 [mh ^"colitis, ulcerative"] 1585  
 #5 [mh ^proctocolitis] 25  
 #6 proctocolitis:ti,ab 18  
 #7 Coloproctitis:ti,ab 0  
 #8 [mh ^"Inflammatory bowel diseases"] 548  
 #9 (Inflammatory bowel disease\* or Inflammatory bowel disorder\* or IBD):ti,ab 3668  
 #10 {or #1-#9} 9864  
 #11 (subcutaneous or sc):ti,ab 29005  
 #12 [mh ^"injections, subcutaneous"] 3742  
 #13 {or #11-#12} 30267  
 #14 [mh ^infliximab] 725  
 #15 infliximab:ti,ab 2126  
 #16 {or #14-#15} 2216  
 #17 [mh ^"Biosimilar Pharmaceuticals"] 166  
 #18 biosimilar\*:ti,ab 1066  
 #19 {or #17-#18} 1072  
 #20 #16 and #19 173  
 #21 #13 and #20 10  
 #22 (remsima or CT-P13 or CTP13 or inflectra):ti,ab 117  
 #23 #21 or #22 119  
 #24 #10 and #23 70  
 #25 #24 in Cochrane Reviews 0  
 #26 "conference":pt or (clinicaltrials or trialsearch):so 512719  
 #27 #24 not #26 13  
 #28 #27 in Trials 13

**Database: INAHTA database**

Platform: INAHTA

Version:

Search date: 06/11/2020

Number of results retrieved: 5

Search strategy:

24 #23 AND #10 5  
 23 #22 OR #21 12  
 22 remsima or CT-P13 or CTP13 or inflectra 12  
 21 #20 AND #13 0  
 20 #19 AND #16 4  
 19 #18 OR #17 8  
 18 Biosimilar\* 8  
 17 "Biosimilar Pharmaceuticals"[mh] 2  
 16 #15 OR #14 92  
 15 Infliximab 92  
 14 "Infliximab"[mh] 12  
 13 #12 OR #11 105  
 12 "Injections, Subcutaneous"[mh] 9



11	subcutaneous or sc	102
10	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	1270
9	Inflammatory bowel disease* or Inflammatory bowel disorder* or IBD	1204
8	"Inflammatory Bowel Diseases"[mh]	17
7	colorectitis	0
6	"Proctocolitis"[mh]	0
5	(proctocolitis)	0
4	"Colitis, Ulcerative"[mh]	10
3	(ulcerative colitis)	32
2	"Crohn Disease"[mh]	26
1	((crohn* and disease))	71

### ***Trials registry search strategies***

#### **Clinicaltrials.gov**

Search date: 05/11/2020

Number of results retrieved: see below

Search strategy:

Remsima (19 results)

CT-P13 (19 results)

Inflectra (18 results)

#### **Clinicaltrialsregister.eu**

Search date:05/11/2020

Number of results retrieved: see below

Search strategy:

Remsima (23 results)

CT-P13 (12 results)

Inflectra (19 results)