European Union Risk Management Plan
REMICADE® (infliximab)

Data lock point for current RMP	23 Aug 2022	Version number	22.1

Procedure EMEA/H/C/00240/II/0247 - Health Authority Approval Date 16/05/2024

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QPPV Name(s):	Dr Laurence Oster-Gozet, PharmD, Ph.D.
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP submission	
Version number	22.1
Rationale for submitting an updated RMP:	Removal of the immunogenicity substudy from the DEVELOP protocol REMICADEPIB4002.
Summary of significant changes in this RMP:	Pharmacovigilance Plan: • Removal of the immunogenicity substudy from the DEVELOP protocol REMICADEPIB4002. • Removal of the dose-escalation substudy from the DEVELOP protocols REMICADEPIB4002 and C0168Z02.

Other RMP Versions Under Evaluation:

RMP Version number	**Submitted on**	**Procedure number**
N/A	N/A	N/A

Details of the Currently Approved RMP:

Version number of last agreed RMP:	21.1
Approved within procedure	EMEA/H/C/000240/II/0241
Date of approval (Competent authority opinion date)	30 November 2023

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PART I: PRODUCT OVERVIEW

Active substance(s) (INN or common name)	Infliximab
Pharmacotherapeutic group(s) (ATC Code)	Tumor necrosis factor alpha (TNFα) inhibitors (L04AB02)
Marketing Authorization Holder	Janssen Biologics BV
Medicinal products to which this RMP refers	Infliximab (REMICADE®)
Invented name(s) in the European Economic Area (EEA)	REMICADE
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class** Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNFα but not to lymphotoxin α (tumor necrosis factor beta [TNFß]). Infliximab inhibits the functional activity of TNFα in a wide variety of in vitro bioassays. In vivo, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα bioactivity. **Summary of mode of action** Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis (RA) patients and correlate with elevated disease activity. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalization of keratinocyte differentiation in psoriatic plaques. In psoriatic arthritis, short term treatment with REMICADE reduced the number of T-cells and blood vessels in the synovium and psoriatic skin. Histological evaluation of colonic biopsies, obtained before and 4 weeks after administration of infliximab, revealed a substantial reduction in detectable TNFα. Infliximab treatment of Crohn's disease (CD) patients was also associated with a substantial reduction of the commonly elevated serum inflammatory marker, C reactive protein. **Important information about its composition** None.
Reference to the Product Information	Mod1.3.1/SPC, Labeling and Package Leaflet
Indication(s) in the EEA	Current: **<u>Rheumatoid arthritis:</u>** In combination with methotrexate for the reduction of signs and symptoms as well as the improvement in physical function in: • Adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate. • Adult patients with severe, active, and progressive disease not

previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated.

Adult Crohn's disease:

Treatment of moderately to severely active CD 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 fistulizing, active CD in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage, and immunosuppressive therapy).

Pediatric Crohn's disease:

Treatment of severe, active CD in pediatric patients aged 6 to 17 years who have not responded to conventional therapy, including a corticosteroid, an immunomodulator, and primary nutrition therapy, or who are intolerant to or have contraindications for such therapies. REMICADE has been studied only in combination with conventional immunosuppressive therapy.

Adult ulcerative colitis:

Treatment of moderately to severely active ulcerative colitis (UC) 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.

Pediatric ulcerative colitis:

Treatment of severely active UC in pediatric patients aged 6 to 17 years 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.

Ankylosing spondylitis:

Treatment of severe, active ankylosing spondylitis (AS) in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis:

Treatment of active and progressive psoriatic arthritis (PsA) in adult patients when the response to previous DMARD therapy has been inadequate.

REMICADE should be administered in combination with methotrexate or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

REMICADE has been shown to improve physical function in patients with PsA and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Psoriasis:

Treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, have a contraindication to, or are intolerant to other systemic therapy, including cyclosporin, methotrexate, or psoralen plus ultraviolet A (PUVA).

	Proposed: Not applicable
Dosage in the EEA	Current: ***ADULTS (≥18 years)*** **<u>Rheumatoid arthritis</u>** Patients not previously treated with REMICADE: 3 mg/kg given as an intravenous infusion, followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. REMICADE must be given concomitantly with methotrexate. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. If a patient has an inadequate response or loses response after this period, consideration may be given to increasing the dose step-wise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. If adequate response is achieved, patients should be continued on the selected dose or dose frequency. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment. **<u>Moderately to severely active Crohn's disease</u>** 5 mg/kg given as an intravenous infusion, followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment in patients not responding within 6 weeks of the initial infusion. In responding patients, the alternative strategies for continued treatment are: • Maintenance: Additional infusions of 5 mg/kg at 6 weeks after the initial dose, followed by infusions every 8 weeks or • Readministration: Infusion of 5 mg/kg if signs and symptoms of the disease recur. Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lose response indicate that some patients may regain response with dose escalation. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment. **<u>Fistulizing, active Crohn's disease</u>** 5 mg/kg given as an intravenous infusion, followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with infliximab should be given. In responding patients, the strategies for continued treatment are: • Maintenance: Additional infusions of 5 mg/kg every 8 weeks or • Readministration: Infusion of 5 mg/kg if signs and symptoms of the disease recur, followed by infusions of 5 mg/kg every 8 weeks. Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lose response indicate that some

patients may regain response with dose escalation. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

In CD, experience with readministration if signs and symptoms of disease recur is limited, and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking.

Ulcerative colitis

5 mg/kg given as an intravenous infusion, followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, ie, 3 doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Ankylosing spondylitis

5 mg/kg given as an intravenous infusion, followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks thereafter. If a patient does not respond by 6 weeks (ie, after 2 doses), no additional treatment with infliximab should be given.

Psoriatic arthritis

5 mg/kg given as an intravenous infusion, followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Psoriasis

5 mg/kg given as an intravenous infusion, followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (ie, after 4 doses), no additional treatment with infliximab should be given.

Readministration for Crohn's disease and rheumatoid arthritis

If the signs and symptoms of disease recur, REMICADE can be readministered within 16 weeks following the last infusion. In clinical trials, delayed hypersensitivity reactions have been uncommon and have occurred after REMICADE-free intervals of less than 1 year. The safety and efficacy of readministration after a REMICADE-free interval of more than 16 weeks has not been established. This applies to both CD patients and RA patients.

Readministration for ulcerative colitis, ankylosing spondylitis, and psoriatic arthritis

The safety and efficacy of readministration, other than every 8 weeks, has not been established.

Readministration for psoriasis

Limited experience from retreatment with 1 single infliximab dose in psoriasis after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen.

Limited experience from retreatment following disease flare by a re-induction regimen suggests a higher incidence of infusion reactions, including serious ones, when compared to 8-weekly maintenance

	treatment. **<u>Readministration across indications</u>** In case maintenance therapy is interrupted and there is a need to restart treatment, use of a re-induction regimen is not recommended. In this situation, infliximab should be re-initiated as a single dose, followed by the maintenance dose recommendations described above. ***ELDERLY (≥65 years)*** Specific studies of REMICADE in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical trials. No dose adjustment is required. ***PEDIATRIC POPULATION*** **<u>Crohn's disease (6 to 17 years)</u>** 5 mg/kg given as an intravenous infusion, followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Available data do not support further infliximab treatment in children and adolescents not responding within the first 10 weeks of treatment. **<u>Ulcerative colitis (6 to 17 years)</u>** 5 mg/kg given as an intravenous infusion over a 2-hour period, followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in pediatric patients not responding within the first 8 weeks of treatment.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Powder for concentrate for solution for infusion; 100 mg infliximab; packs with 1, 2, 3, 4, or 5 vials.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	☐ **Yes** ☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indications and Target Populations

Indication: Rheumatoid Arthritis

Incidence:

The incidence of RA varies by country. The median annual incidence observed in south European countries was 16.5 cases per 100,000 persons (Alamanos et al, 2006). For north European countries the median annual incidence observed was 29, and for North American countries 38 (Alamanos et al, 2006). In Sweden, Eriksson et al studied the Swedish National Patient Register for patients diagnosed with RA between 2006 and 2008; the overall incidence of RA was 41 per 100,000 persons (56 for women and 25 for men) (Eriksson et al, 2013). An Italian study estimated the annual incidence of RA for that country to be 35 per 100,000 persons (95% confidence interval [CI]: 29-42) (Rossini et al, 2014). A study in the United Kingdom (UK) using the Clinical Practice Research Datalink (CPRD), a database of longitudinal medical records from primary care, reported an incidence of 3.81 (95% CI: 3.61-4.02) per 10,000 person-years in 2014 (Abhishek et al, 2017).

In the United States (US), a study in Olmsted County, Minnesota, included RA data from 1995 to 2007 for residents 18 or older. Similar to the Swedish study, the overall age- and sex-adjusted annual incidence among residents was 40.9 per 100,000 population (Myasoedova et al, 2010).

Prevalence:

The overall world prevalence of RA is approximately 0.5% to 1% (Gibrofsky, 2012). A population survey for the prevalence of rheumatic diseases in adults was conducted in central Greece. Of 1705 individuals that responded to the questionnaire, 420 (24.6%) reported rheumatic disease and were confirmed by a rheumatologist. The prevalence of RA was 0.57% (Anagnostopoulos et al, 2010) of the population.

In the UK, RA is the second most common form of arthritis and the most common inflammatory joint disorder. Estimated number of cases of RA in the UK are listed below (Rheumatoid Arthritis. Arthritis Research UK).

Prevalence of RA in the UK

Age	Males (%)	UK Estimate	Females (%)	UK Estimate
16-44	0.02	2500	0.12	15,100
45-64	0.58	42,900	1.67	126,900
64-74	1.14	27,100	2.56	67,800
75+	2.18	39,100	2.99	85,700
Total Adult Population	0.44	106,500	1.16	297,600

In the aforementioned study by Myasoedova et al, 2010, in Olmsted County, Minnesota, the overall age- and sex- adjusted prevalence of RA among individuals who were 18 years of age or older on 01 Jan 2005 was 0.72%, which represents an increase from the estimates of 0.62% on 01 Jan 1995. When the prevalence of RA on 01 Jan 2005 was applied to the US population in 2005, it showed that an estimated 1.5 million US adults were affected by RA.

Demographics of the Population in the Rheumatoid Arthritis Indication (Age and Sex) and Risk Factors for the Disease:

Females are approximately 3 times more likely to develop RA than males (Lipsky, 2008). In the Swedish study by Eriksson et al, 2013, women had a higher incidence rate in all age categories compared to men though the difference decreased with age. In the previously described prevalence study in Greece, female to male ratio with RA was defined as 2.3:1 (Anagnostopoulos et al, 2010). In the UK, incidence and prevalence rates appear to be higher for females in all age groups with the exception of the incidence rate in the 75 and over age group (Rheumatoid Arthritis. Arthritis Research UK).

The peak incidence of onset is between the ages of 35 and 50 (Lipsky, 2008), the most economically productive years of an individual's life (Wolfe, 1996), but RA may begin at any time from early adulthood to advanced old age.

Factors that may increase the risk of RA include: female sex, age between 40 and 60 years, family history of the disease, and smoking. Also, people who are overweight or obese seem to have a somewhat higher risk of developing RA (Rheumatoid Arthritis: Risk Factors, Mayo Clinic 2017).

Main Existing Treatment Options:

There is no cure for RA. Medications are used to reduce inflammation in joints in order to relieve pain and prevent or slow joint damage. Occupational and physical therapy can teach the patient how to protect their joints, and surgery may be necessary if the joints are severely damaged by RA. Some of the medications that are prescribed include:

- *Nonsteroidal anti-inflammatory drugs (NSAIDs)*: used to relieve and reduce inflammations which include ibuprofen and naproxen.
- *Steroids*: Corticosteroids such as prednisone reduce inflammation and pain and slow joint damage.
- *Conventional DMARDs*: These drugs can slow the progression of RA and save the joints and other tissues from permanent damage. Common DMARDs include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and minocycline.
- *Targeted synthetic DMARDs*: Drugs that inhibit kinases such as Janus kinase (JAK) and can ease joint pain and swelling. JAK inhibitors include tofacitinib, baricitinib, upadacitinib, and filgotinib.
- *Immunosuppressants*: These medications act to tame the immune system. Examples include azathioprine, cyclosporine and cyclophosphamide.
- *Biologics:* These therapies block cytokines or cluster of differentiation receptors involved in the inflammatory process. Biologics include interleukin (IL)-1 inhibitors, IL-6 inhibitors, TNFα inhibitors, cluster of differentiation-20 inhibitors, and T-cell co-stimulation modulators.

Surgery may be required to restore the ability to use the joints. It can also reduce pain and correct deformities. Rheumatoid Arthritis surgery may involve one or more of the following: total joint replacement, tendon repair or joint fusion (Rheumatoid Arthritis: Treatment and Drugs, Mayo Clinic, 2017).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

As patients with RA are invariably treated, it is no longer possible to dissociate the effects of treatment from the natural history of the disease (Scott and Steer, 2007). The natural disease progression of RA results in persistent joint inflammation, progressive joint damage, and continuing functional decline (Scott et al, 2010). As the disease progresses, cartilage and bone within the joint become damaged and surrounding muscles, ligaments and tendons become weak (NIAMSa, 2017). Some patients with RA experience periods of disease flare and periods of remission (NIAMSa, 2017). A study conducted in Sweden reported that, at baseline, about 95% of RA patients fell into the moderate or severe category and over a period of 3 years of receiving appropriate physician directed care, these proportions changed such that about 25% met the criteria for remission, 10% had low activity, 50% had moderate activity, and about 15% had high activity (Hallert, 2006).

Patients with RA have about a 50% increased risk of premature mortality and their life expectancy is decreased by 3 to 10 years compared with the general population (Myasoedova et al, 2010).

A meta-analysis by Dadoun et al. 2013 found a pooled incident mortality rate (IMR) for RA of 2.7 per 100 person-years (95% CI: 2.2-3.3). The rates ranged from 1.0 per 100 person-years to 5.2 per 100 person-years. The analysis revealed a significant decrease in IMR over 3 periods. The estimated pooled IMR was 4.7 per 100 person-years (95% CI: 4.0-5.4) for studies starting before 1970, 3.0 per 100 person-years (95% CI: 2.3-4.0) for those starting between 1970 and 1985; and 2.0 per 100 person-years (95% CI: 1.3-2.8) for those starting after 1985. Older age at diagnosis and longer length of follow-up were found to be significant factors for higher IMR. The mean standardized mortality ratio (SMR) for 8 studies was 2.01 (95% CI: 1.99-2.03). The Norfolk Arthritis Registry (NOAR) in the UK reported that for patients who had been followed for 20 years, the age- and sex-standardized SMR was 1.25 [95% CI: 1.11-1.42], and reported that older age at onset and male gender were associated with increased risk of death during that time period (Gwinnutt et al, 2017).

Important Co-morbidities:

Co-morbidities that occur in adult patients with RA include hypertension, myocardial infarction, congestive heart failure (CHF), neuropathy, keratoconjunctivitis sicca, scleritis/episcleritis, interstitial pulmonary disease, inflammatory bowel disease, renal amyloidosis, renal vasculitis, cutaneous vasculitis, osteoporosis, and depression (Norton et al, 2013; Aviña-Zubieta et al, 2008; Myasoedova et al, 2012; Ramos-Remus et al, 2012; Myasoedova et al, 2011; Hochberg et al, 2008; Pappas et al, 2010; Wolfe et al, 2010; Avouac et al, 2012).

Indication: Adult Crohn's Disease

Incidence:

A systematic review of worldwide incidence rates of CD was conducted. The annual incidence rates varied by geographic region with estimates ranging from 0.3 to 12.7 per 100,000 in Europe and 0 to 20.2 per 100,000 in North America. The incidence rates covered the years 1930 to 2008 for European studies and 1920 to 2004 for North American studies. The highest report incidence rates were in Canada (20.2 per 100,000) and the UK (10.6 per 100,000) (Molodecky et al, 2012).

Recent studies in Europe show similar rates. A study in Finland between 2000 and 2007 revealed an overall incidence rate of 9.2 per 100,000 inhabitants (Hovde and Moum, 2012 and Jussila et al, 2012) Another study that included data from irritable bowel disease patients recorded in the EPIMAD registry in France between 1988 and 2007 found that CD incidence rates increased from 5.2 per 100,000 in 1988-1990 to 6.7 in 2006 to 2007, stabilizing after a peak at 7.1 in 1997-1999 (Chouraki et al, 2011). A national study conducted in Denmark estimated the incidence rate of CD in 2012 to be 9.5 (95% CI: 8.3-10.7) per 100,000 person-years for women and 8.8 (95% CI: 7.2-10.1) per 100,000 person-years for men. This is an increase from 1995 when the rates were 6.8 (95% CI: 5.6-7.7) per 100,000 person-years for women and 4.6 (95% CI: 3.6-5.3) per 100,000 person-years for men (Norgard et al, 2014). In the Netherlands, the incidence rate has been reported at 10.5 per 100,000 person-years (de Groof et al, 2016). In general, the incidence of CD has increased in the western world, including North America, Europe, Australia, and New Zealand (Aniwan et al, 2017).

Prevalence:

The aforementioned study by Molodecky et al. also analyzed prevalence rates in the literature. The estimates ranged from 0.62 to 322 per 100,000 in Europe and 16.7 to 318.5 in North America. Prevalence rates were highest in Italy (322 per 100,000) and Canada (319 per 100,000) (Molodecky et al, 2012). In the Netherlands, the point prevalence rate of CD has been reported as 171.8 per 100,000 inhabitants for 2004-2010 (de Groof et al, 2016).

Another literature review shows that the prevalence of CD in Europe varies from less than 10 to about 150 per 100,000 inhabitants (Hovde and Moum, 2012). A total of about 150,000 people have inflammatory bowel disease (IBD) in the UK, and a total of approximately 2.2 million across Europe. The prevalence of CD in the UK is currently about 55-140 per 100,000 population (Megraud, 2007). There are approximately 436,000 Americans living with CD (Kappelman et al, 2008).

Demographics of the Population in the Crohn's Disease Indication (Sex, Ethnicity, and Geographical Location) and Risk Factors for the Disease:

Sex: In general, there is a slight female predominance in CD, although in certain low-incidence areas a male predominance exists (Loftus, 2004). A literature review showed that a slight predominance of women in multiple studies, one study in the UK from 1986-2003 found 62% of CD patients were female and another study in Denmark showed 54% of CD patients were female (Hovde and Moum, 2012). The aforementioned study by Chouraki et al. in France also showed a predominance of women with CD (56%) between 1988 and 2007. A regional study conducted in Spain from 2007 to 2008 reported the incidence rate for CD as 5.1 per 100,000 population for both men and women (Cueto Torreblanca et al, 2017).

Ethnicity: The frequency of CD varies among different ethnic groups, with increased prevalence rates reported for Ashkenazi Jews compared with the non-Jewish population living in the same geographic area. In a study of a southern California health management organization, the prevalence of CD among blacks was approximately two-thirds that of whites although the rates of hospitalization for CD were similar (Loftus, 2004). In addition, Hispanics in the US are less prone to develop IBD than the non-Hispanic population (Hovde and Moum, 2012).

Geographical Location: Occurrence of CD seems to vary according to geographical location. Crohn's disease is more common in the industrialized world compared with non-industrialized countries (Feuerstein and Cheifetz, 2017). A north-south axis has been found in both Europe and the US, with higher incidence and prevalence in the northern regions (Hovde and Moum,

2012). In a study that used US claims from approximately 12 million Americans, it was found that there was a significant regional variation. The prevalence was lower in the south and west as compared with the northeast and Midwest (Kappelman et al, 2013).

Risk factors for CD include being younger than 30 years of age, being of Ashkenazi-Jewish descent or Caucasian, having a close relative with the disease, and living in an urban area or an industrialized area. A low‑fiber and high-fat diet and certain medications (such as antibiotics, NSAIDs, and oral contraceptives) are also identified as risk factors for Crohn's disease (Aniwan et al, 2017). The most important controllable risk factor is cigarette smoking (Crohn's Disease: Risk Factors, Mayo Clinic, 2017).

Main Existing Treatment Options:

The goal of medical treatment is to reduce inflammation that triggers signs and symptoms. It is also to improve long-term prognosis by limiting complications. In the best cases, treatment may lead not only to symptom relief but also to long-term remission. Drugs used to treat CD include:

- *Anti-inflammatory drugs*: These are often used as a first step in the treatment of CD. Examples include sulfasalazine, mesalamine, and corticosteroids.
- *Immunosuppressants*: The drugs also reduce inflammation by suppressing the immune response. Sometimes, the drugs are used in combination. Some examples include azathioprine and mercaptopurine, methotrexate, and cyclosporine.
- *Antibiotics*: These drugs can reduce the amount of drainage and sometimes heal fistulas and abscesses in people with CD. It is also believed that antibiotics help reduce harmful intestinal bacteria and suppress the intestine's immune system, which can trigger symptoms. Examples of antibiotics used for CD include metronidazole and ciprofloxacin.
- *Biologics*: These include TNFα inhibitors (infliximab), IL-12/23 inhibitors (ustekinumab), and integrin receptor antagonists (vedolizumab).

In addition to controlling inflammation, some medications may help relieve signs and symptoms. These drugs include antidiarrheals, laxatives, pain relievers, iron supplements, vitamin B-12 shots, and calcium and vitamin D supplements.

If lifestyle change, drug therapy or other treatments do not relieve signs and symptoms, surgery may be required to remove the damaged portion of the digestive tract, close fistulas, and drain abscesses (Crohn's disease: Treatments and drugs, Mayo Clinic, 2020).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Since observational studies generally include a treated population, it is difficult to describe the course of the disease in the untreated population, and to dissociate the effects of treatment from the natural history of the disease. Crohn's disease begins gradually, becoming worse over time, with a naturally recurring and remitting disease course (NIDDK, 2017; Lashner, 2013). Possible complications include: intestinal obstruction, fistulas, abscesses, anal fissures, ulcers, malnutrition and inflammation in other parts of the body. People with CD in the large intestine are more likely to develop colon cancer (NIDDK, 2017). Surgery is frequently required with rates of bowel resection procedures ranging from 12% within 1 year of diagnosis in Denmark to 35% within 5 years in the UK. Additionally, approximately 25-46% of patients with CD are likely to experience extra-intestinal manifestations (Hovde and Moum, 2012). One study

conducted in Hungary reported that the probability of developing more complicated disease in adult onset CD patients was 12.1%, 26.4%, and 37.5% after 1, 5, and 10 years of follow-up, respectively (Lovasz et al, 2013). It has also been reported that within 10 years of follow-up, 27.1% of CD patients in Europe develop stricturing disease and 29.4% develop penetrating disease (Burisch, 2013).

A meta-analysis from 2010, found a slightly increased mortality in patients with CD (SMR: 1.39, 95% CI: 1.30-1.50) (Hovde and Moum, 2012; Duricova et al, 2010).

Data based on a prospective IBD register in the catchment area of Finland followed CD patients from 1986-2007. Below are the SMRs for CD by cause of death (Manninen et al, 2012).

Standardized Mortality Rates (SMRs) for Crohn's Disease; O=observed, E=expected

	Female			Male			Total		
Causes of Death	**O/E**	**SMR**	**95% CI**	**O/E**	**SMR**	**95% CI**	**O/E**	**SMR**	**95% CI**
All deaths	22/19	1.16	0.73-1.76	28/26	1.12	0.75-1.61	53/45	1.14	0.84-1.49
Diseases of Circulatory System	5/4	1.28	0.42-2.99	8/6	1.28	0.55-2.50	13/10	1.28	0.68-2.18
Diseases of Digestive System	3/0.6	5.08	1.02-14.61	4/0.6	6.76	1.82-17.07	7/1.2	5.83	2.35-12.02
Malignant Neoplasm of Colon and Rectum	1/0.5	1.91	0.05-10.61	1/0.5	1.86	0.05-10.36	2/1.1	1.88	0.23-6.80
Mental and Behavioral Disorders due to use of alcohol	0/0.4	0.00	0.00-8.38	0/2	0.00	0.00-1.80	0/2.5	0.00	0.00-1.48

Another report found no difference between CD patients and controls in overall mortality (hazard ratio [HR]=1.35, 95% CI: 0.94-1.94, p=0.10). The inflammatory bowel south-eastern Norway study followed all patients diagnosed with CD in the period between 1990 and 1993 followed for 20 years. There were no marked differences in deaths from gastrointestinal (GI) cancer, other cancers or cardiovascular disease (CVD) in the CD group compared with controls. In the CD group, 13.9% had died compared with 12.7% in the control group (p=0.578). The table below shows the causes of death for the CD patients. No explanation for the possible difference from other studies was described (Hovde et al, 2013).

Causes of Death for Patients with CD

Cause of Death	Number (n=33)	%
GI Cancer	3	9
Other Cancer	7	21
CVD	12	37
Other Causes	11	33

Important Co-morbidities:

Co-morbidities that occur in Crohn's disease patients include small bowel or colorectal cancer, uveitis, episcleritis, arthritis, hepatobiliary disorders, nephrolithiasis, fat malabsorption, pancreatic disease, obesity, cardiovascular conditions including venous thromboembolism and atherosclerosis, and depression (Román and Muñoz, 2011; Burisch et al, 2013; Cury et al, 2013; Crohn's and Colitis Foundation, 2011).

Indication: Pediatric Crohn's Disease

Incidence:

Inflammatory bowel disease develops during childhood or adolescence in up to 25% of patients (Benchimol et al, 2011). Pediatric IBD accounts for 7% to 20% of all IBD cases, based on varying results from population-based studies (Cosnes et al, 2011).

An analysis conducted in France included all patients from the EPIMAD registry who were diagnosed with IBD between January 1988 and December 2011. This analysis reported the incidence rate (IR) for pediatric onset CD (age <17 years) as 3.2 per 100,000 population (95% CI: 3.0-3.4). Incidence rates in the 0-17 age group increased steadily over the entire study period, from 2.1 per 100,000 population (95% CI: 1.7-2.6) to 4.7 per 100,000 population (95% CI: 4.0-5.4). Further analyses showed that in the 10-17 year old age group the rate increased from 6.0 (95% CI: 4.9-7.4) per 100,000 population for 1988-1990 to 13.8 (95% CI: 12.0-15.7) per 100,000 for 2009-2011, whereas the incidence rates in the 0-9 year old age group increased from 0.6 (95% CI: 0.3-1.0) per 100,000 for 1988-1990 to 1.2 (95% CI: 0.8-1.7) per 100,000 for 2009-2011 (Ghione et al, 2017). In Denmark, the incidence rate for CD for children <15 years old was reported as 2.8 (95% CI: 2.5-3.2) per 100,000 person-years for women and 3.3 (95% CI: 2.9-3.7) per 100,000 person-years for men (Norgard et al, 2014).

A study in the US analyzed the Kaiser Permanente Northern California IBD Registry for all patients ages 0 to 17 with confirmed IBD. The average standardized incidence per 100,000 was 2.7. During the 11-year study period, the annual incidence increased from 2.2 per 100,000 to 4.3 per 100,000 (Abramson et al, 2010).

Prevalence:

Using claims from approximately 12 million Americans, 3 consecutive 2-year cross-section studies were performed. In 2009, the prevalence of CD in children was 58 per 100,000 (95% CI: 55-60). It was estimated that about 38,000 children in America have CD (Kappelman et al, 2013). The aforementioned study using the Kaiser Permanente IBD Registry showed a lower prevalence rate. On 31 Dec 2006, the age-standardized point prevalence per 100,000 was 12.0.

The prevalence of pediatric CD (per 100,000) in the US, using Pharmetrics Patient-Centric Database, was reported as follows: ages 2 to less than 5 years, 2.3; ages 5 to less than 10 years, 9.4; ages 10 to less than 15 years, 45; ages 15 to less than 20 years, (Kappelman et al, 2007).

Demographics of the Population in the Pediatric Crohn's Disease Indication (Sex and Geographical Location) and Risk Factors for the Disease:

Sex: The study by Kappelman et al, 2013 in the US showed a lower prevalence in girls that in boys (odds ratio [OR]: 0.88; 95% CI: 0.81-0.97). Similarly, in the Kaiser Permanente study in the US, the authors observed a male-to-female prevalence ratio of 1.2.

Geographical Location: Kappelman et al, 2013 found that there was a significant regional variation in the US for children. The prevalence was lower in the south and west as compared with the northeast and Midwest.

Risk factors for CD include being of Ashkenazi-Jewish descent or Caucasian, having a close relative with the disease, and living in an urban area or in an industrialized area (Crohn's disease: Risk Factors, Mayo Clinic, 2017).

Main Existing Treatment Options:

Children require individualized treatment that takes numerous factors into account: the specific disease manifestations (location of inflammation in the intestines, duration, and prior response to therapy), the psychosocial adaptation of the child and family, and the child's age and size. Drug dosages also must be tailored based upon the child's weight. All of the medications used for adults with CD are also used for children and the indications and contraindications are similar. These medications include aminosalicylates, corticosteroids, antibiotics, immunomodulators, biologics, antidiarrheal agents, and acne medications (Treating Children and Adolescents, Crohn's & Colitis Foundation of America, 2011).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Since observational studies generally include a treated population, it is difficult to describe the course of the disease in the untreated population, and to dissociate the effects of treatment from the natural history of the disease. Pediatric onset CD is more likely to present as ileocolonic disease at diagnosis (69%) compared with adult onset (32%), whereas only 8% of pediatric onset CD presents as colonic disease (Duricova et al, 2014). Disease progression of pediatric onset CD is similar to adult onset CD. One study conducted in Hungary reported the probability of developing complicated disease in pediatric onset CD to be 7.6% within 1 year of follow-up and 27.5% and 42.0% after 5 and 10 years of follow-up respectively (Lovasz et al, 2013). Children with extensive small bowel involvement may have growth retardation and delayed puberty (Lashner, 2013).

Data from patients in Denmark from 1982 to 2010 were compared with data from matched individuals from the general population. Patients diagnosed with UC in childhood (ages 0-19 years) had a 1.62-fold higher relative mortality (95 % CI: 1.25-2.09) than patients diagnosed at 60-70 years (Jess et al, 2013b).

In a 10-year cohort study, increased mortality risks were observed for both males (SMR 1.90; 95% CI: 1.14 to 2.97) and females (SMR 2.13; 95% CI: 1.16 to 3.57) older than 40 years at diagnosis. Male patients, patients older than 40 years at diagnosis, and patients with inflammatory disease behavior at diagnosis were observed to have excess risks for mortality due to cancer, gastrointestinal, and all causes. Female patients and patients with isolated colonic disease at diagnosis had increased mortality risks for both gastrointestinal and all causes. Increased risk of mortality due to gastrointestinal causes (SMR 9.77; 95% CI: 4.20 to 19.2) was observed, including patients younger than 40 years at diagnosis (SMR 22.6; 95% CI: 2.54 to 81.8), those with upper gastrointestinal disease location at diagnosis (SMR 117; 95% CI: 13.1 to 422), and those with penetrating disease behavior at diagnosis (SMR 9.77; 95% CI: 4.20 to 19.2). A substantial part of the observed increased mortality risk in the male population with isolated colonic disease localization at diagnosis was due to pulmonary causes (SMR 6.14; 95% CI: 1.23 to 18.0). The majority of deaths in female patients with inflammatory disease behavior at diagnosis were due to cardiovascular causes (SMR 3.25; 95% CI: 1.05 to 7.59). A tendency to increased mortality was observed in a group of female patients with isolated colonic disease localization at diagnosis (8 deaths observed vs. 4.24 expected; SMR 1.81 [95% CI: 0.78 to 3.57]) (Wolters et al, 2006).

Important Co-morbidities:

In the pediatric CD patient population, certain medical conditions can coexist along with the disease. In the literature, there appears to be no evidence suggesting differences in such expected conditions between the pediatric and adult population. Hence, the list of co-morbidities listed in the adult population also apply to pediatric CD patients.

Indication: Adult Ulcerative Colitis

Incidence:

A systematic review of worldwide incidence rates of UC was conducted. The annual incidence rates varied by geographic region with estimates ranging from 0.6 to 24.3 per 100,000 in Europe and 0 to 19.2 per 100,000 in North America. The incidence rates covered the years 1930 to 2008 for European studies and 1920 to 2004 for North American studies. The highest report incidence rates were in Canada (19.2 per 100,000) and Iceland (24.3 per 100,000) (Molodecky et al, 2012).

All new UC patients in Uppsala County in Sweden were prospectively registered during 2005 2006 and the same for all new UC patients in the Uppsala Region during 2007-2009. The mean overall incidence for the time period was 20.0 (95% CI: 16.1-23.9) cases per 100,000 inhabitants (Sjöberg et al, 2013). Another regional Swedish study reported an IR of 18.1 per 100,000 population in 2010 (Eriksson et al, 2017). A national study conducted in Denmark, which included all ages, estimated the incidence rate of UC in 2011 to be 22.4 (95% CI: 20.6-24.2) per 100,000 person-years for women and 23.5 (95% CI: 22.7-25.5) per 100,000 person-years for men. This is an increase from 1995 when the rates were 13.9 (95% CI: 12.1-15.0) per 100,000 person-years for women and 13.6 (95% CI: 11.9-14.8) per 100,000 person-years for men (Norgard et al, 2014). In the Netherlands, the incidence rate has been reported at 17.2 per 100,000 person-years (de Groof et al, 2016).

In the US, the incidence of UC was reported as follows in the Nurses' Health Study I and Nurses' Health study II, which includes over 20 years of data: ages under 30 years, 12.9; ages 30-39 years, 9.1; ages 40-49 years, 6.9; ages 50-59 years, 7.4; ages 60-69 years, 9.4; ages 70 and older, 6.2. The age-adjusted incidence of UC per 100,000 person-years ranged from 6.2 to 12.9 (Khalili et al, 2012).

Prevalence:

Based on published prevalence rates, the UC population in Europe is estimated to be 603,000 to 1,210,000 (Cohen et al, 2010). In the Netherlands, the point prevalence of UC has been reported as 225.6 per 100,000 population for 2004-2010 (de Groof et al, 2016). A regional study in Sweden reported the point prevalence for 2010 to be 474 (95% CI: 444-506) per 100,000 inhabitants (Eriksson et al, 2017).

The aforementioned study by Molodecky et al. also analyzed prevalence rates in the literature. The estimates ranged from 4.9 to 505 per 100,000 in Europe and 37.5 to 248.6 in North America. Prevalence rates were highest in Norway (505 per 100,000) and Canada (248 per 100,000) (Molodecky et al, 2012).

The prevalence of UC in the US, using Pharmetrics Patient-Centric Database, was reported as 263 per 100,000. It is estimated that 593,000 Americans are living with UC (Kappelman et al, 2013).

Demographics of the Population in the Adult Ulcerative Colitis Indication (Age and Sex) and Risk Factors for the Disease

Ulcerative colitis is most commonly diagnosed in late adolescence and early adulthood, but the diagnosis may occur at all ages. In some studies of UC, there are sex-related differences in late-onset disease. Men are significantly more likely than women to be diagnosed in the fifth and sixth decades of life. A regional study conducted in Spain reported the incidence rate for UC in women was 2.7 per 100,000 population and 5.1 per 100,000 in men for 2007-2008 (Cueto Torreblanca et al, 2017).

Main Existing Treatment Options:

The goal of medical treatment is to reduce the inflammation that triggers signs and symptoms of UC. In the best cases, this may lead not only to symptoms relief but also to long-term remission. UC treatment usually involves drug therapy or surgery. Drug therapies include:

- *Anti-inflammatory drugs*: Often the first step in treatment and include sulfasalazine, mesalamine, and corticosteroids. They may also be used in conjunction with other medications as a means to induce remission.
- *Immunosuppressants*: These drugs reduce inflammation as well as target the immune system. Examples of these drugs include azathioprine and cyclosporine.
- *Biologics:* These include TNFα inhibitors (infliximab, adalimumab, and golimumab), IL-12/23 inhibitors (ustekinumab), and integrin receptor antagonists (vedolizumab).
- *Targeted synthetic DMARDs:* Tofacitinib is a JAK inhibitor approved for treatment of UC.

Other medications that may be used in the treatment of UC are antibiotics, antidiarrheals, pain relievers, and iron supplements.

If diet and lifestyle change, drug therapy, or other treatments do not relieve signs and symptoms of UC, surgery may be recommended. Surgery can often eliminate UC but usually means removing the entire colon and rectum (Ulcerative Colitis: Treatments and Drugs, Mayo Clinic, 2017).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Since observational studies generally include a treated population, it is difficult to describe the course of the disease in the untreated population, and to dissociate the effects of treatment from the natural history of the disease. The natural course of UC is characterized by periods of flare alternating with periods of remission, and disease activity can decrease over time (Cosnes, 2011). A study conducted in Denmark reported that after the first 2 years of follow-up, approximately 50% of patients were in remission and the proportion of patients with active disease gradually reduced to 30%. There was a cumulative probability of clinical relapse of 81.6% after 5 years. In adults with UC, extension from the initial location was reported to vary from 10% to 19% of patients after 5 years of disease, and from 11% to 28% after 10 years (Duricova et al, 2014).

Data based on a prospective IBD register in the catchment area of Finland followed UC patients from 1986-2007. Below are the SMRs for UC by cause of death (Manninen et al, 2012).

Standardized Mortality Ratios (SMRs) for Ulcerative Colitis; O=observed, E=expected

	Female			Male			Total		
Causes of Death	**O/E**	**SMR**	**95% CI**	**O/E**	**SMR**	**95% CI**	**O/E**	**SMR**	**95% CI**
All deaths	52/57	0.90	0.67-1.18	98/109	0.90	0.73-1.10	150/166	0.90	0.77-1.06
Diseases of circulatory system	17/13	1.33	0.77-2.12	27/29	0.93	0.61-1.35	44/42	1.04	0.76-1.41
Diseases of digestive system	2/2	1.08	0.13-3.80	7/2.5	2.77	1.13-5.77	9/4	2.05	0.94-3.88
Malignant neoplasm of colon and rectum	3/1.6	1.91	0.39-5.48	4/2.3	1.71	0.47-4.45	7/3.9	1.80	0.72-3.70
Mental and behavioral disorders due to use of alcohol	0/0.4	0.00	0.00-3.55	0/6.1	0.00	0.00-0.60	0/7.2	0.00	0.00-0.51

Important Co-morbidities:

Co-morbidities that occur in adult patients with UC include demyelination disorders (multiple sclerosis, optic neuritis), uveitis, urinary calculus disease, cutaneous ulcers, erythema nodosum, pyoderma gangrenosum, peripheral arthritis, obesity, and depression/anxiety (Figueroa et al, 2013; Langholz, 2010; Larsen, et al 2010; Huang et al, 2012; Friedman and Blumberg, 2011; Trikudanathan et al, 2012; Román and Muñoz, 2011; Sajadinejad et al, 2012).

Indication: Pediatric Ulcerative Colitis

Incidence:

Inflammatory bowel disease develops during childhood or adolescence in up to 25% of patients (Benchimol et al, 2011). Pediatric IBD accounts for 7% to 20% of all IBD cases, based on varying results from population-based studies (Cosnes et al, 2011).

The incidence of pediatric UC in Europe ranges from approximately 1 to 133 per 100,000 with most countries reporting around approximately 10 to 20 cases of pediatric UC per 100,000 individuals (Benchimol et al, 2010). In Denmark, the incidence rate for UC for children <15 years old was reported as 3.0 (95% CI: 2.6-3.4) per 100,000 person-years for women and 2.4 (95% CI: 2.1-2.7) per 100,000 person-years for men (Norgard et al, 2014). In France, the EPIMAD registry for the years 1988-2011 reported the IR for pediatric onset (age <17 years) UC as 1.1 (95% CI: 1.0-1.2) per 100,000 population. In adolescents (age 10-16) the rate increased from 1.6 (95% CI: 1.0-2.3) per 100,000 population in 1988-1990 to 4.1 (95% CI: 3.2-5.2) per 100,000 in 2009-2011 and for those under 10 years, the rate increased from 0.3 (95% CI: 0.1-0.6) per 100,000 in 1988-1990 to 0.6 (95% CI: 0.3 1.0) per 100,000 in 2009-2011 (Ghione et al, 2017).

A study in the US analyzed the Kaiser Permanente Northern California IBD Registry for all patients aged 0 to 17 with confirmed IBD. The average standardized incidence per 100,000 was 3.2. The annual incidence of UC per 100,000 was reported as follows in males vs. females: ages 0-4 years, 0.6 vs. 0.8; ages 5-9 years, 1.2 vs. 1.2; ages 10-14 years, 4.2 vs. 5.0; ages 15-17 years, 8.7 vs. 7.7; overall crude, 3.3 vs. 3.4; overall age-standardized, 3.2 vs. 3.3. The authors observed a 2.7-fold rise in the incidence of UC over the 11-year period of the study (Abramson et al, 2010).

Prevalence:

Using claims from approximately 12 million Americans, 3 consecutive 2-year cross-section studies were performed. In 2009, the prevalence of UC in children was 34 per 100,000 (95% CI: 55-60). It was estimated that about 38,000 children in America have CD (Kappelman et al, 2013).

Demographics of the Population in the Pediatric Ulcerative Colitis Indication (Age) and Risk Factors for the Disease

Approximately 25% of patients with UC present before the age of 20 years with disease being extensive in 50-80% of these patients (Van Limbergen et al, 2008). While the peak occurrence of UC is in late adolescence, all ages can be affected, and 4% of pediatric IBD patients are diagnosed in early (age <5 years) childhood (Kelsen and Baldassano, 2008).

Risk factors for UC include age, the onset of the disease usually being before the age of 30, being Caucasian or of Ashkenazi-Jewish descent, and having a family history of the disease (Ulcerative Colitis: Risk Factors, Mayo Clinic, 2012).

Main Existing Treatment Options:

Children require individualized treatment that takes numerous factors into account: the specific disease manifestations (location of inflammation in the intestines, duration, and prior response to therapy), the psychosocial adaptation of the child and family, and the child's age and size. Drug dosages also must be tailored based upon the child's weight. All of the medications used for adults with CD are also used for children and the indications and contraindications are similar. These medications include: aminosalicylates, corticosteroids, antibiotics, immunomodulators, biologics, antidiarrheal agents, and acne medications (Treating Children and Adolescents, Crohn's & Colitis Foundation of America, 2011).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Since observational studies generally include a treated population, it is difficult to describe the course of the disease in the untreated population, and to dissociate the effects of treatment from the natural history of the disease. The natural course of pediatric UC is considered more severe than that of adults. It is characterized by a widespread location at diagnosis and a high rate of disease extension, with one study reporting extensive colitis in 60% of the pediatric population after 6.5 years of follow-up (Duricova et al, 2014).

Data from patients in Denmark from 1982 to 2010 were compared with data from matched individuals from the general population. Patients diagnosed with UC in childhood (ages 0-19 years) had a 2.15-fold higher relative mortality (95% CI: 1.67-2.76) than patients diagnosed at 60-70 years (Jess et al, 2013b).

Important Co-morbidities:

In the pediatric UC patient population, certain medical conditions can coexist along with the disease. In the literature, there appears to be no evidence suggesting differences in such expected conditions between the pediatric and adult population. Hence, the co-morbidities listed for adult patients also apply to pediatric UC patients.

Indication: Ankylosing Spondylitis

Incidence:

Few studies examine the incidence and prevalence of AS. The incidence of AS is reported to be between 0.5 and 14 per 100,000 per year (Jacobs et al, 2008). Estimated rates of the incidence for AS vary significantly among populations. Specifically, a study from Norway reported an annual incidence of AS between the periods of 1982 to 1993 of 14.1 per year compared with 5.2 per year in the rest of the region (Bakland et al, 2005). A study from Greece reported that incidence rates were higher in the age group 35 to 44 years for men and in the age group 25 to 34 years for women. The age-adjusted mean annual incidence rate for the population aged ≥16 years of age was 1.5 cases per 100,000 inhabitants (Alamanos et al, 2006; Gabriel and Michaud, 2009).

Prevalence:

A systematic review of 10 studies estimated the prevalence of AS in Europe to be 0.25% (95% CI: 0.18-0.33) (Stolwijk et al, 2016). Similarly, another systematic literature review using 14 studies, estimated the prevalence of AS in Europe to be 23.8 per 10,000 (Dean et al, 2014). In Germany, the age-specific prevalence of self-reported doctor-diagnosed AS in the general population was reported as follows: age 18 to 44 years, 0.6%; age 45 to 64 years, 1.6%; age 65 to 74 years. 1.9%; age 75 to 79 years, 1.4%; total 1.1% (Westhoff et al, 2009). In Sweden, the point prevalence of AS was estimated at 0.18% in 2009 for the population aged 16-64 (Exarchou et al, 2015).

A US study using claims data from 1996-2009 for the population over age 18 estimated a point prevalence for AS of 1.07 per 1,000 (Curtis et al, 2016).

Demographics of the Population in the Ankylosing Spondylitis Indication – (Age, and Sex) and Risk Factors for the Disease:

The symptoms of the disease are usually first observed in late adolescence or early adulthood. A Swiss study that included 1,199 AS patients reported mean age of onset of symptoms as 26.3 years for men and 29.3 years for women (Ciurea et al, 2014). Symptoms begin after age 40 in 5% of patients (Taurog, 2011). The male-to-female ratio is approximately 3.8, based on a systematic literature review (Dean et al, 2014).

The risk factors associated with AS include being male, age (onset generally occurs in late adolescence or early adulthood), and having the human leukocyte antigen (HLA)-B27 gene (Ankylosing Spondylitis: Risk Factors, Mayo Clinic, 2017).

Main Existing Treatment Options:

The goal of treatment is to relieve pain and stiffness and to prevent or delay complications and spinal deformity. Ankylosing spondylitis treatment is most successful before the disease causes irreversible damage to joints. Medications used to treat this condition include:

- *NSAIDs*: These include naproxen and indomethacin and are the medications doctors most commonly used to treat AS to relive inflammation, pain, and stiffness.
- *Biologics*: These therapies block cytokines and help reduce pain, stiffness, and tender or swollen joints. Examples include IL-17 inhibitors (secukinumab and ixekizumab) and TNFα inhibitors (adalimumab, etanercept, infliximab, and golimumab).

- *Targeted synthetic DMARDs:* Upadacitinib is a JAK inhibitor approved for the treatment of AS.

Other forms of treatment include physical therapy and surgery if there is severe pain or joint damage or if a hip joint is damaged and needs to be replaced (Ankylosing Spondylitis: Treatments and Drugs, Mayo Clinic, 2016).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Since observational studies generally include a treated population it is difficult to describe the course of the disease in the untreated population, and to dissociate the effects of treatment from the natural history of the disease. Many people with AS have mild episodes of back pain that come and go. Symptoms can also be severe with ongoing pain accompanied by loss of flexibility of the spine. In the most severe cases, long-term inflammation leads to calcification that causes 2 or more bones of the spine to fuse (NIAMS, 2016). In the European population, it has been reported that 42% also had peripheral arthritis, enthesitis was present in 38% of AS patients, and uveitis in 24% (Benegas et al, 2012). In patients with severe involvement, which is approximately 33% of the AS population, most loss of function and damage occurs during the first 10 years of disease (Braun and Pincus, 2002).

A total of 677 patients with AS were followed at a hospital in Norway from 1977 to May 2009. Patients were matched by gender, age, and postal area to 3 controls from the general population. The crude mortality among patients with AS was 14.5% (98 patients); SMR was only significantly increased among male patients compared with female patients (1.63% vs. 1.38%, $p<0.001$). Circulatory disease was the most frequent cause of death (40.0%), followed by malignant (26.8%) and infectious (23.3%) diseases (Bakland et al, 2011).

Important Co-morbidities:

Co-morbidities that occur in AS patients include cardiac disorders including myocardial infarction and stroke, uveitis, interstitial lung disease and atypical fibrosis, bronchiectasis, renal amyloidosis, glomerulonephritis, osteopenia and osteoporosis, and depression (Mathieu et al, 2011; El Maghraoui, 2011; El Maghraoui, 2005; Carter and Lories, 2011; Hyphantis et al, 2013).

Indication: Psoriasis

Incidence:

Two studies from the US gave similar estimates for the incidence of psoriasis (78.9 per 100,000 person-years [95% CI: 75.0-82.9] and 82 per 100,000 person-years [95% CI: 77-89]), the latter estimate being confined to women) (Icen et al, 2009; Setty et al, 2007). An Italian study reported a much higher incidence rate of 230 per 100,000 person-years in 2005 (Vena et al, 2010). Using CPRD data, Springate et al (2017) reported the incidence of psoriasis in the UK as 129 per 100,000 person-years between 1999 and 2013.

Prevalence:

Psoriasis is a chronic inflammatory disease affecting 1% to 3% of the population. Approximately 15-20% of patients have extensive skin involvement or severe disease requiring systemic therapy (Abuabara et al, 2010).

According to the Global Burden of Disease (GBD) study, there were approximately 65 million people with psoriasis in 2016 (GBD, 2017). Prevalence estimates in the UK, using data from the CPRD, were 2.8% between 1999 and 2013 (Springate et al, 2017). Other countries in North-East and South Europe report higher values than the UK ranging from 3.20% in Italy to 8.50% in Norway. Prevalence estimates in the US range from 2.2% to 3.15% (Parisi et al, 2013). In a large, multinational, population-based survey of psoriasis and PsA patients in North America and Europe, the prevalence of psoriasis/PsA ranged from 1.4% to 3.3% (79% had psoriasis alone and 21% had PsA) (Lebwohl et al, 2014).

Findings from a nationally representative sample survey from the US that gathered data from 2009-2010 reported prevalence of psoriasis among adults aged 20 years and older as 3.2% (95% CI: 2.6-3.7). A total of 7.2 million US adults had psoriasis in 2010 and an estimated 7.4 million US adults were affected in 2013 (Rachakonda et al, 2014). Consistent results reporting overall prevalence of psoriasis as 3.1% were published in another national US study (Helmick et al, 2014).

Demographics of the Population in the Psoriasis Indication (Age, Sex, Ethnicity, and Geographical Location) and Risk Factors for the Disease

Age: All studies reviewed by Parisi et al, showed a similar trend of increasing psoriasis incidence with age up to 39 years. The incidence then reduced at the age of 40-49 years of age before increasing again with a second peak around 50-59 years of age in the UK and around 60-69 years of age in the US. Age-specific estimates of incidence decreased toward the end of life (Parisi et al, 2013).

Also, Parisi et al reviewed 14 studies of psoriasis prevalence at all ages and found there was an increasing trend with age. Psoriasis was uncommon before the age of 9 years, varying from 0% in Norway to 0.55% in the UK. Studies in Norway, Scotland, Spain, and Taiwan showed a first peak of psoriasis at either 20-29 or 30-39 years of age. Studies from the UK, Germany, Russia and the US showed an increasing trend with age until around 60 years, after which the prevalence reduced.

Sex: There is no agreement about whether the prevalence of psoriasis differs between men and women. Parisi et al. found no differences in the frequency of psoriasis between genders in Taiwanese children, in the US and Norway in adults, or in individuals of any age in the US, Taiwan, Norway, Spain, Scotland, and the UK. Other studies in Sweden, Germany, the US,

and Norway reported a slightly higher prevalence of psoriasis in female subjects. Studies in Denmark, Australia, and China show psoriasis to be more frequent in men than in women (Parisi et al, 2013).

Ethnicity: Reports from ethnically representative data in the US for patients between 20 and 59 years of age estimated the prevalence of psoriasis to be highest in the white population (3.6%), followed by African Americans (1.9%), Hispanics (1.6%), and other races (1.4%) from 2009 to 2010 (Rachakonda et al, 2014).

Geographical Location: A weak correlation between geographic latitude and psoriasis prevalence has been reported with psoriasis appearing to occur most frequently in northern European countries and least frequently in populations of eastern Asia (World Health Organization, Global Report on Psoriasis, 2016).

Risk factors for developing psoriasis include having a family history of the disease; about 40% of people with psoriasis have a family member with the disease. Another risk factor is having viral or bacterial infections. People with human immunodeficiency virus (HIV), as well as children and young adults with recurring infections, particularly strep throat, are more likely to develop psoriasis than people with healthy immune systems. Other identified risk factors include high stress levels, obesity, and smoking tobacco (Psoriasis: Risk Factors, Mayo Clinic, 2017). Genetics play a key role with several studies finding a strong association between psoriasis and HLA class I genes, located in the major histocompatibility complex (Eder et al, 2015).

Main Existing Treatment Options:

Psoriasis treatments aim to interrupt the cycle that causes an increased production of skin cells, thereby reducing inflammation and plaque formation as well as aiming to remove scales and smooth the skin. Psoriasis treatment can be divided into 3 main types: topical treatments, light therapy, and systemic medications.

- *Topical therapies*: This therapy includes creams and ointments that are applied to the skin. When the disease is more severe, creams are likely to be combined with oral medications or light therapy. These creams and ointments include topical corticosteroids which are the most frequently prescribed medications for psoriasis, vitamin D analogues, anthralin, topical retinoids calcineurin inhibitors, salicylic acid, coal tar, and moisturizers.
- *Light therapy*: This treatment works by exposing the skin to natural or artificial ultraviolet light.
- *Systemic medications (oral or injected medications)*: This therapy is used for patients with the moderate to the severe form of the disease and includes retinoids, methotrexate, hydroxyurea, phosphodiesterase 4 inhibitors (including apremilast), immunomodulator drugs (including azathioprine, cyclosporine, and leflunomide), biologics (including TNFα inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, and IL-23 inhibitors), and thioguanine (Psoriasis: Treatments and Drugs, Mayo Clinic, 2018).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Since observational studies generally include a treated population, it is difficult to describe the course of the disease in the untreated population, and to dissociate the effects of treatment from the natural history of the disease. In the UK, one study reported that 51.8% of patients, between the ages of 25 and 64 with at least 1 psoriasis diagnosis in the previous 2 years, had mild psoriasis (≤2% body surface area [BSA] affected), while moderate psoriasis (3-10% BSA) was found in 35.8% and 12.4% had severe psoriasis (>10% BSA) (Yeung et al, 2013). People with psoriasis may experience significant physical discomfort and some disability. Itching and pain can interfere with basic functions (NIAMSb, 2017). Potential complications include certain eye disorders, obesity, type 2 diabetes, high blood pressure, CVD, and other autoimmune diseases (Psoriasis: Mayo Clinic, 2017). Severity of disease has been shown to also affect the prevalence of certain co-morbidities, such as diabetes. People with severe disease are also at greater risk of developing renal disease (OR=1.83) and rheumatologic disease (OR=2.89) compared to those with mild disease, with OR of 0.97 and 2.01 for renal and rheumatologic disease, respectively (Yeung et al, 2013).

In the US, a mortality rate of 1.5% was reported in patients with hospital admission diagnosis of psoriasis (Pearce et al, 2006). In the UK, the risk of all-cause mortality for patients with psoriasis remains elevated compared with people without psoriasis (HR 1.21; 95% CI: 1.13-1.3) (Springate et al, 2017).

An independent risk of myocardial infarction in psoriasis patients may contribute to the increase in mortality in this population (Gelfand et al, 2006). Patients with psoriasis are more likely to demonstrate cardiovascular risk factors such as obesity, diabetes, hyperlipidemia, history of myocardial infarction, hypertension, and current smoking (Neimann et al, 2006; Gelfand et al, 2006).

A cohort study from 1987-2002 of patients ≥18 years was conducted in the General Practice Research Database (GPRD) in the UK. It was found that patients with severe psoriasis were at increased risk of death from CVD (HR: 1.57; 95% CI: 1.26-1.96), malignancies (HR: 1.41; 95% CI: 1.07-1.86), chronic lower respiratory disease (HR: 2.08; 95% CI: 1.24-3.48), diabetes (HR: 2.86; 95% CI: 1.08-7.59), dementia (HR: 3.64; 95% CI: 1.36-9.72), infection (HR: 1.65; 95% CI: 1.26-2.18). The absolute and excess risk of death was highest for CVD (61.9 and 3.5 per 1,000 patient-years respectively). The overall death rate per 1,000 patients was 26 (95% CI: 23-29). Overall, psoriasis patients died at a younger age than unexposed patients (mean age of 73 vs. 79 years respectively, $p<0.001$). The relationship was similar for all causes of death, even when the data were examined by sex. The largest differential in age at death was for kidney disease (Abuabara et al, 2010).

Important Co-morbidities:

Co-morbidities that occur in adult patients with psoriasis include PsA, IBD, non‑melanoma skin cancer (probably due to light therapy psoriasis), depression, uveitis, obesity, metabolic syndrome (or components of it), CVD, and type 2 diabetes (Pouplard et al, 2013; Psoriasis: Mayo Clinic, 2018).

Indication: Psoriatic Arthritis

Incidence:

A meta-analysis of 28 population studies reported a pooled incidence of PsA of 8.3 per 100,000 patient-years (95% CI: 4.1-16.7). Interstudy heterogeneity was high, with incidence ranging from 3.0 to 41.3 cases per 100,000 patient-years (Scotti et al, 2018). Psoriatic arthritis occurs in 6% to 42% of psoriasis cases (Li et al, 2012). The Adelphi Psoriasis Disease Specific program was a cross-sectional observational study conducted in the UK, Spain, France, Italy, and Germany in 2006. The incidence of PsA in the population of patients with psoriasis remained relatively constant, largely below 1% per year during the 30 years examined (74 per 1000 person-years) (Christophers et al, 2010).

A literature review found that the incidence of PsA was similar between 5 European studies and one US study where it ranged between 2 and 23.1 per 100,000 population. Population-based studies using the Classification of Psoriatic Arthritis group's criteria for PsA found an incidence between 6 and 7.2 per 100,000 persons in Denmark and the US, respectively (Tam et al, 2009).

Prevalence:

Scotti et al (2018) reported a pooled prevalence of PsA of 133 per 100,000 population, ranging from 20 to 670 cases per 100,000 population. Interstudy heterogeneity was high, with some of the differences being explained by PsA detection criteria. Christophers et al (2010) reported that PsA prevalence increased with time since psoriasis diagnosis, reaching 20.5% after 30 years. A systematic review of 10 studies estimated the prevalence of PsA in Europe to be 0.19% (95% CI: 0.16-0.32) (Stolwijk et al, 2016). A study was conducted using Kaiser Permanente Northern California Data. Patients included were adults with one or more ICD-9 diagnosis codes from PsA between 1996 and 2009. The number of persons with a diagnosis for PsA was 5,187 with a point prevalence of 12.6 (95% CI: 11.6-13.7) per 100,000 persons, standardized to age and sex distribution of the 2000 census on 31 Dec 2009. The point prevalence of PsA with or without psoriasis was 68 (95% CI: 54-84) per 100,000 (Asagari et al, 2013).

Ogdie et al (2013) used The Health Information Network (THIN) in the UK to conduct a cross-sectional study to determine the prevalence of PsA. Data were collected between 1994 and 2010. Among 4.8 million patients between 18 and 90 years of age, 9,045 patients had at least one medical code for PsA, giving an overall prevalence of 0.19% (95% CI: 0.185-0.193). The prevalence by age and sex are reported in the table below.

Prevalence by Age and Sex of PsA in the THIN Database (1994-2010)

	Men		Women		All	
Age	**PsA (n)**	**Prevalence (%)**	**PsA (n)**	**Prevalence (%)**	**PsA (n)**	**Prevalence (%)**
18-29	316	0.05	353	0.05	669	0.05
30-39	916	0.17	819	0.16	1735	0.16
40-49	1157	0.29	952	0.26	2109	0.28
50-59	1115	0.36	1092	0.36	2207	0.36
60-69	675	0.31	733	0.32	1408	0.31
70-80	334	0.23	380	0.20	714	0.21
80-90	75	0.12	128	0.10	203	0.11
All	4591	0.20	4461	0.18	9045	0.19

Globally, the prevalence of PsA is 0.04% to 1.2%, depending on the population studied (Gladman et al, 2005). A survey conducted in the US found the prevalence rate of PsA to be 0.25% in the general public and 11% among patients with psoriasis (Gelfand et al, 2005).

Demographics of the Population in the Psoriatic Arthritis Indication (Sex) and Risk Factors for the Disease:

Overall, men and women are affected by PsA with equal frequency, although the actual male:female ratio may vary depending upon the subset in question. The demographic profile is probably consistent with that of psoriasis.

Risk factors for PsA include having psoriasis, which is the single greatest risk factor for developing the condition. People who have psoriasis lesions on their nails are especially likely to develop PsA. Family history is also a risk factor for PsA, along with age. Most people have an onset between the ages of 30 and 50 (Psoriatic Arthritis: Risk Factors, Mayo Clinic, 2010.)

Main Existing Treatment Options:

No curative treatment exists for PsA so treatment focuses on controlling inflammation in the affected joints to prevent joint pain and disabilities. Medications used to treat PsA include:

- *NSAIDs*: These drugs help to control pain, swelling, and morning stiffness. NSAIDs are usually the first treatment tried for PsA and include ibuprofen and naproxen.
- *Conventional DMARDs*: Rather than just reducing pain and inflammation, this class of drugs helps limit the amount of joint damage that occurs in PsA patients. Examples of DMARDs include methotrexate, the most common used to treat PsA, sulfasalazine, and lefluonomide.
- *Targeted synthetic DMARDs:* Drugs that inhibit kinases such as JAK and can ease joint pain and swelling. JAK inhibitors include tofacitinib and upadacitinib.
- *Immunosuppressants*: These medications act to suppress the immune system which attacks healthy tissue in PsA patients. Commonly used immunosuppressants include azathioprine and cyclosporine.
- *Biologics*: These therapies block cytokines involved in the inflammatory process and include TNFα inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, and T-cell co-stimulation modulators (Psoriatic Arthritis: Treatments and Drugs, Mayo Clinic, 2017).
- *Phosphodiesterase inhibitors:* Apremilast is a phosphodiesterase 4 inhibitor that reduces inflammation.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Since observational studies generally include a treated population, it is difficult to describe the course of the disease in the untreated population, and to dissociate the effects of treatment from the natural history of the disease. Spondylitis (inflammation of the vertebra) has been reported to be present in 40% of PsA patients, and 87% have psoriatic lesions of the nail (Gladman et al, 2005). As the disease progresses 20% of patients develop a very destructive disabling form of arthritis and 47% sustain erosive changes after 2 years of disease (Gladman, 2009). It has been reported that for patients who have been followed for more than 10 years, 55% had 5 or more deformed joints (Gladman et al, 2005).

Patients who were entered into the PsA database at the Royal National Hospital for Rheumatic Diseases, Bath, between 1985 and 2007 were included in a study to examine mortality of PsA patients. Of 453 patients with PsA (232 men, 221 women), there were 37 deaths. Sixteen men and 21 women died. The SMR for men was 67.78% (95% CI: 38.79-110.22) for women, 97.01% (95% CI: 60.05-148.92) and the overall SMR for the PsA cohort was 81.82% (95% CI: 57.61-112.78). The leading causes of death in this cohort were CVD (38%), diseases of the respiratory system (27%), and malignancy (14%) (Buckley et al, 2010).

Mortality results from a literature review by Arumugam et al (2012) are illustrated in the table below.

Mortality in Psoriatic Arthropathy

Study and Location	Year Published	No. Patients	Controls	Findings
Coulton, UK	1989	40	N/A	No Deaths
Wong, Canada	1997	428	General Population	SMR 1.62
Shbeeb, US	2000	66	General Population	Similar survival
Alamanos, Greece	2003	221	N/A	4 deaths
Ali, Canada	2007	680	General Population	SMR 1.36
Wilson, US	2009	147	General Population	SME 0.91
Buckley, UK	2010	453	General Population	SMR 0.82

Important Co-morbidities:

Co-morbidities that occur in PsA patients include diabetes mellitus, obesity, metabolic syndrome (or components of it), CVD, IBD, uveitis, and depression (Haddad and Zisman, 2017).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings	Relevance to Human Usage
Toxicity	
Repeat-dose toxicity	
In chimpanzees, infliximab was well tolerated at doses up to 30 mg/kg per day for at least 3 consecutive days and at doses up to 15 mg/kg per day for at least 5 days. No infliximab-related signs of toxicity, hypersensitivity, immune system suppression, or infections were observed in these studies. In CD-1 mice treated intravenous (IV) with cV1q to determine the toxicity of chronic anti-TNFα antibody treatment, cV1q doses of up to 40 mg/kg administered weekly for 6 months were well tolerated. No effects of cV1q-related signs of toxicity were observed.	The nonclinical data did not identify any safety concerns for humans.
Reproductive toxicity	
Infliximab does not bind to human reproductive tissues in vitro. Fertility studies have not been conducted with infliximab. Fertility studies have been conducted in mice using cV1q. In the mouse fertility study, there was a slight reduction in the number of male mice that mated (91% vs. 100% in controls) and a reduction in the number of successful pregnancies (fertility index 76% vs. 92% in controls). This reduction is only slightly outside of the test facility historical background ranges and semen parameters (sperm motility, count and density) were not affected by treatment. Therefore, the apparent reduction in the fertility index was not considered to be due to a reduction in male fertility.	Results of reproductive toxicity studies suggest that inhibition of TNF is unlikely to adversely affect male or female fertility.
Developmental toxicity	
In pregnant mice dosed with cV1q there was no maternal toxicity and no developmental defects in the offspring. A slight reduction in the humoral immune response to sheep red blood cells was observed in the female offspring from mothers exposed to cV1q at 40 mg/kg weekly IV in one study, but this was not repeated in a second study.	The developmental studies conducted in mice with cV1q have shown no maternal toxicity and no developmental abnormalities in the offspring. Immunoglobulin G (IgG) antibodies are known to cross the human placenta. Because of this transfer it is expected that infants from infliximab treated mothers will have infliximab in their serum at birth and that TNF will be inhibited until the serum concentration fall below a pharmacologically relevant level. The safety implications of this to infants are not fully understood. However, based on the Marketing Authorization Holder's (MAH's)

Key Safety Findings	Relevance to Human Usage
	assessment of a number of spontaneous reports, Bacillus Calmette-Guerin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE is considered as an important identified risk. Infliximab may be secreted in small amounts in the breast milk. However, this is unlikely to contribute to significant infant systemic exposure because IgG antibodies are degraded in the gastrointestinal tract and are not absorbed across the gut.
Genotoxicity	
No clastogenic or mutagenic effects of infliximab were observed in the in vivo mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes.	The nonclinical data did not identify any safety concerns for humans
Carcinogenicity	
The risk of reduced tumor immune surveillance resulting in susceptibility to certain tumors (lymphomas and skin cancer) is a safety concern for immune modulating drugs in general. No tumors were detected in the nonclinical studies conducted with infliximab or cV1q. Rodent 2-year carcinogenicity studies have not been conducted because this bioassay is a poor predictor of malignancy due to immune suppression. Mice that have been genetically modified to lack TNF and wild type mice dosed with anti-mouse TNF inhibitors have not shown an increased incidence of tumors (Martin and Bugelski, 2012).	There is a risk of malignancy associated with administration of infliximab based on the clinical experience with TNF inhibitors and other immune suppressive drugs.
Other Toxicity-related Information or Data	
Infection	
The risk of infection is a safety concern for immune modulating drugs in general. Infection studies were not conducted with infliximab or cV1q. In the mouse developmental study there was a slight decrease in the humoral immune response to SRBCs. Published rodent studies suggest that inhibition of TNF may lead to a reduction in the host protective immune responses to viral, bacterial, intracellular protozoa, and fungal pathogens. (Martin and Bugelski, 2012)	The animal studies have shown that inhibition of TNF may be associated with a slight suppression of immune responses to certain antigenic challenges.

Summary of Nonclinical Safety Concerns

The following theoretical safety concerns (based on nonclinical data) have not been adequately refuted by clinical data:

Important identified risks	Serious infection/sepsis
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

REMICADE is approved across the globe for the treatment of CD (adult and pediatric), RA, UC (adult and pediatric), psoriasis, PsA, and AS; although not all indications have been approved in all countries. REMICADE is also approved in Japan for Behcet's disease and acute Kawasaki disease.

REMICADE is currently being studied or has been studied in a variety of indications including CD (adult and pediatric), RA (including juvenile rheumatoid arthritis [JRA]), UC (adult and pediatric), IBD (pediatric), multiple sclerosis (MS), sepsis, CHF, psoriasis, asthma, sarcoidosis, PsA, AS, chronic obstructive pulmonary disease (COPD), cancer-related cachexia, giant cell arteritis, Kawasaki disease, and Behcet's disease.

The development of REMICADE for the treatment of MS, JRA, cancer-related cachexia, sepsis, COPD, sarcoidosis, asthma, giant cell arteritis, and CHF has been discontinued. Clinical trials of REMICADE have included a formulation for IV administration and/or formulation for subcutaneous (SC) or intramuscular (IM) administration; however, the development of the SC/IM formulation is no longer being pursued.

SIII.2. Clinical Trial Exposure

The tables in SIII.1 through SIII.8 summarize exposure to REMICADE in clinical trials for approved and non-approved indications with Phase 3 trials and exposure in Phase 1/2 trials that supported the approved indications. Exposure is summarized by duration, by age and sex, by dose, and by ethnic origin.

Exposure in Randomized Blinded Clinical Trials

REMICADE exposure by duration; age and sex; dose level; and ethnic origin during the controlled portions of the clinical trials (as described above) are presented in Tables SIII.1, SIII.2, SIII.3, and SIII.4, respectively. Exposure data in clinical trials in pediatric CD and pediatric UC are not included in these tables as there were no controlled periods in these trials. For Table SIII.3, by dose level, it is not meaningful to combine all the clinical trial data because the dosages for the different indications were not the same; therefore, this category was omitted.

Across the controlled portions of all of the clinical trials, a total of 4,421 subjects were exposed to REMICADE. Of these 4,421 subjects, 3,129 were exposed to REMICADE for ≥14 weeks, 1,294 were exposed for ≥30 weeks, and 260 were exposed for ≥54 weeks.

Rheumatoid arthritis was the indication with the greatest exposure to REMICADE during the controlled portion of the clinical trials, both in the number of subjects treated and the total subject-years of follow-up. Across all indications, the majority of subjects received 3 mg/kg, 5 mg/kg, or 10 mg/kg REMICADE with the total number of subjects treated greatest on 5 mg/kg REMICADE. Across all indications, the majority of subjects treated were white females. Overall, 403 subjects were ≥65 years of age (Table SIII.2).

Table SIII.1: Summary of Subject-years of Follow-up During Controlled Portions of Clinical Trials by Infliximab Exposure; Treated Subjects Across Indications

	Subjects Treated	Total Subject-years of Follow-up
RA trials[a]		
Subjects treated with infliximab	1964	1757
Duration of infliximab exposure		
≥ 14 weeks	1627	1621
≥ 30 weeks	929	1279
≥ 54 weeks	260	533
Crohn's disease trials[b]		
Subjects treated with infliximab	488	298
Duration of infliximab exposure		
≥ 14 weeks	271	251
≥ 30 weeks	203	209
≥ 54 weeks	0	0
Psoriasis trials[c]		
Subjects treated with infliximab	1123	444
Duration of infliximab exposure		
≥ 14 weeks	570	221
≥ 30 weeks	0	0
≥ 54 weeks	0	0
Ulcerative colitis trials[d]		
Subjects treated with infliximab	483	333
Duration of infliximab exposure		
≥ 14 weeks	388	301
≥ 30 weeks	162	168
≥ 54 weeks	0	0
PsA trial (C0168T50)		
Subjects treated with infliximab	102	31
Duration of infliximab exposure		
≥ 14 weeks	76	24
≥ 30 weeks	0	0
≥ 54 weeks	0	0
AS trial (C0168T51)		
Subjects treated with infliximab	201	92
Duration of infliximab exposure		
≥ 14 weeks	197	91
≥ 30 weeks	0	0
≥ 54 weeks	0	0
JRA trial (C0168T32)		
Subjects treated with infliximab	60	16
Duration of infliximab exposure		
≥ 14 weeks	0	0
≥ 30 weeks	0	0
≥ 54 weeks	0	0
All trials		
Subjects treated with infliximab	4421	2972
Duration of infliximab exposure		
≥ 14 weeks	3129	2508
≥ 30 weeks	1294	1657
≥ 54 weeks	260	533

[a]C0168T09, C0168T14, C0168T15, C0168T22, C0168T29, C0168T41
[b]C0168T16, C0168T20, C0168T67
[c]C0168T31, C0168T38, C0168T44
[d]C0168T37, C0168T46

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Table SIII.2: Summary of Subject-years of Follow-up During Controlled Portions of Clinical Trials by Age and Sex; Treated Subjects Across Indications

	Male		Female	
	Subjects Treated[a]	Total Subject-years of Follow-up[b]	Subjects Treated[a]	Total Subject-years of Follow-up[b]
RA trials[c]				
Subjects treated with infliximab	492	454	1472	1303
Age (years)				
18 to 64	405	382	1266	1124
65 to 74	81	69	186	166
≥ 75	6	3	20	13
Crohn's disease trials[d]				
Subjects treated with infliximab	246	154	242	144
Age (years)				
18 to 64	240	150	241	143
65 to 74	6	5	0	0
≥ 75	0	0	1	1
Psoriasis trials[e]				
Subjects treated with infliximab	759	306	364	138
Age (years)				
18 to 64	723	291	337	127
65 to 74	34	13	19	8
≥ 75	2	1	8	3
Ulcerative colitis trials[f]				
Subjects treated with infliximab	293	198	190	135
Age (years)				
18 to 64	271	183	185	133
65 to 74	20	13	4	2
≥ 75	2	2	1	0
PsA trial (C0168T50)				
Subjects treated with infliximab	72	22	30	9
Age (years)				
18 to 64	67	21	26	8
65 to 74	5	2	2	1
≥ 75	0	0	2	1
AS trial (C0168T51)				
Subjects treated with infliximab	157	72	44	20
Age (years)				
18 to 64	154	71	43	20
65 to 74	3	1	1	0
≥ 75	0	0	0	0
JRA trial (C0168T32)				
Subjects treated with infliximab	7	2	53	14
Age (years)				
< 18	7	2	53	14
All trials				
Subjects treated with infliximab	2026	1208	2395	1764
Age (years)				
< 18	7	2	53	14
18 to 64	1860	1097	2098	1555
65 to 74	149	103	212	177
≥ 75	10	6	32	17

[a]Number of subjects who received infliximab during the controlled portion of the trial
[b]Time of follow-up starts with first dose of infliximab
[c]C0168T09, C0168T14, C0168T15, C0168T22, C0168T29, C0168T41
[d]C0168T16, C0168T20, C0168T67
[e]C0168T31, C0168T38, C0168T44
[f]C0168T37, C0168T46

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Table SIII.3: Summary of Subject-years of Follow-up During Controlled Portions of Clinical Trials by Dose Level; Treated Subjects Across Indications

	Subjects Treated	Total Subject-years of Follow-up
RA trials[a]		
Subjects treated with infliximab	1964	1757
< 3 mg/kg	54	15
3 mg/kg	933	863
5 mg/kg	7	2
6 mg/kg	374	387
10 mg/kg	589	488
> 10 mg/kg	7	2
Crohn's disease trials[b]		
Subjects treated with infliximab	488	298
5 mg/kg	400	283
10 mg/kg	60	13
> 10 mg/kg	28	2
Psoriasis trials[c]		
Subjects treated with infliximab	1123	444
3 mg/kg	411	153
5 mg/kg	712	291
Ulcerative colitis trials[d]		
Subjects treated with infliximab	483	333
5 mg/kg	241	167
10 mg/kg	242	165
PsA trial (C0168T50)		
Subjects treated with infliximab	102	31
5 mg/kg	102	31
AS trial (C0168T51)		
Subjects treated with infliximab	201	92
5 mg/kg	201	92
JRA trial (C0168T32)		
Subjects treated with infliximab	60	16
3 mg/kg	60	16

[a]C0168T09, C0168T14, C0168T15, C0168T22, C0168T29, C0168T41
[b]C0168T16, C0168T20, C0168T67
[c]C0168T31, C0168T38, C0168T44
[d]C0168T37, C0168T46

Adapted from [TSFEXPPC01A.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2013UPDATE\tsfexppc01a.sas] 15JUL2013, 22:15

Table SIII.4: Summary of Subject-years of Follow-up During Controlled Portions of Clinical Trials by Ethnic Origin; Treated Subjects Across Indications

	Subjects Treated[a]	Total Subject-years of Follow-up[b]
RA trials[c]		
Subjects treated with infliximab	1964	1757
Ethnic origin		
White	1676	1541
Black	66	65
Asian	18	17
Other	204	133
Crohn's disease trials[d]		
Subjects treated with infliximab	488	298
Ethnic origin		
White	431	253
Black	20	13
Asian	2	1
Other	5	3
Psoriasis trials[e]		
Subjects treated with infliximab	1123	444
Ethnic origin		
White	1052	415
Black	22	9
Asian	26	10
Other	23	10
Ulcerative colitis studies[f]		
Subjects treated with infliximab	483	333
Ethnic origin		
White	455	313
Black	7	6
Asian	8	4
Other	13	9
PsA study (C0168T50)		
Subjects treated with infliximab	102	31
Ethnic origin		
White	97	30
Black	2	0
Asian	3	1
Other	0	0
AS trial (C0168T51)		
Subjects treated with infliximab	201	92
Ethnic origin		
White	197	91
Black	2	1
Asian	2	1
Other	0	0
JRA trial (C0168T32)		
Subjects treated with infliximab	60	16
Ethnic origin		
White	50	13
Black	1	0
Asian	1	0
Other	6	2
All trials		
Subjects treated with infliximab	4421	2972
Ethnic origin		
White	3958	2656
Black	120	95
Asian	60	35
Other	251	158

[a]Number of subjects who received infliximab during the controlled portion of the trial
[b]Time of follow-up starts with first dose of infliximab
[c]C0168T09, C0168T14, C0168T15, C0168T22, C0168T29, C0168T41
[d]C0168T16, C0168T20, C0168T67
[e]C0168T31, C0168T38, C0168T44
[f]C0168T37, C0168T46

Table SIII.4: Summary of Subject-years of Follow-up During Controlled Portions of Clinical Trials by Ethnic Origin; Treated Subjects Across Indications

	Subjects Treated[a]	Total Subject-years of Follow-up[b]

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Exposure in All Clinical Trials Including Open Extensions

REMICADE exposure by duration; age and sex; dose level; and ethnic origin in the clinical trials (ie, clinical trials for approved and non-approved indications with Phase 3 trials and exposure in Phase 1/2 trials that supported the approved indications) through the end of the reporting period are presented in SIII.5, SIII.6, SIII.7, and SIII.8, respectively. For Table SIII.7, (exposure by dose level), it is not meaningful to combine all the clinical trial data because the dosages for the different indications are not the same; therefore, this category is omitted. Exposure data from the pediatric CD and pediatric UC trials are included in the tables in this section.

Across all trials, a total of 6,438 subjects were exposed to REMICADE. Of these 6,438 subjects, 4,068 were exposed to REMICADE for ≥30 weeks, 884 were exposed for ≥54 weeks, and 704 were exposed for ≥78 weeks.

Rheumatoid arthritis was the indication with the greatest exposure to REMICADE through the end of the reporting period, both in the number of subjects treated and total subject-years of follow-up. Across all indications, the majority of subjects received 3 mg/kg, 5 mg/kg, or 10 mg/kg REMICADE with the total number of subjects treated greatest on 5 mg/kg REMICADE. The majority of treated subjects across all indications were <65 years of age and white. The majority of treated subjects were female.

Table SIII.5: Summary of Subject-years of Follow-up by Infliximab Exposure; Treated Subjects Across Indications

	Subjects Treated	Total Subject-years of Follow-up
RA trials[a]		
Subjects treated with infliximab	2363	2430
Duration of infliximab exposure		
≥ 30 weeks	1581	1956
≥ 54 weeks	266	541
≥ 78 weeks	220	469
Crohn's disease trials[b]		
Subjects treated with infliximab	1427	1230
Duration of infliximab exposure		
≥ 30 weeks	749	779
≥ 54 weeks	41	48
≥ 78 weeks	0	0
Psoriasis trials[c]		
Subjects treated with infliximab	1373	1106
Duration of infliximab exposure		
≥ 30 weeks	867	800
≥ 54 weeks	0	0
≥ 78 weeks	0	0
Ulcerative colitis trials[d]		
Subjects treated with infliximab	493	833
Duration of infliximab exposure		
≥ 30 weeks	273	730
≥ 54 weeks	210	666
≥ 78 weeks	200	651
PsA trial (C0168T50)		
Subjects treated with infliximab	191	157
Duration of infliximab exposure		
≥ 30 weeks	113	110
≥ 54 weeks	0	0
≥ 78 weeks	0	0
AS trial (C0168T51)		
Subjects treated with infliximab	275	464
Duration of infliximab exposure		
≥ 30 weeks	255	445
≥ 54 weeks	225	410
≥ 78 weeks	158	310
JRA trial (C0168T32)		
Subjects treated with infliximab	117	270
Duration of infliximab exposure		
≥ 30 weeks	94	253
≥ 54 weeks	75	236
≥ 78 weeks	69	226
Pediatric Crohn's disease trials[e]		
Subjects treated with infliximab	139	226
Duration of infliximab exposure		
≥ 30 weeks	102	213
≥ 54 weeks	66	178
≥ 78 weeks	57	166
Pediatric ulcerative colitis trial (C0168T72)		
Subjects treated with infliximab	60	44
Duration of infliximab exposure		
≥ 30 weeks	34	35
≥ 54 weeks	1	1
≥ 78 weeks	0	0
All trials		
Subjects treated with infliximab	6438	6760
Duration of infliximab exposure		
≥ 30 weeks	4068	5322
≥ 54 weeks	884	2080
≥ 78 weeks	704	1821

[a]C0168T07, C0168T09, C0168T14, C0168T15/T17, C0168T18, C0168T22, C0168T29, C0168T41
[b]C0168T08, C0168T11, C0168T16, C0168T20, C0168T21, C0168T26, C0168T67
[c]C0168T31, C0168T38, C0168T44
[d]C0168T12, C0168T37, C0168T46
[e]C0168T23, C0168T47, C0168T55

Adapted from [TSFEXPRP00A.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2013UPDATE\tsfexprp00a.sas] 15JUL2013, 22:16

Table SIII.6: Summary of Subject-years of Follow-up by Age and Sex; Treated Subjects Across Indications

	Male		Female	
	Subjects Treated[a]	Total Subject-years of Follow-up[b]	Subjects Treated[a]	Total Subject-years of Follow-up[b]
RA trials[c]				
Subjects treated with infliximab	563	581	1800	1849
Age (years)				
18 to 64	468	486	1550	1593
65 to 74	87	88	222	230
≥ 75	8	7	28	26
Crohn's disease trials[d]				
Subjects treated with infliximab	673	578	754	652
Age (years)				
18 to 64	654	560	743	642
65 to 74	17	15	8	8
≥ 75	1	1	3	2
Psoriasis trials[e]				
Subjects treated with infliximab	943	758	430	348
Age (years)				
18 to 64	897	721	401	325
65 to 74	44	35	21	17
≥ 75	2	2	8	6
Ulcerative colitis trials[f]				
Subjects treated with infliximab	301	499	192	334
Age (years)				
18 to 64	279	465	187	329
65 to 74	20	33	4	4
≥ 75	2	2	1	0
PsA trial (C0168T50)				
Subjects treated with infliximab	116	98	75	59
Age (years)				
18 to 64	108	91	68	53
65 to 74	8	8	5	4
≥ 75	0	0	2	2
AS trial (C0168T51)				
Subjects treated with infliximab	222	374	53	91
Age (years)				
18 to 64	218	366	52	89
65 to 74	4	7	1	2
≥ 75	0	0	0	0
JRA trial (C0168T32)				
Subjects treated with infliximab	17	38	100	232
Age (years)				
< 18	17	38	100	232
Pediatric Crohn's disease trials[g]				
Subjects treated with infliximab	83	138	56	88
Age (years)				
< 18	83	138	56	88
Pediatric ulcerative colitis trial (C0168T72)				
Subjects treated with infliximab	28	19	32	24
Age (years)				
< 18	28	19	32	24
All trials				
Subjects treated with infliximab	2946	3083	3492	3676
Age (years)				
< 18	128	195	188	345
18 to 64	2624	2689	3001	3031
65 to 74	180	187	261	265
≥ 75	13	12	42	36

[a]Number of subjects who received infliximab during trial
[b]Time of follow-up starts with first dose of infliximab
[c]C0168T07, C0168T09, C0168T14, C0168T15/T17, C0168T18, C0168T22, C0168T29, C0168T41
[d]C0168T08, C0168T11, C0168T16, C0168T20, C0168T21, C0168T26, C0168T67
[e]C0168T31, C0168T38, C0168T44
[f]C0168T12, C0168T37, C0168T46
[g]C0168T23, C0168T47, C0168T55

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Table SIII.7: Summary of Subject-years of Follow-up by Dose Level; Treated Subjects Across Indications

	Subjects Treated	Total Subject-years of Follow-up
RA trials[a]		
Subjects treated with infliximab	2363	2430
< 3 mg/kg	32	13
3 mg/kg	1187	1175
5 mg/kg	114	116
5 mg/kg dose escalation	9	6
6 mg/kg	377	390
10 mg/kg	620	718
> 10 mg/kg	24	11
Crohn's disease trials[b]		
Subjects treated with infliximab	1427	1230
< 3 mg/kg	5	1
5 mg/kg	992	867
5 mg/kg dose escalation	107	106
10 mg/kg	238	184
> 10 mg/kg	85	71
Psoriasis trials[c]		
Subjects treated with infliximab	1373	1106
3 mg/kg	411	332
5 mg/kg	962	774
Ulcerative colitis trials[d]		
Subjects treated with infliximab	493	833
5 mg/kg	245	423
10 mg/kg	246	409
> 10 mg/kg	2	0
PsA trial (C0168T50)		
Subjects treated with infliximab	191	157
5 mg/kg	176	141
5 mg/kg dose escalation	15	16
AS trial (C0168T51)		
Subjects treated with infliximab	275	464
5 mg/kg	169	273
5 mg/kg dose escalation	106	191
JRA trial (C0168T32)		
Subjects treated with infliximab	117	270
3 mg/kg	60	139
6 mg/kg	57	131
Pediatric Crohn's disease trials[e]		
Subjects treated with infliximab	139	226
< 3 mg/kg	6	4
5 mg/kg	125	216
10 mg/kg	8	6
Pediatric ulcerative colitis trial (C0168T72)		
Subjects treated with infliximab	60	44
5 mg/kg	60	44

[a]C0168T07, C0168T09, C0168T14, C0168T15/T17, C0168T18, C0168T22, C0168T29, C0168T41
[b]C0168T08, C0168T11, C0168T16, C0168T20, C0168T21, C0168T26, C0168T67
[c]C0168T31, C0168T38, C0168T44
[d]C0168T12, C0168T37, C0168T46
[e]C0168T23, C0168T47, C0168T55

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Table SIII.8: Summary of Subject-years of Follow-up by Ethnic Origin; Treated Subjects Across Indications

	Subjects Treated[a]	Total Subject-years of Follow-up[b]
RA trials[c]		
Subjects treated with infliximab	2363	2430
Ethnic origin		
White	1987	2066
Black	76	79
Asian	27	23
Other	273	262
Crohn's disease trials[d]		
Subjects treated with infliximab	1427	1230
Ethnic origin		
White	1336	1152
Black	39	33
Asian	7	6
Other	15	12
Psoriasis trials[e]		
Subjects treated with infliximab	1373	1106
Ethnic origin		
White	1283	1036
Black	27	21
Asian	32	26
Other	31	23
Ulcerative colitis trials[f]		
Subjects treated with infliximab	493	833
Ethnic origin		
White	465	793
Black	7	16
Asian	8	10
Other	13	14
PsA trial (C0168T50)		
Subjects treated with infliximab	191	157
Ethnic origin		
White	180	150
Black	5	3
Asian	3	2
Other	3	2
AS trial (C0168T51)		
Subjects treated with infliximab	275	464
Ethnic origin		
White	269	453
Black	2	4
Asian	2	4
Other	2	3
JRA trial (C0168T32)		
Subjects treated with infliximab	117	270
Ethnic origin		
White	99	244
Black	2	4
Asian	2	6
Other	10	12
Pediatric Crohn's disease trials[g]		
Subjects treated with infliximab	139	226
Ethnic origin		
White	119	185
Black	17	32
Asian	1	3
Other	2	5
Pediatric ulcerative colitis trial (C0168T72)		
Subjects treated with infliximab	60	44
Ethnic origin		
White	49	37
Black	5	3
Asian	3	2
Other	3	2

Table SIII.8: Summary of Subject-years of Follow-up by Ethnic Origin; Treated Subjects Across Indications

	Subjects Treated[a]	Total Subject-years of Follow-up[b]
All trials		
Subjects treated with infliximab	6438	6760
Ethnic origin		
White	5787	6116
Black	180	193
Asian	85	82
Other	352	336

[a]Number of subjects who received infliximab during trial
[b]Time of follow-up starts with first dose of infliximab
[c]C0168T07, C0168T09, C0168T14, C0168T15/T17, C0168T18, C0168T22, C0168T29, C0168T41
[d]C0168T08, C0168T11, C0168T16, C0168T20, C0168T21, C0168T26, C0168T67
[e]C0168T31, C0168T38, C0168T44
[f]C0168T12, C0168T37, C0168T46
[g]C0168T23, C0168T47, C0168T55

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion: Had a known allergy to murine or chimeric proteins.	
Reason for being an exclusion criterion	It would not be appropriate to put subjects at risk of allergic reactions by enrolling subjects into infliximab clinical trials if they have a history of hypersensitivity to infliximab, to other murine proteins, or to any of the excipients.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	REMICADE is contraindicated in patients with a history of hypersensitivity to infliximab, to other murine proteins, or to any of the excipients (SmPC section 4.3). This criterion is therefore not considered appropriate for further study under the category of missing information.
Criterion: Had an active infection	
• **Serious infection (eg, hepatitis, pneumonia, pyelonephritis) within the time period specified in the protocol (eg, 2 or 3 months prior to screening).** • **Active tuberculosis (TB) at any time or within the time period specified in the protocol prior to the trial (with the exception of 2 trials that allowed subjects with a history of active TB to enter the trial if treatment had been completed at least 2 years before entering the trial).** • **Opportunistic infection (eg, cytomegalovirus, pneumocystis carinii, aspergillosis, histoplasmosis, or myocbacteria other than TB) within the time period specified in the protocol (eg, 2 or 6 months prior to screening).** • **Chronic or recurrent infectious disease**	

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Reason for being an exclusion criterion	Anti-TNFα agents have been associated with an increased risk of serious infection including TB, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections; these infections are considered a class effect of anti-TNFα agents.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	REMICADE is contraindicated in patients with TB or other severe infections such as sepsis, abscesses, and opportunistic infections (SmPC section 4.3). The SmPC indicates that caution should be exercised when considering the use of REMICADE in patients with chronic infection or a history of recurrent infection (section 4.4). Moreover, evaluation of the risk of infection with the use of REMICADE has led to the designation of 'Serious infection/sepsis' as an important identified risk in the RMP. This criterion is therefore not considered appropriate for further study under the category of missing information.
Criterion: Had concomitant CHF, including medically controlled, asymptomatic patients.	
Reason for being an exclusion criterion	REMICADE has been studied in subjects with stable Class III or IV CHF due to systolic dysfunction. Results of the trial suggested that infliximab at doses of 5 and 10 mg/kg did not improve clinical status in patients with moderate to severe heart failure. The data also suggested that the 10 mg/kg dose was associated with an increased risk of hospitalization for worsening heart failure and death. Based on the results of this study, subjects with CHF were excluded from all subsequent clinical trials. Congestive heart failure is considered a class effect for anti-TNFα agents.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	REMICADE is contraindicated in patients with moderate to severe heart failure (New York Heart Association Class III/IV) (SmPC section 4.3). REMICADE should be used with caution in patients with mild heart failure (SmPC section 4.4). This criterion is therefore not considered appropriate for further study under the category of missing information.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion: Had a history of latent TB or had a history of latent TB without treatment initiated prior to the first infusion.	
Reason for being an exclusion criterion	Treatment with anti-TNFα agents may increase the risk of the development of infections or worsen an existing infection.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	Evaluation of the risk associated with the use of REMICADE has led to the designation of 'Serious infection/sepsis', which includes the risk of TB, as an important identified risk in the RMP. Moreover, the SmPC indicates that caution should be exercised when considering the use of REMICADE in patients with chronic infection or a history of recurrent infection (section 4.4). This criterion is therefore not considered appropriate for further study under the category of missing information.
Criterion: Had documented/were known to have HIV infection.	
Reason for being an exclusion criterion	Treatment with anti-TNFα agents may increase the risk of the development of infections or worsen an existing infection.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	Given the immunosuppressive action of REMICADE, it would not be appropriate to put patients at risk of worsening disease by studying the use of REMICADE in patients with a history of HIV infection. The SmPC indicates that caution should be exercised when considering the use of REMICADE in patients with chronic infection or a history of recurrent infection (section 4.4). This criterion is therefore not considered appropriate for further study under the category of missing information.
Criterion: Had a history of chronic or recurrent infectious disease.	
Reason for being an exclusion criterion	Treatment with anti-TNFα agents may increase the risk of the development of infections or worsen an existing infection.
Considered to be included as missing information: Yes/No	No.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	Given the immunosuppressive action of REMICADE, it would not be appropriate to put patients at risk of worsening disease by studying the use of REMICADE in patients with a history of chronic or recurrent infectious disease. The SmPC indicates that caution should be exercised when considering the use of REMICADE in patients with chronic infection or a history of recurrent infection (section 4.4). This criterion is therefore not considered appropriate for further study under the category of missing information.
Criterion: Had severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurological, or cerebral disease.	
Reason for being an exclusion criterion	This is a typical, prudent, precautionary position applied to clinical trial subjects when a drug was not widely used in humans.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	In subjects with severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurological, or cerebral disease, the benefit/risk balance of the use of REMICADE should be carefully evaluated on a case-by-case basis. The impracticalities of identifying patients with similar progressive concomitant disease in each of these categories precludes the further study of REMICADE in this patient population. This criterion is therefore not considered appropriate for further study under the category of missing information.
Criterion: Had a history of lymphoproliferative disease, including lymphoma, or signs suggestive of possible lymphoproliferative disease such as lymphadenopathy of unusual size or location, or splenomegaly.	
Reason for being an exclusion criterion	Use of anti-TNFα agents has been associated with the occurrence of lymphoma.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	Evaluation of the risk associated with the use of REMICADE has led to the designation of ‘Malignancy’ as an important identified risk in the RMP. The risk of developing lymphomas or other malignancies in patients treated with anti-TNFα agents is described in the SmPC (section 4.4). This criterion is therefore not considered appropriate for further study under the category of missing information.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion: Had a history of malignancy within the past 5 years (with the exception of squamous or basal cell carcinoma that has had been treated with no evidence of recurrence).	
Reason for being an exclusion criterion	Published literature suggests that certain types of malignancies may be adversely affected by TNFα blockade. The potential role of TNF-blocking therapy in the development of certain types of malignancies is not known.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	Evaluation of the risk associated with the use of REMICADE has led to the designation of 'Malignancy' as an important identified risk in the RMP. As indicated in the SmPC (section 4.4), caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy. This criterion is therefore not considered appropriate for further study under the category of missing information.
Criterion: Had a history of known demyelinating diseases such as multiple sclerosis.	
Reason for being an exclusion criterion	Anti-TNFα agents have been associated with demyelinating diseases (central and peripheral) and these events are considered a class effect for these agents.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	Evaluation of the risk associated with the use of REMICADE had led to the designation of 'Demyelinating disorders' as an important identified risk. As indicated in the SmPC (section 4.4), the benefits and risks of anti-TNFα treatment should be carefully considered before initiation of REMICADE therapy in patients with pre-existing or recent onset of demyelinating disorders. This criterion is therefore not considered appropriate for further study under the category of missing information.
Criterion: Had received any therapeutic agent targeted at reducing TNF at any time prior to the trial or within 3 months prior to the trial.	
Reason for being an exclusion criterion	To reduce the risk of adverse events associated with concomitant immunosuppressants and to evaluate baseline disease level, the previous use of anti-TNFα agents was prohibited or required a washout period.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	Published literature in the RA population indicate an increase in adverse events, with no increase in efficacy, when biologics are used in combination for the treatment of disease (Genovese et al, 2004; Weinblatt et al, 2006). As indicated in the SmPC (section 4.4) care should be taken, and patients should continue to be monitored, when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse events, including infection. Therefore, this criterion is not considered as missing information.
Criterion: Had received an immunosuppressive agent that is used to treat the disease under study (eg, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, chlorambucil, cyclophosphamide, nitrogen mustard) within the time period specified in the protocol prior to the trial.	
Reason for being an exclusion criterion	To reduce the risk of adverse events associated with concomitant immunosuppressants and to evaluate baseline disease level, these agents were prohibited or required a washout period.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	Published literature suggests an increase in adverse events, with no increase in efficacy, when biologics are used in combination with other immunosuppressive agents (Genovese et al, 2004; Weinblatt et al, 2006). The risk of immunosuppression with REMICADE and interactions with other medicinal products are addressed in the SmPC (sections 4.4 and 4.5). Therefore, this criterion is not considered as missing information.
Criterion: Were pregnant, nursing, or planning a pregnancy (both men and women) within the time period specified in the protocol (eg, within 18 months of enrollment).	
Reason for being an exclusion criterion	The effect of REMICADE on pregnancy, human sperm, the developing fetus, and lactating women is not known except as noted with agranulocytosis and infection.
Considered to be included as missing information: Yes/No	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	Exposure during pregnancy The risk of REMICADE use during pregnancy is addressed in the SmPC (section 4.6). Exposure during pregnancy is not considered appropriate for further study under the category of missing information. Use of drug during lactation Periodic analysis of medically confirmed cases of REMICADE exposure through lactation has revealed no specific safety concerns. Treatment guidelines acknowledge the limited biological plausibility for adverse events to be linked to the transfer of drug via breast milk. The use of REMICADE during lactation is therefore not considered as missing information. Guidance for the use of REMICADE during breast-feeding is provided in the SmPC (section 4.6).
Criterion: Had a known substance abuse (drug or alcohol) abuse within the time period specified in the protocol prior to the trial.	
Reason for being an exclusion criterion	These subjects may not have been able to comply with the requirements of a clinical trial and were not appropriate for enrollment.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	Poor adherence to treatment among individuals engaged in substance abuse is well documented and so it would not be appropriate to study the use of REMICADE in this population. This criterion is therefore not considered as missing information.
Criterion: Had a transplanted organ (with the exception of a corneal transplant >3 months prior to screening).	
Reason for being an exclusion criterion	The risk of concomitant major immunosuppression was unclear at the start of the clinical development program.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	Patients with transplanted organs are generally receiving other immunosuppressants and so it would not be appropriate to put these patients at risk by studying the use of REMICADE in this population. This criterion is therefore not considered as missing information.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions due to prolonged exposure, adverse reactions due to cumulative effect, and adverse reactions that have a long latency.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table SIV.1: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breast-feeding women	Although prohibited by protocol, exposure to REMICADE during pregnancy occurred. However, because drug exposure during pregnancy is not considered an adverse event, exposure data cannot be extracted from the clinical trial database. Therefore, the exact number of reports of pregnancy in subjects exposed to REMICADE in clinical trials is unknown.
Patients with relevant co-morbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	In the REMICADE clinical trials, 5787/6438 (89.9%) of treated subjects were white.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Elderly	Of 6,438 subjects treated with REMICADE in clinical trials, 496 were ≥65 years old. Of these 496 subjects, 55 were ≥75 years old.
Children	Of 6,438 subjects treated with REMICADE in clinical trials, 316 were <18 years old.

Summary of Missing Information Due to Limitations of the Clinical Trial Program

None.

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method Used to Calculate Exposure

Estimates of patients exposed to commercial REMICADE (infliximab) cumulatively since launch (ie, cumulative patient exposure) are presented in this section. These numbers include patients exposed only in the setting of commercial use (including registries, postmarketing surveillance studies, and epidemiology studies) and do not include patients exposed to non-commercial drug, that is, Company-sponsored studies and investigator-initiated studies using Company-provided study drug.

The patient exposure estimates for commercially used drug are calculated using models generated by the market research departments at the Company and its sister companies in the US, Canada, and remaining countries around the world which are not the responsibility of its 2 distributors: Mitsubishi-Tanabe is responsible for Indonesia, Japan, and Taiwan; Merck Sharp & Dohme is responsible for Albania, Belarus, European Union (EU), Iceland, Norway, Russia, Switzerland, the UK, the former Yugoslavia, and Turkey. A model has been developed for each indication and has been refined over time as usage has changed and as the companies have come to understand this usage better. These models incorporate various usage patterns identified in physician surveys and other market research, such as known vial sales (100 mg infliximab each) in each indication with both current, labeled, and actual doses used, patient weight, age, dose, frequency of infusions, and proportion of patients treated during a period who were newly exposed vs. previously exposed.

Caveats should be noted when reviewing the methodologies used to estimate exposure numbers. The dose of REMICADE (infliximab) varies by indication and sometimes even within indication. Likewise, marketed indications vary by country. Deriving estimates of patient exposure requires making assumptions about both dose and retreatment use by disease and by country. Although attempts are made to calculate accurate exposure numbers, it is imperative that these exposure numbers be regarded as estimates only.

Considerations used in the market research models include variations in dosing regimens for each indication:

- In RA, the indicated dose of REMICADE is the same in the 4 major markets (the EU, the US, Canada, and Japan): 3 mg/kg, starting with an induction regimen with infusions at 0, 2, and 6 weeks followed by maintenance infusions every 8 weeks thereafter. Current labeling in all 4 major markets recommends an increase to as high as 10 mg/kg (US, Canada, Japan) and 7.5 mg/kg (EU) in patients not responding to 3 mg/kg or for a shortening of the interval to 4 weeks.
- In CD, the indicated dose of REMICADE is the same in all 4 major markets (the EU, the US, Canada, and Japan): 5 mg/kg, starting with an induction regimen (infusions at Weeks 0, 2, and 6) followed by maintenance infusions every 8 weeks thereafter. The labels in the US, Canada, and Japan also allow an increase in dose to 10 mg/kg for patients not responding to 5 mg/kg and the Japanese label allows for the dosing interval to be shortened to 4 weeks. The EU label notes some patients may regain response with dose escalation but does not explicitly recommend dose escalation or a dose to use in such cases. The EU label also allows for episodic (on demand) retreatment. REMICADE is indicated in

pediatric CD in the EU, the US, and Canada. The indicated dose is the same as the adult dose.

- In AS, REMICADE is indicated in all 4 of the major markets (the EU, the US, Canada, and Japan). In all 4 markets, the indicated induction dose is 5 mg/kg given at Weeks 0, 2, and 6. In the EU, Canada, and Japan, maintenance infusions are to be given every 6 to 8 weeks thereafter; whereas in the US, maintenance infusions are to be given every 6 weeks.
- In PsA, the indicated dose of REMICADE is identical in the EU, the US, Canada, and Japan: 5 mg/kg to be given as a 3-dose induction at Weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks thereafter. The Japanese label allows for increasing the dose to 10 mg/kg or shortening the interval to every 4 weeks in patients not responding to 5 mg/kg.
- In psoriasis, the indicated dose of REMICADE is identical in the EU, the US, Canada, and Japan: 5 mg/kg to be given as a 3-dose induction at Weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks thereafter. The Japanese label allows for increasing the dose to 10 mg/kg or shortening the interval to every 4 weeks in patients not responding to 5 mg/kg.
- In UC, the indicated dose of REMICADE is identical in the EU, the US, Canada, and Japan: 5 mg/kg to be given as a 3-dose induction at Weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks thereafter. The Canadian label allows for increasing the dose to 10 mg/kg in patients not responding to 5 mg/kg. REMICADE is indicated in pediatric UC in the EU, the US, and Canada. The indicated dose is 5 mg/kg.
- REMICADE is indicated for the treatment of refractory retinouveitis associated with Behcet's disease, neuro-, and vasculo-Behcet's disease in Japan, where the indicated dose of REMICADE is 5 mg/kg with the induction dosing regimen at Weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks thereafter. Except for refractory retinouveitis associated with Behcet's disease, the Japanese label allows for increasing the dose to10 mg/kg in patients with an inadequate response or loss of response to 5 mg/kg. REMICADE is also indicated for the treatment of intestinal/entero-Behcet's disease in Japan, Thailand, and South Korea.
- REMICADE is indicated for the treatment of Kawasaki's disease in Japan, where the indicated dose of REMICADE is 5 mg/kg as a single dose. REMICADE is not indicated for Kawasaki's disease elsewhere.

SV.1.2. Exposure

Table SV.1: Cumulative (24 August 1998 to 23 August 2022) Commercial Vials of REMICADE Sold BY REGION

	Region							
	EU/N	US	Canada	Japan	India	Saudi Arabia	RoW	Total
Number of vials sold	CCI							

Key: EU/N=European Union/Norway, RoW=Rest of World; US=United States.

Between the first commercial launch (24 August 1998) and 23 August 2022, a total of 212,070,782 vials of REMICADE (infliximab) were sold worldwide. The exposure to commercial REMICADE during this period is estimated to be 3,139,819 patients and approximately 9,598,206 patient-years.

Table SV.2: Estimated Cumulative Commercial Patient Exposure to REMICADE From the First Commercial Launch (24 August 1998) to 23 August 2022 BY INDICATION

	RA	CD	AS	PsA	PSO	UC	Other	Total
EU/N	CCI							
US								
Canada								
Japan								
India								
Saudi Arabia								
RoW								
Worldwide TOTAL	**1,046,717**	**1,056,285**	**148,355**	**246,390**	**87,118**	**535,253**	**19,701**	**3,139,819**

Key: AS=Ankylosing Spondylitis; CD=Crohn's Disease; EU/N=European Union/Norway; PSA=Psoriatic Arthritis; PSO=Psoriasis; RA=Rheumatoid arthritis; RoW=Rest of World, UC=Ulcerative Colitis; US=United States

Table SV.3: Estimated Cumulative Commercial Patient Exposure to REMICADE From the First Commercial Launch (24 August 1998) to 23 August 2022 BY INDICATION and EU REGION

	RA	CD	AS	PsA	PSO	UC	Other	Total
EU/N TOTAL	CCI							
Austria								
Baltics								
Belg/Lux								
Bulgaria								
Croatia[a]								
Czech Rep								
Denmark								
Finland								
France								
Germany								
Greece/Cyprus								
Hungary								
Italy								
Malta								
Netherlands								
Norway								
Poland								
Portugal								
Romania								
Slovakia								
Slovenia								
Spain								
Sweden								
UK/Ireland								

Key: AS=Ankylosing Spondylitis; Belg/Lux=Belgium/Luxemburg; CD=Crohn's Disease; EU/N=European Union/Norway; PSA=Psoriatic Arthritis; PSO=Psoriasis; RA=Rheumatoid arthritis; UC=Ulcerative Colitis; UK=United Kingdom.

a: Cumulative figures for Croatia include 2014 forward and do not include figures prior to 2014.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

No trials have been conducted to evaluate dependence potential of REMICADE. The available data suggest that REMICADE is unlikely to cause dependence. Drugs with abuse potential generally include drugs that affect the central nervous system, drugs that are chemically or pharmacologically similar to other drugs with known abuse potential, and drugs that produce psychoactive effects such as sedation, euphoria, or mood change (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidance for Industry, [FDA, 1997]). There is no known potential for misuse for illegal purposes.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks:

- Serious infection/sepsis
- BCG breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE
- Demyelinating disorders
- Malignancy

Important potential risks:

- Colon carcinoma/dysplasia (in pediatric UC)

Missing information: None

For the characterization of each risk in section SVII.3.1, clinical trial, epidemiological, and/or postmarketing data are included as applicable and as available.

Clinical trial data are presented in tabular format for relevant events which have been reported during REMICADE clinical trials. The tables show the frequency (reporting rate) of events across indications for the ‘All Randomized, Blinded Trials Population’ (controlled period) and for the ‘All Clinical Trials Population’ (controlled and uncontrolled periods).

Tables are not provided for risks for which no events were reported in REMICADE clinical trials.

Analyses presented in the tables include incidence, odds ratio, and 95% CI of subjects with relevant events in the clinical trials as well as seriousness, outcome, and severity. The odds ratio was not calculated if no events were reported in either the REMICADE or the placebo/comparator group or if the total number of events in the REMICADE and the placebo/comparator groups was ≤5.

The World Health Organization Adverse Reaction Terminology (WHOART) dictionary was used to code the clinical trial adverse event information that is summarized in this Module.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk – Serious Infection/Sepsis

Potential Mechanisms:

TNFα is a mediator of cellular immune responses and inflammation, which are important in host defense against certain pathogens, especially intracellular pathogens (Hehlgans and Pfeffer, 2005). Anti-TNFα agent therapy reduces the ability to mount an inflammatory response against such pathogens. REMICADE may therefore allow reactivation of hepatitis B and inhibit protective immune responses to intracellular bacteria (including mycobacteria) and opportunistic infections. Sepsis constitutes a systemic response to infection which is characterized by both a pro-inflammatory response mediated by cytokines such as TNF and IL-1 and an anti-inflammatory indicated by the expression of IL-10 and TGF-beta (Hehlgans and Pfeffer, 2005). In animal models of abdominal sepsis such as cecal ligation and puncture, the injection of TNF can be beneficial by preventing a bacterial superinfection (Hehlgans and Pfeffer, 2005). Hence inhibition of TNF by REMICADE may increase the potential for bacterial infection to become systemic.

Evidence Source(s) and Strength of Evidence:

REMICADE acts by inhibiting the activity of TNFα and reduces the immune response and inflammation in the body. Patients may therefore get infections more easily when receiving treatment with REMICADE. These infections may be serious and may, in rare cases, be life-threatening.

Serious infections/sepsis, including opportunistic infections, TB, and hepatitis B reactivation, have been reported in patients treated with REMICADE in clinical trials and in the postmarketing setting. These findings are consistent with published medical literature and experience with other medicines that also act by inhibiting TNF.

Serious infection/sepsis is considered an important identified risk because the impact of this risk on the individual patient can be potentially significant and the risk needs to be carefully weighed against the benefit conferred by the use of the medicine.

REMICADE is contraindicated in patients with TB or other severe infections, such as sepsis, abscesses, and opportunistic infections (section 4.3 of the SmPC).

Characterization of the Risk – Data:

For the important identified risk of Serious infection/sepsis, the data from REMICADE clinical trials are presented for the following subtypes in Tables SVII.1 through SVII.8: serious infection/sepsis (excluding opportunistic infection and TB); opportunistic infection; tuberculosis; and hepatitis B reactivation.

Table SVII.1: Serious Infection/Sepsis (Excluding Opportunistic Infection and TB) Reported During Clinical Trials in Approved Indications for REMICADE

	RA Trials		Psoriasis Trials		PsA Trial (C0168T50)	
	All Randomised, Blinded Trials Population (N=1964) n (%)	All Clinical Trials Population (N=2363) n (%)	All Randomised, Blinded Trials Population (N=1123) n (%)	All Clinical Trials Population (N=1373) n (%)	All Randomised, Blinded Trials Population (N=102) n (%)	All Clinical Trials Population (N=191) n (%)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	4.7% vs 2.9%	5.2% vs 2.9%	0.6% vs 0.6%	1.3% vs 0.6%	2.0% vs 2.0%	1.6% vs 2.0%
Odds ratio	1.390	-	1.487	-	-	-
(95% CI)	(0.967, 1.997)		(0.324, 6.822)			
Seriousness/Outcomes						
Was Serious	92 (4.7%)	120 (5.1%)	7 (0.6%)	18 (1.3%)	2 (2.0%)	3 (1.6%)
Resulted in Death	1 (0.1%)	1 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Recovered	81 (4.1%)	110 (4.7%)	6 (0.5%)	16 (1.2%)	2 (2.0%)	3 (1.6%)
Did not recover (Persisted)	10 (0.5%)	10 (0.4%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Missing	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	6 (0.3%)	8 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	22 (1.1%)	35 (1.5%)	1 (0.1%)	6 (0.4%)	1 (1.0%)	1 (0.5%)
Severe	25 (1.3%)	39 (1.7%)	6 (0.5%)	12 (0.9%)	1 (1.0%)	2 (1.0%)
Missing	40 (2.0%)	40 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.1: Serious Infection/Sepsis (Excluding Opportunistic Infection and TB) Reported During Clinical Trials in Approved Indications for REMICADE

	Crohns Disease Trials		Ulcerative Colitis Trials		AS Trial (C0168T51)	
	All Randomised, Blinded Trials Population (N=488) n (%)	All Clinical Trials Population (N=1427) n (%)	All Randomised, Blinded Trials Population (N=483) n (%)	All Clinical Trials Population (N=493) n (%)	All Randomised, Blinded Trials Population (N=201) n (%)	All Clinical Trials Population (N=275) n (%)
Frequency [c]						
REMICADE vs Placebo/Comparator [d]	3.9% vs 4.6%	4.3% vs 4.6%	3.3% vs 2.4%	5.1% vs 2.4%	1.5% vs 0.0%	3.6% vs 0.0%
Odds ratio	0.927	-	1.962	-	-	-
(95% CI)	(0.429, 2.003)		(0.788, 4.883)			
Seriousness/Outcomes						
Was Serious	19 (3.9%)	61 (4.3%)	16 (3.3%)	25 (5.1%)	3 (1.5%)	10 (3.6%)
Resulted in Death	0 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Recovered	17 (3.5%)	47 (3.3%)	14 (2.9%)	21 (4.3%)	3 (1.5%)	10 (3.6%)
Did not recover (Persisted)	2 (0.4%)	11 (0.8%)	2 (0.4%)	3 (0.6%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	6 (0.4%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Moderate	10 (2.0%)	20 (1.4%)	7 (1.4%)	11 (2.2%)	1 (0.5%)	4 (1.5%)
Severe	9 (1.8%)	35 (2.5%)	9 (1.9%)	13 (2.6%)	2 (1.0%)	6 (2.2%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.1: Serious Infection/Sepsis (Excluding Opportunistic Infection and TB) Reported During Clinical Trials in Approved Indications for REMICADE

	JRA Trial (C0168T32)		Pediatric Crohns Disease Trials		Pediatric Ulcerative Colitis Trial (C0168T72)	
	All Randomised, Blinded Trials Population (N=60) n (%)	All Clinical Trials Population (N=117) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=139) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=60) n (%)
Frequency [e]						
REMICADE vs Placebo/Comparator [f]	3.3% vs 3.3%	10.3% vs 3.3%	-	15.8%	-	11.7%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	2 (3.3%)	12 (10.3%)	-	22 (15.8%)	-	7 (11.7%)
Resulted in Death	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Recovered	2 (3.3%)	11 (9.4%)	-	17 (12.2%)	-	7 (11.7%)
Did not recover (Persisted)	0 (0.0%)	1 (0.9%)	-	5 (3.6%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	-	1 (0.7%)	-	1 (1.7%)
Moderate	0 (0.0%)	0 (0.0%)	-	11 (7.9%)	-	4 (6.7%)
Severe	0 (0.0%)	0 (0.0%)	-	10 (7.2%)	-	2 (3.3%)
Missing	2 (3.3%)	12 (10.3%)	-	0 (0.0%)	-	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are:
RA - Randomised, Blinded (N=788),
RA - All Clinical Trials (N=788),
Psoriasis - Randomised, Blinded (N=334),
Psoriasis - All Clinical Trials (N=334),
PsA - Randomised, Blinded (N=98),
PsA - All Clinical Trials (N=98).

[c] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[d] The denominators for the combined comparator groups are:
Crohn's Disease - Randomised, Blinded (N=217),
Crohn's Disease - All Clinical Trials (N=217),
UC - Randomised, Blinded (N=245),
UC - All Clinical Trials (N=248),
AS - Randomised, Blinded (N=76),

Table SVII.1: Serious Infection/Sepsis (Excluding Opportunistic Infection and TB) Reported During Clinical Trials in Approved Indications for REMICADE

AS - All Clinical Trials (N=76).

[e] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[f] The denominators for the combined comparator groups are:
JRA - Randomised, Blinded (N=60), JRA - All Clinical Trials (N=60),
Peds CD - Randomised, Blinded (N=0), Peds CD - All Clinical Trials (N=0),
Peds UC - Randomised, Blinded (N=0), Peds UC - All Clinical Trials (N=0).

Table SVII.2: Serious Infection/Sepsis (Excluding Opportunistic Infection and TB) Reported in REMICADE clinical trials

	All Trials	
	All Randomised, Blinded Trials Population (N=4421)	**All Clinical Trials Population (N=6438)**
Frequency [a]		
REMICADE vs Placebo/Comparator [b]	3.2% vs 2.5%	4.3% vs 2.5%
Odds ratio (95% CI)	1.343 (1.005, 1.795)	-
Seriousness/Outcomes		
Was Serious	141 (3.2%)	278 (4.3%)
Resulted in Death	2 (< 0.1%)	5 (0.1%)
Recovered	125 (2.8%)	242 (3.8%)
Did not recover (Persisted)	14 (0.3%)	31 (0.5%)
Missing	1 (< 0.1%)	2 (< 0.1%)
Severity/Nature of Risk		
Mild	6 (0.1%)	17 (0.3%)
Moderate	42 (1.0%)	92 (1.4%)
Severe	52 (1.2%)	119 (1.8%)
Missing	42 (1.0%)	52 (0.8%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences

[b] The denominators for the combined comparator groups are:
Adults trials - Randomised, Blinded (N=1818), Adults trials - All Clinical Trials (N=1821)

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Table SVII.3: Opportunistic Infections Reported During Clinical Trials in Approved Indications for REMICADE

	RA Trials		Psoriasis Trials		PsA Trial (C0168T50)	
	All Randomised, Blinded Trials Population (N=1964) n (%)	All Clinical Trials Population (N=2363) n (%)	All Randomised, Blinded Trials Population (N=1123) n (%)	All Clinical Trials Population (N=1373) n (%)	All Randomised, Blinded Trials Population (N=102) n (%)	All Clinical Trials Population (N=191) n (%)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.5% vs 0.0%	0.6% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	10 (0.5%)	13 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	4 (0.2%)	7 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	5 (0.3%)	5 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	3 (0.2%)	5 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	3 (0.2%)	4 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	3 (0.2%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.3: Opportunistic Infections Reported During Clinical Trials in Approved Indications for REMICADE

	Crohns Disease trials		Ulcerative Colitis Trials		AS Trial (C0168T51)	
	All Randomised, Blinded Trials Population (N=488) n (%)	All Clinical Trials Population (N=1427) n (%)	All Randomised, Blinded Trials Population (N=483) n (%)	All Clinical Trials Population (N=493) n (%)	All Randomised, Blinded Trials Population (N=201) n (%)	All Clinical Trials Population (N=275) n (%)
Frequency [c]						
REMICADE vs Placebo/Comparator [d]	0.0% vs 0.0%	0.1% vs 0.0%	0.0% vs 0.0%	0.2% vs 0.0%	0.0% vs 0.0%	0.4% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.4%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Did not recover (Persisted)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Moderate	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.3: Opportunistic Infections Reported During Clinical Trials in Approved Indications for REMICADE

	JRA Trial (C0168T32)		Pediatric Crohns Disease Trials		Pediatric Ulcerative Colitis Trial (C0168T72)	
	All Randomised, Blinded Trials Population (N=60) n (%)	All Clinical Trials Population (N=117) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=139) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=60) n (%)
Frequency [e]						
REMICADE vs Placebo/Comparator [f]	0.0% vs 0.0%	0.0% vs 0.0%	-	0.0%	-	0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are:
RA - Randomised, Blinded (N=788), RA - All Clinical Trials (N=788),
Psoriasis - Randomised, Blinded (N=334), Psoriasis - All Clinical Trials (N=334),
PsA - Randomised, Blinded (N=98), PsA - All Clinical Trials (N=98).)

[c] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[d] The denominators for the combined comparator groups are:
Crohn's Disease - Randomised, Blinded (N=217), Crohn's Disease - All Clinical Trials (N=217),
UC - Randomised, Blinded (N=245), UC - All Clinical Trials (N=248),
AS - Randomised, Blinded (N=76), AS - All Clinical Trials (N=76).

Table SVII.3: Opportunistic Infections Reported During Clinical Trials in Approved Indications for REMICADE

[e] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[f] The denominators for the combined comparator groups are:
JRA - Randomised, Blinded (N=60), JRA - All Clinical Trials (N=60),
Peds CD - Randomised, Blinded (N=0), Peds CD - All Clinical Trials (N=0),
Peds UC - Randomised, Blinded (N=0), Peds UC - All Clinical Trials (N=0).

Table SVII.4: Opportunistic Infections Reported in REMICADE Clinical Trials

	All Trials	
	All Randomised, Blinded Trials Population (N=4421)	**All Clinical Trials Population (N=6438)**
Frequency [a]		
REMICADE vs Placebo/Comparator [b]	0.2% vs 0.0%	0.3% vs 0.0%
Odds ratio (95% CI)	-	-
Seriousness/Outcomes		
Was Serious	10 (0.2%)	17 (0.3%)
Resulted in Death	1 (< 0.1%)	2 (< 0.1%)
Recovered	4 (0.1%)	8 (0.1%)
Did not recover (Persisted)	5 (0.1%)	7 (0.1%)
Missing	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk		
Mild	1 (< 0.1%)	2 (< 0.1%)
Moderate	3 (0.1%)	6 (0.1%)
Severe	3 (0.1%)	6 (0.1%)
Missing	3 (0.1%)	3 (< 0.1%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences

[b] The denominators for the combined comparator groups are:
Adults trials - Randomised, Blinded (N=1818), Adults trials - All Clinical Trials (N=1821)

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Table SVII.5: Tuberculosis Reported During Clinical Trials in Approved Indications for REMICADE

	RA Trials		Psoriasis Trials		PsA Trial (C0168T50)	
	All Randomised, Blinded Trials Population (N=1964) n (%)	All Clinical Trials Population (N=2363) n (%)	All Randomised, Blinded Trials Population (N=1123) n (%)	All Clinical Trials Population (N=1373) n (%)	All Randomised, Blinded Trials Population (N=102) n (%)	All Clinical Trials Population (N=191) n (%)
Frequency [a, b]						
REMICADE vs Placebo/Comparator [c]	0.5% vs 0.1%	0.6% vs 0.1%	0.0% vs 0.0%	0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	4.830 (0.627, 37.210)	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	9 (0.5%)	13 (0.6%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Resulted in Death	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	2 (0.1%)	5 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	5 (0.3%)	6 (0.3%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	3 (0.2%)	4 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	4 (0.2%)	6 (0.3%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Missing	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.5: Tuberculosis Reported During Clinical Trials in Approved Indications for REMICADE

	Crohns Disease Trials		Ulcerative Colitis Trials		AS Trial (C0168T51)	
	All Randomised, Blinded Trials Population (N=488) n (%)	All Clinical Trials Population (N=1427) n (%)	All Randomised, Blinded Trials Population (N=483) n (%)	All Clinical Trials Population (N=493) n (%)	All Randomised, Blinded Trials Population (N=201) n (%)	All Clinical Trials Population (N=275) n (%)
Frequency [d]						
REMICADE vs Placebo/Comparator [e]	0.2% vs 0.0%	0.2% vs 0.0%	0.6% vs 0.0%	1.2% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	1 (0.2%)	2 (0.1%)	1 (0.2%)	2 (0.4%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	1 (0.2%)	2 (0.1%)	2 (0.4%)	3 (0.6%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	1 (0.1%)	1 (0.2%)	3 (0.6%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	2 (0.4%)	5 (1.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	1 (0.2%)	2 (0.1%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.5: Tuberculosis Reported During Clinical Trials in Approved Indications for REMICADE

	JRA Trial (C0168T32)		Pediatric Crohns Disease Trials		Pediatric Ulcerative Colitis Trial (C0168T72)	
	All Randomised, Blinded Trials Population (N=60) n (%)	All Clinical Trials Population (N=117) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=139) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=60) n (%)
Frequency [f]						
REMICADE vs Placebo/Comparator [g]	0.0% vs 0.0%	0.9% vs 0.0%	-	0.0%	-	0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	1 (0.9%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	1 (0.9%)	-	0 (0.0%)	-	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The search terms capture both active and latent TB.

[c] The denominators for the combined comparator groups are:
RA - Randomised, Blinded (N=788), RA - All Clinical Trials (N=788),
Psoriasis - Randomised, Blinded (N=334), Psoriasis - All Clinical Trials (N=334),
PsA - Randomised, Blinded (N=98), PsA - All Clinical Trials (N=98).)

[d] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[e] The denominators for the combined comparator groups are:
Crohn's Disease - Randomised, Blinded (N=217), Crohn's Disease - All Clinical Trials (N=217),
UC - Randomised, Blinded (N=245), UC - All Clinical Trials (N=248),
AS - Randomised, Blinded (N=76), AS - All Clinical Trials (N=76).

[f] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[g] The denominators for the combined comparator groups are:
JRA - Randomised, Blinded (N=60), JRA - All Clinical Trials (N=60),
Peds CD - Randomised, Blinded (N=0), Peds CD - All Clinical Trials (N=0),
Peds UC - Randomised, Blinded (N=0), Peds UC - All Clinical Trials (N=0).

Table SVII.6: Tuberculosis Reported in REMICADE Clinical Trials

	All Trials	
	All Randomised, Blinded Trials Population (N=4421)	**All Clinical Trials Population (N=6438)**
Frequency [a, b]		
REMICADE vs Placebo/Comparator [c]	0.3% vs 0.1%	0.4% vs 0.1%
Odds ratio (95% CI)	7.414 (0.990, 55.530)	-
Seriousness/Outcomes		
Was Serious	11 (0.2%)	19 (0.3%)
Resulted in Death	2 (< 0.1%)	2 (< 0.1%)
Recovered	5 (0.1%)	10 (0.2%)
Did not recover (Persisted)	6 (0.1%)	13 (0.2%)
Missing	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk		
Mild	3 (0.1%)	7 (0.1%)
Moderate	3 (0.1%)	5 (0.1%)
Severe	6 (0.1%)	11 (0.2%)
Missing	1 (< 0.1%)	2 (< 0.1%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b] The search terms capture both active and latent TB.
[c] The denominators for the combined comparator groups are:
Adults trials - Randomised, Blinded (N=1818), Adults trials - All Clinical Trials (N=1821)

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Table SVII.7: Hepatitis B Reactivation Reported During Clinical Trials in Approved Indications for REMICADE

	RA Trials		Psoriasis Trials		PsA Trial (C0168T50)	
	All Randomised, Blinded Trials Population (N=1964) n (%)	All Clinical Trials Population (N=2363) n (%)	All Randomised, Blinded Trials Population (N=1123) n (%)	All Clinical Trials Population (N=1373) n (%)	All Randomised, Blinded Trials Population (N=102) n (%)	All Clinical Trials Population (N=191) n (%)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/ Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.7: Hepatitis B Reactivation Reported During Clinical Trials in Approved Indications for REMICADE

	Crohns Disease Trials		Ulcerative Colitis Trials		AS Trial (C0168T51)	
	All Randomised, Blinded Trials Population (N=488) n (%)	All Clinical Trials Population (N=1427) n (%)	All Randomised, Blinded Trials Population (N=483) n (%)	All Clinical Trials Population (N=493) n (%)	All Randomised, Blinded Trials Population (N=201) n (%)	All Clinical Trials Population (N=275) n (%)
Frequency [c]						
REMICADE vs Placebo/Comparator [d]	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.1%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/ Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.7: Hepatitis B Reactivation Reported During Clinical Trials in Approved Indications for REMICADE

	JRA Trial (C0168T32)		Pediatric Crohns Disease Trials		Pediatric Ulcerative Colitis Trial (C0168T72)	
	All Randomised, Blinded Trials Population (N=60) n (%)	All Clinical Trials Population (N=117) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=139) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=60) n (%)
Frequency [e]						
REMICADE vs Placebo/Comparator [f]	0.0% vs 0.0%	0.0% vs 0.0%	-	0.0%	-	0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severity/ Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are:
RA - Randomised, Blinded (N=788), RA - All Clinical Trials (N=788),
Psoriasis - Randomised, Blinded (N=334), Psoriasis - All Clinical Trials (N=334),
PsA - Randomised, Blinded (N=98), PsA - All Clinical Trials (N=98).

[c] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[d] The denominators for the combined comparator groups are:
Crohn's Disease - Randomised, Blinded (N=217), Crohn's Disease - All Clinical Trials (N=217),
UC - Randomised, Blinded (N=245), UC - All Clinical Trials (N=248),
AS - Randomised, Blinded (N=76), AS - All Clinical Trials (N=76).

[e] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[f] The denominators for the combined comparator groups are:
JRA - Randomised, Blinded (N=60), JRA - All Clinical Trials (N=60),
Peds CD - Randomised, Blinded (N=0), Peds CD - All Clinical Trials (N=0),
Peds UC - Randomised, Blinded (N=0), Peds UC - All Clinical Trials (N=0).

Table SVII.8: Hepatitis B Reactivation Reported in REMICADE Clinical Trials

	All Trials	
	All Randomised, Blinded Trials Population (N=4421)	**All Clinical Trials Population (N=6438)**
Frequency [a]		
REMICADE vs Placebo/Comparator [b]	0.0% vs 0.0%	< 0.1% vs 0.0%
Odds ratio (95% CI)	-	-
Seriousness/Outcomes		
Was Serious	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	1 (< 0.1%)
Missing	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk		
Mild	0 (0.0%)	1 (< 0.1%)
Moderate	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences

[b] The denominators for the combined comparator groups are:
Adults trials - Randomised, Blinded (N=1818), Adults trials - All Clinical Trials (N=1821)

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Characterization of the Risk – Discussion:

Serious infections are considered a class effect of anti-TNFα agents. Data from clinical trials in REMICADE (see tables above) support the classification of serious infection/sepsis as an important identified risk.

In REMICADE clinical trials, in the blinded, randomized population for all trials, the frequency of serious infections (excluding opportunistic infections and TB) in infliximab subjects was 3.2% compared with 2.5% for those who received placebo or comparator. The frequency of opportunistic infections and TB in the blinded, randomized population for all trials, was similar for infliximab treated subjects and those who received placebo or comparator. After hepatitis B reactivation was identified as a class effect based on review of the postmarketing data for all TNF inhibitors, subjects with a history of hepatitis B were excluded from clinical trials. One case of hepatitis B reactivation was reported during REMICADE clinical trials.

Infections, opportunistic infections, TB, and hepatitis B reactivation are described in the tabulated list of adverse drug reactions (ADRs) in the SmPC. Postmarketing data as described in the Periodic Benefit Risk Evaluation Reports (PBRERs)/Periodic Safety Update Reports (PSURs) to date are consistent with what is currently known about these risks in patients treated with REMICADE.

The impact of this risk on the individual patient can be potentially significant. Patients who are exposed to and subsequently infected with an infectious agent may have a more severe course due to use of the product.

Risk Factors and Risk Groups:

Serious Infection/Sepsis

Because REMICADE suppresses the activity of TNFα, which mediates inflammation and regulates immune responses, patients treated with REMICADE are more susceptible to serious infections.

Elderly Patients

In clinical trials, the incidence of serious infection in REMICADE-treated patients 65 years of age and older was greater than that seen in those under 65 years of age. In addition, there is a greater incidence of infections in the elderly population in general.

Children

In clinical trials, more children who received REMICADE developed infections than adults who received REMICADE.

Opportunistic Infections

The risk of developing opportunistic infections increases dramatically with progressive impairment of the immune system.

Patients with chronic infection or a history of recurrent infection, including those who use other immunosuppressive medications, such as methotrexate, are at a greater risk of developing an opportunistic infection during REMICADE therapy.

Patients who have resided in or traveled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, and blastomycosis are widespread, are also at increased risk of developing an opportunistic infection during REMICADE therapy.

Tuberculosis

The most common risk factors for the development of TB include conditions that weaken the immune system, such as advanced age, HIV infection, alcohol abuse, malignancy, use of corticosteroids or other immunosuppressive therapy, connective tissue disease, renal failure, diabetes, and pregnancy.

Other risk factors for the development of TB include contact with a person(s) with active TB infection and having been born in, or lived in, or traveled to countries where the incidence of TB is high. Exposure to TB may occur through various health care settings (eg, hospitals and nursing homes) or high-density institutions (eg, prisons).

Hepatitis B Reactivation

Approximately 14% to 50% of immunosuppressed patients who are chronic carriers of hepatitis B virus (HBV) will experience acute reactivations during the natural history of their disease (Shibolet et al, 2002). Thus, risk factors for HBV reactivation in patients with a history of HBV infection include the concomitant use of medications that suppress the immune system (eg, chemotherapy, corticosteroids, methotrexate, azathioprine, TNFα inhibitors). Other risk factors that may contribute to HBV reactivation include HIV infection, transplantation (especially bone marrow), and withdrawal from immunosuppressive therapies (Ocama et al, 2005).

Preventability:

REMICADE is contraindicated in patients with TB or other severe infections, such as sepsis, abscesses, and opportunistic infections (section 4.3 of the SmPC). The risk of serious infection/sepsis, including opportunistic infections, TB, and hepatitis B reactivation, is also described in the patient reminder card (see Part V.2). In addition, the patient reminder card includes recommendations for the use of live vaccines in infants exposed to infliximab in utero or during breast-feeding (see Part V.2).

Serious Infection/Sepsis and Opportunistic Infections

REMICADE should not be given to patients with a clinically important, active infection (Special warnings and precautions for use section of the SmPC). The SmPC indicates that caution should be exercised when considering the use of REMICADE in patients with chronic infection or a history of recurrent infections, including concomitant immunosuppressive therapy. Patients should be advised of and avoid exposure to potential risk factors for infections as appropriate. Early recognition of atypical clinical presentations of serious infections is critical in order to minimize delays in diagnosis and treatment.

Invasive Fungal Infections

For patients who have resided in or traveled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of REMICADE treatment should be carefully considered before initiation of REMICADE therapy (Special warnings and precautions for use section of the SmPC).

Tuberculosis

All patients must be evaluated for both active and inactive TB before starting treatment with REMICADE (Special warnings and precautions for use section of the SmPC).

This evaluation includes a detailed medical history with a personal history of TB or possible previous exposure to TB and previous and/or current exposure to immunosuppressive therapy. Appropriate screening tests (eg, tuberculin skin test, chest X-ray, and/or Interferon Gamma Release Assay) should be performed in all patients (local recommendations may apply). Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If latent TB is suspected, a physician with expertise in the treatment of TB should be consulted and the benefit/risk balance of REMICADE therapy should be very carefully considered. If inactive ('latent') TB is diagnosed, treatment with anti-TB therapy before the initiation of REMICADE must be started. Anti-TB therapy should also be considered before the initiation of REMICADE in patients who have several or significant risk factors for TB and have a negative test for latent TB, as well as in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Hepatitis B Reactivation

All patients should be tested for evidence of HBV infection before initiating treatment with immunosuppressants, including REMICADE. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Chronic carriers of hepatitis B who require treatment with REMICADE should be appropriately evaluated and monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination therapy (Special warnings and precautions for use section of the SmPC).

Impact on the Risk-Benefit Balance of the Product:

The observed incidence of serious infection/sepsis has not had a significant impact on the risk-benefit balance of the product. The SmPC, package leaflet (PL), and patient reminder card provide information to the prescriber and patient on how to manage this important identified risk. In addition, the safety concern is addressed in the patient reminder card as an additional risk minimization measure.

Public Health Impact:

In postmarketing spontaneous reporting, infections are the most common serious adverse event in patients treated with REMICADE. Some of the cases have resulted in a fatal outcome. Nearly 50% of reported deaths have been associated with infection. The public health impact of serious infection/sepsis during treatment with REMICADE is not known.

Annex 1 MedDRA Term:

System Organ Class: Infections and infestations.

Important Identified Risk – Bacille Calmette-Guérin (BCG) Breakthrough Infection and Agranulocytosis in Infants with In Utero Exposure to REMICADE

Potential Mechanisms:

BCG Breakthrough Infection in Infants With In Utero Exposure to REMICADE

TNF acts to regulate and enhance appropriate inflammatory, innate and adaptive immune responses to pathogenic organisms (Hehlgans and Pfeffer, 2005), and hence inhibition of TNF by REMICADE may suppress these beneficial activities of TNF and increase the potential for infection. REMICADE crosses the placenta and has been detected up to 12 months in the serum of infants born to women treated with infliximab during pregnancy.

Agranulocytosis in Infants With In Utero Exposure to REMICADE

The causal relationship between TNF inhibitors and agranulocytosis is poorly understood. Bone marrow suppression has been reported, albeit rarely, in patients after treatment with etanercept (Hyrich et al, 2004). TNF up-regulates the expression of proinflammatory cytokines involved in the differentiation and maturation of hemopoietic stem cells, it is thus possible that its blockade could mediate bone marrow failure by inhibiting stem cell differentiation (Keystone, 2001). REMICADE crosses the placenta and has been detected up to 12 months in the serum of infants born to women treated with infliximab during pregnancy.

Evidence Source and Strength of Evidence:

REMICADE crosses the placenta. REMICADE acts by inhibiting the activity of TNFα and reduces the immune response. If REMICADE is given during pregnancy, it may cause some rare side-effects in the baby for up to 12 months after birth such as specific types of infection after the baby receives a live vaccine or has low white blood cell count.

Cases of BCG breakthrough infection and agranulocytosis have been reported in postmarketing reports in babies whose mothers used REMICADE while pregnant. These findings are consistent with published medical literature.

Bacille Calmette-Guérin breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE is considered an important identified risk because the impact of this risk on an infant exposed to REMICADE in utero is significant.

Characterization of the Risk – Data and Discussion:

REMICADE Clinical Trial Data

No cases of BCG breakthrough infection or agranulocytosis have been reported in infants exposed to REMICADE in utero as a result of their mother's participation in REMICADE clinical trials; therefore, frequency from clinical trial data could not be determined. Women who were pregnant, nursing, or planning a pregnancy were excluded from REMICADE clinical trials. In addition, if a woman became pregnant while participating in a clinical trial, the study agent was discontinued.

Postmarketing Experience

BCG Breakthrough Infection in Infants With In Utero Exposure to REMICADE

After case reconciliation in the Janssen global safety database, it was confirmed that 5 cases of infants with in utero exposure to REMICADE developing mycobacterial infection have been reported through 23 August 2019. All cases had a fatal outcome. Four cases reported very limited information and a medical assessment could not be performed. The fifth reported case involved a PPD old white male. The infant's mother was initially treated with infliximab 5 mg/kg and increased to 10 mg/kg every 8 weeks approximately 2 years later (continuing as monotherapy throughout pregnancy) for refractory CD with pancolitis and secondary erythema nodosum. A baby boy was born healthy at 36 weeks +3 days gestation. The infant was not breastfed. He progressed well until PPD of age when he received a BCG vaccination, after which his condition deteriorated (eg, lag in weight gain, head lag, skin eczema, irritability, difficulty feeding). The infant died at PPD of disseminated granulomatous inflammation with multiple non-caseating tuberculoid granulomas in the lungs, liver, and dura. There was no history of TB in the family or contacts.

Agranulocytosis in Infants With In Utero Exposure to REMICADE

As of 23 August 2019, 7 cases of agranulocytosis after in utero exposure to infliximab were identified. Three cases involved neonates (triplets) who were exposed to infliximab in utero and developed agranulocytosis shortly after birth. One case involved a full-term infant with a normal APGAR score that reported resolution of neutropenia within PPD of delivery. The remaining 3 cases involved the delivery of premature infants 2 of which had concurrent infections. The triplet cases are included in a literature article by Guiddir et al, published in 2014.

Risk Factors and Risk Groups:

Infants exposed to REMICADE in utero and who receive BCG vaccine within 12 months after birth are at risk for developing disseminated BCG infection. Infants exposed in utero to REMICADE are also at increased risk of developing agranulocytosis.

Preventability:

A 12-month waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab (SmPC). Infants up to 12 months of age exposed in utero to REMICADE should be closely monitored by pediatricians for signs of infection or low white blood cell count such as persistent fever. The patient reminder card includes recommendations for the use of live vaccines in infants exposed to infliximab in utero or during breast-feeding (see Part V.2).

Impact on the Risk-Benefit Balance of the Product:

Bacille Calmette-Guérin breakthrough infection and agranulocytosis have rarely occurred in neonates exposed to REMICADE. When these events occur, they are potentially serious and life-threatening. The observed incidence of BCG breakthrough infection and agranulocytosis has not had a significant impact on the risk-benefit balance of the product. The SmPC, PL, and patient reminder card provide information to the prescriber and patient on how to manage the risk.

Public Health Impact:

The potential public health impact is not known.

Annex 1 MedDRA Term:

Preferred term: Maternal exposure during pregnancy.

Important Identified Risk – Demyelinating Disorders

Potential Mechanisms:

The role that TNF plays as an immunomodulator suggests that TNF blockade may promote the development of drug-induced neuropathies by augmenting the number of activated peripheral T cells and thereby enhance autoimmune responses by altering antigen presenting cell function, potentiating T-cell receptor signaling, and/or decreasing apoptosis of autoreactive T cells. These autoreactive T cells might also drive the maturation of B cells into cells secreting autoantibodies to neuronal-specific antigens (Stubgen, 2008). A report in a murine model of experimental autoimmune encephalomyelitis suggests that membrane TNF is neuroprotective (Taoufik et al, 2011). Since TNF inhibitors can neutralize both soluble and membrane TNF, they may remove the neuroprotection provided by membrane TNF.

Evidence Source and Strength of Evidence:

Serious nervous system disorders such as transverse myelitis, multiple sclerosis-like disease, optic neuritis, and Guillain-Barré syndrome are rare side effects of REMICADE.

In clinical trials, demyelinating disorders have been reported in patients treated with REMICADE. Reports have been noted in the postmarketing setting and are consistent with published medical literature and experience with other medicines that also act by inhibiting TNF.

Demyelinating disorders are considered an important identified risk because of the consistency of evidence across multiple sources, including data from products in the same class.

Characterization of the Risk – Data:

Table SVII.9: Demyelinating Disorders Reported During Clinical Trials in Approved Indications for REMICADE

	RA Trials		Psoriasis Trials		PsA Trial (C0168T50)	
	All Randomised, Blinded Trials Population (N=1964) n (%)	All Clinical Trials Population (N=2363) n (%)	All Randomised, Blinded Trials Population (N=1123) n (%)	All Clinical Trials Population (N=1373) n (%)	All Randomised, Blinded Trials Population (N=102) n (%)	All Clinical Trials Population (N=191) n (%)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.9: Demyelinating Disorders Reported During Clinical Trials in Approved Indications for REMICADE

	Crohns Disease Trials		Ulcerative Colitis Trials		AS Trial (C0168T51)	
	All Randomised, Blinded Trials Population (N=488) n (%)	All Clinical Trials Population (N=1427) n (%)	All Randomised, Blinded Trials Population (N=483) n (%)	All Clinical Trials Population (N=493) n (%)	All Randomised, Blinded Trials Population (N=201) n (%)	All Clinical Trials Population (N=275) n (%)
Frequency [c]						
REMICADE vs Placebo/Comparator [d]	0.0% vs 0.5%	0.3% vs 0.5%	0.2% vs 0.0%	0.2% vs 0.0%	0.0% vs 1.3%	0.4% vs 1.3%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	3 (0.2%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	1 (0.4%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Did not recover (Persisted)	0 (0.0%)	2 (0.1%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.9: Demyelinating Disorders Reported During Clinical Trials in Approved Indications for REMICADE

	JRA Trial (C0168T32)		Pediatric Crohns Disease Trials		Pediatric Ulcerative Colitis Trial (C0168T72)	
	All Randomised, Blinded Trials Population (N=60) n (%)	All Clinical Trials Population (N=117) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=139) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=60) n (%)
Frequency [e]						
REMICADE vs Placebo/Comparator [f]	0.0% vs 0.0%	0.0% vs 0.0%	-	0.0%	-	0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	-	0 (0.0%)		0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)
Moderate	0 (0.0%)	-	1 (0.2%)	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are:
RA - Randomised, Blinded (N=788), RA - All Clinical Trials (N=788),
Psoriasis - Randomised, Blinded (N=334), Psoriasis - All Clinical Trials (N=334),
PsA - Randomised, Blinded (N=98), PsA - All Clinical Trials (N=98).)

[c] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[d] The denominators for the combined comparator groups are:
Crohn's Disease - Randomised, Blinded (N=217), Crohn's Disease - All Clinical Trials (N=217),
UC - Randomised, Blinded (N=245), UC - All Clinical Trials (N=248),
AS - Randomised, Blinded (N=76), AS - All Clinical Trials (N=76).

[e] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[f] The denominators for the combined comparator groups are:
JRA - Randomised, Blinded (N=60), JRA - All Clinical Trials (N=60),
Peds CD - Randomised, Blinded (N=0), Peds CD - All Clinical Trials (N=0),
Peds UC - Randomised, Blinded (N=0), Peds UC - All Clinical Trials (N=0).

Table SVII.10: Demyelinating Disorders Reported in REMICADE Clinical Trials

	All Trials	
	All Randomised, Blinded Trials Population (N=4421)	**All Clinical Trials Population (N=6438)**
Frequency [a]		
REMICADE vs Placebo/Comparator [b]	< 0.1% vs 0.1%	0.1% vs 0.1%
Odds ratio (95% CI)	-	-
Seriousness/outcomes		
Was Serious	1 (< 0.1%)	6 (0.1%)
Resulted in Death	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	3 (< 0.1%)
Did not recover (Persisted)	1 (< 0.1%)	4 (0.1%)
Missing	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk		
Mild	0 (0.0%)	2 (< 0.1%)
Moderate	1 (< 0.1%)	2 (< 0.1%)
Severe	0 (0.0%)	3 (< 0.1%)
Missing	0 (0.0%)	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences

[b] The denominators for the combined comparator groups are:
Adults trials - Randomised, Blinded (N=1818), Adults trials - All Clinical Trials (N=1821)

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Characterization of the Risk – Discussion:

Demyelinating disorders are considered a class effect for anti-TNFα agents. Demyelinating disorders are listed in the REMICADE SmPC (section 4.4, Special warnings and precautions for use, and section 4.8, Undesirable effects).

In REMICADE clinical trials, in the blinded, randomized population for all trials, the frequency of demyelinating disorders was <0.1% for infliximab-treated subjects compared with 0.1% for those who received placebo or comparator. Postmarketing data as described in the PBRERs/PSURs to date are consistent with what is currently known about the risk of demyelinating disorders in patients treated with REMICADE.

The impact of this risk on the individual patient can vary from minimal to significant. Patients with pre-existing or recent onset of demyelinating disorders may have a more severe course due to use of the product. This risk needs to be carefully weighed against the benefit conferred by use of the medication.

Risk Factors and Risk Groups:

Multiple Sclerosis (MS) and other autoimmune diseases have been linked to genetic and environmental factors. First-degree relatives of MS patients are at greater risk to develop MS than the general population (Didonna and Oksenberg, 2015). Whites, particularly of northern European descent, are also more likely to develop MS (Ascherio and Munger, 2016).

Several studies have suggested an association between smoking and MS (Ascherio and Munger, 2016). Obesity in early life and Epstein-Barr virus have also been identified as risk factors for MS (Ascherio and Munger, 2016).

Preventability:

Predictability and preventability of the development of demyelination is not known. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of REMICADE treatment should be carefully considered before initiation of REMICADE therapy and discontinuation of REMICADE therapy should be considered if signs or symptoms of demyelinating disorders develop (Special warnings and precautions for use section of the SmPC).

Impact on the Risk-Benefit Balance of the Product:

The observed incidence of demyelinating disorders has not had a significant impact on the risk-benefit balance of the product. The SmPC and PL provide information to the prescriber and patient on how to manage the important identified risk of demyelinating disorders.

Public Health Impact:

The potential public health impact is not known.

Annex 1 MedDRA Term:

High Level Group Term (HLGT): Demyelinating disorders.

Important Identified Risk – Malignancy

As part of the broad term of malignancy, information relating to specific subtypes of malignancy (lymphoma, hepatosplenic T-cell lymphoma [HSTCL], leukemia, melanoma, Merkel cell carcinoma, cervical cancer, Kaposis's sarcoma, and pediatric malignancy) are described in this section of the RMP. These subtypes are identified as ADRs in the REMICADE SmPC.

Potential Mechanisms:

TNF has been shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumor cell lines (Mocellin et al, 2005). Low doses of TNF can increase tumor blood vessel permeability, thus augmenting tissue concentrations of chemotherapeutic agents, as well as enhance the cytolytic effect of NK and CD8+ T cell killing of immunogenic tumor cells (Balkwill, 2009). Therefore, the neutralization of TNF by REMICADE may allow some types of tumor cells to survive.

Immunosuppression, either from treatment with a TNF inhibitor or other immunosuppressive drugs such as methotrexate and thiopurines, is associated with an increased risk of lymphoma (Subramaniam et al, 2013), possibly due to reduced tumor surveillance. TNFα blockers decrease host defense against viral infections, which may be of clinical relevance (eg, reactivation of herpes zoster). Whether TNFα blockers increase the risk of virus-associated malignancies is not known.

No specific mechanism of action is known for why TNFα blockers may increase the rate of melanoma. The immunosuppressive properties associated with inhibition of TNF may increase occurrence of malignancies or reactivation of latent malignancies, although details regarding the mechanism of action are lacking (Kouklakis et al, 2013).

Evidence Source and Strength of Evidence:

TNF blockers, including REMICADE, decrease the activity of the immune system. This may increase the risk of cancer. Certain cancers have been seen more commonly in TNFα treated patients than expected. Although this has not been seen with all cancer types, it is possible that REMICADE may have some effect on other cancers.

Malignancies, including the subtypes of lymphoma, HSTCL, leukemia, melanoma, Merkel cell carcinoma, cervical cancer, Kaposi's sarcoma, and pediatric malignancy, have been reported in clinical trials with REMICADE, the postmarketing setting, published medical literature, or epidemiological studies.

Some children and teenage patients who have received TNF blockers such as REMICADE have developed cancers, including unusual types such as HSTCL, which sometimes resulted in death. Most of the patients were receiving concomitant immunosuppressants, such as methotrexate, azathioprine, or 6-mercaptopurine (Deepak et al, 2013).

Characterization of the Risk – Data:

For the important identified risk of malignancy, the data from REMICADE clinical trials are presented for the following subtypes in Tables SVII.11 through SVII.20: lymphoma (excluding HSTCL); leukemia; melanoma; cervical cancer; and malignancy (excluding lymphoma, HSTCL, pediatric malignancy, leukemia, melanoma, Merkel cell carcinoma, and cervical cancer). These subtypes (eg, lymphoma, HSTCL, leukemia, melanoma, Merkel cell carcinoma, cervical cancer, and pediatric malignancy) were identified as ADRs in the REMICADE SmPC and were previous important identified risks in the REMICADE RMP. As there were no cases of HSTCL, Merkel cell carcinoma, Kaposi's sarcoma, or pediatric malignancy reported in REMICADE clinical trials, no tables on these subtypes are presented in this section.

Table SVII.11: Lymphoma (excluding HSTCL) Reported During Clinical Trials in Approved Indications for REMICADE

	RA Trials		Psoriasis Trials		PsA Trial (C0168T50)	
	All Randomised, Blinded Trials Population (N=1964) n (%)	All Clinical Trials Population (N=2363) n (%)	All Randomised, Blinded Trials Population (N=1123) n (%)	All Clinical Trials Population (N=1373) n (%)	All Randomised, Blinded Trials Population (N=102) n (%)	All Clinical Trials Population (N=191) n (%)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.1% vs 0.0%	0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.5% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Missing	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.11: Lymphoma (excluding HSTCL) Reported During Clinical Trials in Approved Indications for REMICADE

	Crohns Disease Trials		Ulcerative Colitis Trials		AS Trial (C0168T51)	
	All Randomised, Blinded Trials Population (N=488) n (%)	All Clinical Trials Population (N=1427) n (%)	All Randomised, Blinded Trials Population (N=483) n (%)	All Clinical Trials Population (N=493) n (%)	All Randomised, Blinded Trials Population (N=201) n (%)	All Clinical Trials Population (N=275) n (%)
Frequency [c]						
REMICADE vs Placebo/Comparator [d]	0.0% vs 0.0%	0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	JRA Trial (C0168T32)		**Pediatric Crohns Disease Trials**		**Pediatric Ulcerative Colitis Trial (C0168T72)**	
	All Randomised, Blinded Trials Population (N=60) n (%)	All Clinical Trials Population (N=117) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=139) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=60) n (%)
Frequency [e]						
REMICADE vs Placebo/Comparator [f]	0.0% vs 0.0%	0.0% vs 0.0%	-	0.0%	-	0.0%
Odds ratio (95% CI)	-	-	-	-	-	-

Table SVII.11: Lymphoma (excluding HSTCL) Reported During Clinical Trials in Approved Indications for REMICADE

Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are:
RA - Randomised, Blinded (N=788), RA - All Clinical Trials (N=788),
Psoriasis - Randomised, Blinded (N=334), Psoriasis - All Clinical Trials (N=334),
PsA - Randomised, Blinded (N=98), PsA - All Clinical Trials (N=98).)

[c] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[d] The denominators for the combined comparator groups are:
Crohn's Disease - Randomised, Blinded (N=217), Crohn's Disease - All Clinical Trials (N=217),
UC - Randomised, Blinded (N=245), UC - All Clinical Trials (N=248),
AS - Randomised, Blinded (N=76), AS - All Clinical Trials (N=76).

[e] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[f] The denominators for the combined comparator groups are:
JRA - Randomised, Blinded (N=60), JRA - All Clinical Trials (N=60),
Peds CD - Randomised, Blinded (N=0), Peds CD - All Clinical Trials (N=0),
Peds UC - Randomised, Blinded (N=0), Peds UC - All Clinical Trials (N=0).

Table SVII.12: Lymphoma (excluding HSTCL) Reported in REMICADE Clinical Trials

	All Trials	
	All Randomised, Blinded Trials Population (N=4421)	**All Clinical Trials Population (N=6438)**
Frequency [a]		
REMICADE vs Placebo/Comparator [b]	< 0.1% vs 0.0%	0.1% vs 0.0%
Odds ratio (95% CI)	-	-
Seriousness/Outcomes		
Was Serious	2 (< 0.1%)	5 (0.1%)
Resulted in Death	0 (0.0%)	1 (< 0.1%)
Recovered	1 (< 0.1%)	1 (< 0.1%)
Did not recover (Persisted)	1 (< 0.1%)	3 (< 0.1%)
Missing	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk		
Mild	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)
Severe	1 (< 0.1%)	4 (0.1%)
Missing	1 (< 0.1%)	1 (< 0.1%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences

[b] The denominators for the combined comparator groups are:
Adults trials - Randomised, Blinded (N=1818), Adults trials - All Clinical Trials (N=1821)

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Table SVII.13: Leukemia Reported During Clinical Trials in Approved Indications for REMICADE

	RA Trials		Psoriasis Trials		PsA Trial (C0168T50)	
	All Randomised, Blinded Trials Population (N=1964) n (%)	All Clinical Trials Population (N=2363) n (%)	All Randomised, Blinded Trials Population (N=1123) n (%)	All Clinical Trials Population (N=1373) n (%)	All Randomised, Blinded Trials Population (N=102) n (%)	All Clinical Trials Population (N=191) n (%)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	1 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.13: Leukemia Reported During Clinical Trials in Approved Indications for REMICADE

	Crohns Disease Trials		Ulcerative Colitis Trials		AS Trial (C0168T51)	
	All Randomised, Blinded Trials Population (N=488) n (%)	All Clinical Trials Population (N=1427) n (%)	All Randomised, Blinded Trials Population (N=483) n (%)	All Clinical Trials Population (N=493) n (%)	All Randomised, Blinded Trials Population (N=201) n (%)	All Clinical Trials Population (N=275) n (%)
Frequency [c]						
REMICADE vs Placebo/Comparator [d]	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	JRA Trial (C0168T32)		**Pediatric Crohns Disease Trials**		**Pediatric Ulcerative Colitis Trial (C0168T72)**	
	All Randomised, Blinded Trials Population (N=60) n (%)	All Clinical Trials Population (N=117) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=139) n (%)	All Randomised, Blinded Trials Population (N=0) n (%)	All Clinical Trials Population (N=60) n (%)
Frequency [e]						
REMICADE vs Placebo/Comparator [f]	0.0% vs 0.0%	0.0% vs 0.0%	-	0.0%	-	0.0%
Odds ratio (95% CI)	-	-	-	-	-	-

Table SVII.13: Leukemia Reported During Clinical Trials in Approved Indications for REMICADE

Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)		0 (0.0%)		0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are:
RA - Randomised, Blinded (N=788), RA - All Clinical Trials (N=788),
Psoriasis - Randomised, Blinded (N=334), Psoriasis - All Clinical Trials (N=334),
PsA - Randomised, Blinded (N=98), PsA - All Clinical Trials (N=98).)

[c] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[d] The denominators for the combined comparator groups are:
Crohn's Disease - Randomised, Blinded (N=217), Crohn's Disease - All Clinical Trials (N=217),
UC - Randomised, Blinded (N=245), UC - All Clinical Trials (N=248),
AS - Randomised, Blinded (N=76), AS - All Clinical Trials (N=76).

[e] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[f] The denominators for the combined comparator groups are:
JRA - Randomised, Blinded (N=60), JRA - All Clinical Trials (N=60),
Peds CD - Randomised, Blinded (N=0), Peds CD - All Clinical Trials (N=0),
Peds UC - Randomised, Blinded (N=0), Peds UC - All Clinical Trials (N=0).

Table SVII.14: Leukemia Reported in REMICADE Clinical Trials

	All Trials	
	All Randomised, Blinded Trials Population (N=4421)	**All Clinical Trials Population (N=6438)**
Frequency [a]		
REMICADE vs Placebo/Comparator [b]	< 0.1% vs 0.0%	< 0.1% vs 0.0%
Odds ratio (95% CI)	-	-
Seriousness/Outcomes		
Was Serious	1 (< 0.1%)	1 (< 0.1%)
Resulted in Death	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	1 (< 0.1%)	1 (< 0.1%)
Missing	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk		
Mild	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)
Severe	1 (< 0.1%)	1 (< 0.1%)
Missing	0 (0.0%)	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences

[b] The denominators for the combined comparator groups are:
Adults trials - Randomised, Blinded (N=1818), Adults trials - All Clinical Trials (N=1821)

Adapted from [TSFLEUKEMIAF.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2013UPDATE\tsfrisksf.sas] 23JUL2013, 16:09

Table SVII.15: Melanoma Reported During Clinical Trials in Approved Indications for REMICADE

	RA Trials		Psoriasis Trials		PsA Trial (C0168T50)	
	All Randomised, Blinded Trials Population (N=1964)	All Clinical Trials Population (N=2363)	All Randomised, Blinded Trials Population (N=1123)	All Clinical Trials Population (N=1373)	All Randomised, Blinded Trials Population (N=102)	All Clinical Trials Population (N=191)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.1% vs 0.0%	0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	1 (0.1%)	1 (< 0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	1 (0.1%)	1 (< 0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.15: Melanoma Reported During Clinical Trials in Approved Indications for REMICADE

	Crohns Disease Trials		Ulcerative Colitis Trials		AS Trial (C0168T51)	
	All Randomised, Blinded Trials Population (N=488)	All Clinical Trials Population (N=1427)	All Randomised, Blinded Trials Population (N=483)	All Clinical Trials Population (N=493)	All Randomised, Blinded Trials Population (N=201)	All Clinical Trials Population (N=275)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.15: Melanoma Reported During Clinical Trials in Approved Indications for REMICADE

	JRA Trial (C0168T32)		Pediatric Crohns Disease Trial		Pediatric Ulcerative Colitis Trial (C0168T72)	
	All Randomised, Blinded Trials Population (N=60)	All Clinical Trials Population (N=117)	All Randomised, Blinded Trials Population (N=0)	All Clinical Trials Population (N=139)	All Randomised, Blinded Trials Population (N=0)	All Clinical Trials Population (N=60)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.0% vs 0.0%	0.0% vs 0.0%	-	0.0%	-	0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severity/Nature of Risk						
Mild	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences

[b] The denominators for the combined comparator groups are:
RA - Randomised, Blinded (N=788), RA - All Clinical Trials (N=788)
Psoriasis - Randomised, Blinded (N=334), Psoriasis - All Clinical Trials (N=334)
PsA - Randomised, Blinded (N=98), PsA - All Clinical Trials (N=98)
Crohns disease - Randomised, Blinded (N=217), Crohns disease - All Clinical Trials (N=217)
Ulcerative colitis - Randomised, Blinded (N=245), Ulcerative colitis - All Clinical Trials (N=248)
AS - Randomised, Blinded (N=76), AS - All Clinical Trials (N=76)
JRA - Randomised, Blinded (N=60), JRA - All Clinical Trials (N=60)
Pediatric CD - Randomised, Blinded (N=0), Pediatric CD - All Clinical Trials (N=0)
Pediatric UC - Randomised, Blinded (N=0), Pediatric UC - All Clinical Trials (N=0)

Adapted from[TSFMELANOMAA.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2013UPDATE\tsfrisksa.sas] 23JUL2013, 15:23; [TSFMELANOMAB.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2013UPDATE\tsfrisksb.sas] 23JUL2013, 15:42 ; [TSFMELANOMAC.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2013UPDATE\tsfrisksc.sas] 23JUL2013, 15:56

Table SVII.16: Melanoma Reported in REMICADE Clinical Trials

	All Trials	
	All Randomised, Blinded Trials Population (N=4421)	**All Clinical Trials Population (N=6438)**
Frequency [a]		
REMICADE vs Placebo/Comparator [b]	< 0.1% vs 0.0%	< 0.1% vs 0.0%
Odds ratio (95% CI)	-	-
Seriousness/Outcomes		
Was Serious	2 (< 0.1%)	2 (< 0.1%)
Resulted in Death	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	1 (< 0.1%)	1 (< 0.1%)
Missing	1 (< 0.1%)	1 (< 0.1%)
Severity/Nature of Risk		
Mild	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)
Missing	2 (< 0.1%)	2 (< 0.1%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences

[b] The denominators for the combined comparator groups are:
Adults trials - Randomised, Blinded (N=1818), Adults trials - All Clinical Trials (N=1821)

[TSFMELANOMAF.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2013UPDATE\tsfrisksf.sas] 23JUL2013, 16:09

Table SVII.17: Cervical Cancer Reported During Clinical Trials in Approved Indications for REMICADE

	RA Studies		Psoriasis Studies		PsA Study (C0168T50)	
	All Randomised, Blinded Trials Population (N=1964)	All Clinical Trials Population (N=2363)	All Randomised, Blinded Trials Population (N=1123)	All Clinical Trials Population (N=1373)	All Randomised, Blinded Trials Population (N=102)	All Clinical Trials Population (N=191)
Frequency [a]						
REMICADE vs Placebo/ Comparator [b]	0.0% vs 0.0%	< 0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	1 (< 0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	1 (< 0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	1 (< 0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.17: Cervical Cancer Reported During Clinical Trials in Approved Indications for REMICADE

	Crohns Disease Studies		Ulcerative Colitis Studies		AS Study (C0168T51)	
	All Randomised, Blinded Trials Population (N=488)	All Clinical Trials Population (N=1427)	All Randomised, Blinded Trials Population (N=483)	All Clinical Trials Population (N=493)	All Randomised, Blinded Trials Population (N=201)	All Clinical Trials Population (N=275)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.17: Cervical Cancer Reported During Clinical Trials in Approved Indications for REMICADE

	JRA Study (C0168T32)		Pediatric Crohns Disease Studies		Pediatric Ulcerative Colitis Study (C0168T72)	
	All Randomised, Blinded Trials Population (N=60)	All Clinical Trials Population (N=117)	All Randomised, Blinded Trials Population (N=0)	All Clinical Trials Population (N=139)	All Randomised, Blinded Trials Population (N=0)	All Clinical Trials Population (N=60)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.0% vs 0.0%	0.0% vs 0.0%	-	0.0%	-	0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Resulted in Death	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Recovered	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severity						
Mild	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are:
RA - Randomized, Blinded (N=788), RA - All Clinical Trials (N=788)
Psoriasis - Randomized, Blinded (N=334), Psoriasis - All Clinical Trials (N=334)
PsA - Randomized, Blinded (N=98), PsA - All Clinical Trials (N=98)
Crohns disease - Randomized, Blinded (N=217), Crohns disease - All Clinical Trials (N=217)
Ulcerative colitis - Randomized, Blinded (N=245), Ulcerative colitis - All Clinical Trials (N=248)
AS - Randomized, Blinded (N=76), AS - All Clinical Trials (N=76)
JRA - Randomized, Blinded (N=60), JRA - All Clinical Trials (N=60)
Pediatric CD - Randomized, Blinded (N=0), Pediatric CD - All Clinical Trials (N=0)
Pediatric UC - Randomized, Blinded (N=0), Pediatric UC - All Clinical Trials (N=0)

Adapted from: [TSFCERVIXCAA.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2015UPDATE\tsfcervixca.sas] 24APR2015, 18:19; [TSFCERVIXCAB.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2015UPDATE\tsfcervixca.sas] 24APR2015, 18:19; [TSFCERVIXCAC.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2015UPDATE\tsfcervixca.sas] 24APR2015, 18:19

Table SVII.18: Cervical Cancer Reported in REMICADE Clinical Trials

	All Studies	
	All Randomised, Blinded Trials Population (N=4421)	**All Clinical Trials Population (N=6438)**
Frequency [a]		
REMICADE vs Placebo/Comparator [b]	0.0% vs 0.0%	< 0.1% vs 0.0%
Odds ratio (95% CI)	-	-
Seriousness/Outcomes		
Was Serious	0 (0.0%)	1 (< 0.1%)
Resulted in Death	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	1 (< 0.1%)
Did not recover (Persisted)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)
Severity		
Mild	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	1 (< 0.1%)
Missing	0 (0.0%)	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are:
Adults studies - Randomized, Blinded (N=1818), Adults studies - All Clinical Trials (N=1821)

Adapted from:[TSFCERVIXCAF rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2015UPDATE\tsfcervixca.sas] 24APR2015, 18:19

Table SVII.19: Malignancy (Excluding Lymphoma, HSTCL, Pediatric Malignancy, Leukemia, Melanoma, Merkel Cell Carcinoma, and Cervical Cancer) Reported During Clinical Trials in Approved Indications for REMICADE

	RA Trials		Psoriasis Trials		PsA Trial (C0168T50)	
	All Randomised, Blinded Trials Population (N=1964)	All Clinical Trials Population (N=2363)	All Randomised, Blinded Trials Population (N=1123)	All Clinical Trials Population (N=1373)	All Randomised, Blinded Trials Population (N=102)	All Clinical Trials Population (N=191)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.4% vs 0.1%	0.5% vs 0.1%	0.0% vs 0.0%	0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	1.475 (0.410, 5.302)	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	8 (0.4%)	12 (0.5%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Resulted in Death	3 (0.2%)	4 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	3 (0.2%)	4 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	2 (0.1%)	4 (0.2%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	1 (0.1%)	2 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Severe	5 (0.3%)	8 (0.3%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Missing	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table SVII.19: Malignancy (Excluding Lymphoma, HSTCL, Pediatric Malignancy, Leukemia, Melanoma, Merkel Cell Carcinoma, and Cervical Cancer) Reported During Clinical Trials in Approved Indications for REMICADE

	Crohns Disease Trials		Ulcerative Colitis Trials		AS Trial (C0168T51)	
	All Randomised, Blinded Trials Population (N=488)	All Clinical Trials Population (N=1427)	All Randomised, Blinded Trials Population (N=483)	All Clinical Trials Population (N=493)	All Randomised, Blinded Trials Population (N=201)	All Clinical Trials Population (N=275)
Frequency [a]						
REMICADE vs Placebo/Comparator [b]	0.0% vs 0.9%	0.3% vs 0.9%	0.2% vs 0.0%	0.8% vs 0.0%	0.0% vs 0.0%	0.7% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/Outcomes						
Was Serious	0 (0.0%)	4 (0.3%)	1 (0.2%)	4 (0.8%)	0 (0.0%)	2 (0.7%)
Resulted in Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered	0 (0.0%)	3 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Did not recover (Persisted)	0 (0.0%)	1 (0.1%)	1 (0.2%)	3 (0.6%)	0 (0.0%)	2 (0.7%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity						
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	2 (0.1%)	1 (0.2%)	4 (0.8%)	0 (0.0%)	2 (0.7%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences

[b] The denominators for the combined comparator groups are:
RA - Randomised, Blinded (N=788), RA - All Clinical Trials (N=788)
Psoriasis - Randomised, Blinded (N=334), Psoriasis - All Clinical Trials (N=334)
PsA - Randomised, Blinded (N=98), PsA - All Clinical Trials (N=98)
Crohns disease - Randomised, Blinded (N=217), Crohns disease - All Clinical Trials (N=217)
Ulcerative colitis - Randomised, Blinded (N=245), Ulcerative colitis - All Clinical Trials (N=248)
AS - Randomised, Blinded (N=76), AS - All Clinical Trials (N=76)

Adapted from [TSFNLMALIGA.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2013UPDATE\tsfrisksa.sas] 23JUL2013, 15:23; [TSFNLMALIGB.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2013UPDATE\tsfrisksb.sas] 23JUL2013, 15:42

Table SVII.20: Malignancy (Excluding Lymphoma, HSTCL, Pediatric Malignancy, Leukemia, Melanoma, Merkel Cell Carcinoma, and Cervical Cancer) Reported in REMICADE Clinical Trials

	All Trials	
	All Randomised, Blinded Trials Population (N=4421)	**All Clinical Trials Population (N=6438)**
Frequency [a]		
REMICADE vs Placebo/Comparator [b]	0.2% vs 0.2%	0.4% vs 0.2%
Odds ratio (95% CI)	0.987 (0.347, 2.806)	-
Seriousness/Outcomes		
Was Serious	9 (0.2%)	24 (0.4%)
Resulted in Death	3 (0.1%)	4 (0.1%)
Recovered	3 (0.1%)	8 (0.1%)
Did not recover (Persisted)	3 (0.1%)	12 (0.2%)
Missing	0 (0.0%)	0 (0.0%)
Severity		
Mild	0 (0.0%)	0 (0.0%)
Moderate	1 (< 0.1%)	5 (0.1%)
Severe	6 (0.1%)	17 (0.3%)
Missing	2 (< 0.1%)	2 (< 0.1%)

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences

[b] The denominators for the combined comparator groups are:
Adults trials - Randomised, Blinded (N=1818), Adult trials - All Clinical Trials (N=1821)

Adapted from [TSFNLMALIGF.rtf] [CNTO312\Z_RMP\DBR_RE224\RE_2013UPDATE\tsfrisksf.sas] 23JUL2013, 16:09

Characterization of the Risk – Discussion:

Lymphoma, leukemia, melanoma, cervical cancer, HSTCL, Merkel cell carcinoma, Kaposi's sarcoma, and pediatric malignancy are known ADRs for REMICADE listed in the SmPC.

REMICADE Clinical Trial Data

As displayed in the risk tables above, the frequency of malignancy in the all randomized, blinded trials REMICADE population versus the placebo/comparator group was similar for various subtypes:

- Lymphoma (excluding HSTCL), <0.1% vs 0.0%
- Leukemia, <0.1% vs 0.0%
- Melanoma, <0.1% vs 0.0%
- Cervical cancer, 0.0% vs 0.0%
- Malignancy (excluding lymphoma, HSTCL, pediatric malignancy, leukemia, melanoma, Merkel cell carcinoma, and cervical cancer), 0.2% vs 0.2%

There were no reports of HSTCL, Merkel cell cancer, Kaposi's sarcoma, or pediatric malignancy in subjects participating in randomized clinical trials of REMICADE; therefore, frequency from clinical trial data could not be determined.

Postmarketing Experience

Postmarketing data for malignancies (including the subtypes of lymphoma, HSTCL, leukemia, Merkel cell carcinoma, melanoma, Kaposi's sarcoma, and cervical cancer) as described in the PBRERs/PSURs to date are consistent with what is currently known about this risk in patients treated with REMICADE.

Postmarketing cases of malignancy have been reported in pediatric patients exposed to REMICADE. When these events occur, they are potentially serious and life-threatening. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. These also included malignancies that are not usually observed in children and adolescents.

The impact of this risk on the individual patient is potentially significant, particularly in patients with an existing malignancy, a history of malignancy, or significant risk factors for malignancy such as a history of heavy smoking.

Risk Factors and Risk Groups:

Because disease severity, cumulative disease activity, and disease duration may also contribute to an increased risk of malignancy in patients with immune-mediated diseases, it is difficult to distinguish the individual contribution of immunosuppressive medications, including those like REMICADE that inhibit TNFα, from other risk factors for the development of malignancy (Jones et al, 1996; Tennis et al, 1993; Silman et al, 1988). This is further complicated by the fact that patients with severe disease are more likely to have been treated with one or more immunosuppressive medications. A risk for the development of malignancies other than the types noted specifically above in patients treated with TNF blockers cannot be excluded.

Preventability:

Caution should be exercised when considering TNFα-antagonist therapy for patients with a history of malignant disease or when considering continuing treatment in patients who develop any form of malignancy (Special warnings and precautions for use section of the SmPC). Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with REMICADE is not established, the risk and benefits of continued therapy to the individual patient should be carefully considered by the clinician.

Caution should also be exercised in considering treatment of patients with increased risk of malignancy due to heavy smoking.

Impact on the Risk-Benefit Balance of the Product:

The observed incidence of malignancy (including lymphoma, HSTCL, leukemia, melanoma, Merkel cell carcinoma, cervical cancer, Kaposi's sarcoma, and pediatric malignancy) has not had a significant impact on the risk-benefit balance of the product. The SmPC and PL provide information to the prescriber and patient on how to manage the important identified risk of malignancy.

Public Health Impact:

The potential public health impact is not known.

Annex 1 MedDRA Term:

Standardised MedDRA Query: Malignant or unspecified tumors.

Important Potential Risk – Colon Carcinoma/Dysplasia (in Pediatric UC)

Potential Mechanisms:

Tumor necrosis factor has been shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumor cell lines (Mocellin et al, 2005). Low doses of TNF can increase tumor blood vessel permeability, thus augmenting tissue concentrations of chemotherapeutic agents, as well as enhance the cytolytic effect of NK and CD8+ T cell killing of immunogenic tumor cells (Balkwill, 2009). Therefore, the neutralization of TNF by REMICADE may allow some types of tumor cells to survive.

Evidence Source and Strength of Evidence:

Colorectal cancer is known to occur at a higher rate in patients with chronic UC than in the general population. Tumor necrosis factor blocking agents, including REMICADE, decrease the activity of the immune system and as a result, there may be an increased risk of intestinal cancer if abnormal growth in the intestine develops in patients with UC who are treated with REMICADE. Therefore, colon carcinoma/dysplasia (in pediatric UC) is considered an important potential risk that needs to be carefully weighed against the benefit conferred by use of the medication.

Characterization of the Risk – Data and Discussion:

There were no reports of colon carcinoma/dysplasia in children treated with REMICADE in the pediatric UC clinical trial (C0168T72).

Given the latency period for the development of certain events, including malignancies, the MAH followed children who had participated in the C0168T72 clinical trial for 5 years in a long-term safety study (RESULTS UC); no malignancies were reported in children through 5 years of follow-up.

Postmarketing Experience

Cumulatively through 23 August 2019, one postmarketing report of colon cancer in a pediatric patient who was treated with REMICADE for UC has been reported. During the same time period, a small number of cases of colon cancer have been reported in young adults between the ages of 18 and 30 years who were treated with REMICADE for UC.

The impact of this risk on the individual patient could vary from minimal to potentially significant. Patients with a history of colon carcinoma/dysplasia may be more prone to recurrence of the condition and patients who develop colon carcinoma/dysplasia may have a more severe course due to use of the product.

Risk Factors and Risk Groups:

Patients with long-standing UC or primary sclerosing cholangitis, or those who had a prior history of dysplasia or colon carcinoma, are at a higher risk for developing colon cancer or dysplasia. Other risk factors for development of colorectal dysplasia and cancer in patients with UC include extent of disease, family history of colorectal cancer, young age at diagnosis, and the presence of backwash ileitis (ileal inflammation in the context of UC).

Preventability:

All patients with UC who are at increased risk for dysplasia or colon carcinoma (eg, patients with long-standing UC or primary sclerosing cholangitis) or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course (Special warnings and precautions for use section of the SmPC). This evaluation should include colonoscopy and biopsies per local recommendations.

Impact on the Risk-Benefit Balance of the Product:

The observed incidence of colon carcinoma/dysplasia (in pediatric UC) has not had a significant impact on the risk-benefit balance of the product. The SmPC and PL provide information to the prescriber and patient on how to manage the risk.

Public Health Impact:

The public health impact is not known.

Annex 1 MedDRA Term:

HLGT: Gastrointestinal neoplasms malignant and unspecified.

SVII.3.2. Presentation of the Missing Information

Missing information: None.

Evidence source: Not applicable.

Population in need of further characterization OR Anticipated risk/consequence of the missing information: Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns	
Important identified risks	Serious infection/sepsis BCG breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE Demyelinating disorders Malignancy
Important potential risks	Colon carcinoma/dysplasia (in pediatric UC)
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires	
Safety Concern	**Purpose/Description**
Not applicable	

Other Forms of Routine Pharmacovigilance Activities		
Activity	**Objective/Description**	**Milestones**
None	Not applicable	Not applicable

III.2. Additional Pharmacovigilance Activities

Study name and title	DEVELOP
Rationale and study objectives	To obtain long-term safety and clinical status information on pediatric patients (under 17 years of age) with IBD (ie, CD, UC, or indeterminate colitis [IC]) who were treated with REMICADE and/or other medical therapies for IBD.
Safety concerns addressed	• Serious infection/sepsis • Demyelinating disorders • Malignancy • Colon carcinoma/dysplasia (in pediatric UC)
Study design	DEVELOP consists of 3 separate protocols to comply with differences in regional regulatory commitments and local regulations for clinical research: • C0168Z02: Multicenter, prospective, long-term, observational registry conducted in the US and Canada. This protocol includes an immunogenicity substudy. • REMICADEPIB4002: Multicenter, prospective, long-term registry conducted in the Netherlands. This is an EU-specific registry and the protocol is noninterventional. • REMICADEPIB4003: Multicenter, observational, prospective, long-term registry conducted in Denmark, Germany, France, Italy, Belgium, and the UK. This is an EU-specific registry and the protocol is noninterventional. Data from the 3 studies will be pooled, analyzed, and presented in the DEVELOP report.
Study population	Pediatric patients (under 17 years of age) with IBD (ie, CD, UC, or IC) who were treated with REMICADE and/or other medical therapies for IBD.
Milestones	Next interim report: 31 Dec 2030 Final report: 31 Dec 2045

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization **not applicable**				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances **not applicable**				
Category 3 - Required additional pharmacovigilance activities				
DEVELOP (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) Ongoing	To obtain long-term safety and clinical status information on pediatric patients (under 17 years of age) with IBD (ie, CD, UC, or IC) who were treated with REMICADE and/or other medical therapies for IBD. Data from the 3 studies will be pooled, analyzed, and presented in the DEVELOP report.	• Serious infection/sepsis • Demyelinating disorders • Malignancy • Colon carcinoma/dysplasia (in pediatric UC)	Next interim report	31 Dec 2030
			Final report	31 Dec 2045

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Not applicable.

PART V: RISK MINIMIZATION MEASURES

(Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Serious infection/sepsis	Routine risk communication: • SmPC section 4.3 (Contraindications) • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • SmPC section 4.6 (Fertility, pregnancy and lactation) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Guidance for monitoring patients for infections before, during, and after REMICADE treatment, as well as guidance regarding diagnostic evaluation, discontinuation of REMICADE treatment, and administration of appropriate antimicrobial or antifungal therapy in patients who develop infection, is provided in SmPC section 4.4. Guidance regarding infections, including a list of the signs of infection, is also provided in PL section 2. • Guidance regarding concomitant use of live vaccines in patients treated with REMICADE is provided in SmPC sections 4.4 and 4.5 and in PL section 2. • Recommendations regarding the administration of live vaccines to an infant exposed to infliximab in utero or during breast-feeding to minimize the risk of BCG breakthrough infection are provided in SmPC sections 4.4, 4.5, and 4.6 and in PL section 2. Other routine risk minimization measures beyond the Product Information: • Legal status: Restricted medical prescription

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
BCG breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE	Routine risk communication: • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • SmPC section 4.6 (Fertility, pregnancy and lactation) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations regarding the administration of live vaccines to an infant exposed to infliximab in utero or during breast-feeding to minimize the risk of BCG breakthrough infection are provided in SmPC sections 4.4, 4.5, and 4.6 and in PL section 2. • Guidance for preventing pregnancy during and after treatment with REMICADE is provided in SmPC section 4.6 and in PL section 2. Other routine risk minimization measures beyond the Product Information: • Legal status: Restricted medical prescription
Demyelinating disorders	Routine risk communication: • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Guidance to discontinue REMICADE treatment in patients who develop demyelinating disorders is provided in SmPC section 4.4. • Guidance regarding nervous system disease, including a list of the signs of such disease, is provided in PL section 2. Other routine risk minimization measures beyond the Product Information: • Legal status: Restricted medical prescription
Malignancy	Routine risk communication: • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.8 (Undesirable effects) • PL section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for periodic skin examination and cervical cancer screening are provided in SmPC section 4.4. Other routine risk minimization measures beyond the Product Information: • Legal status: Restricted medical prescription

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern	
Safety Concern	**Routine Risk Minimization Activities**
Colon carcinoma/dysplasia (in pediatric UC)	Routine risk communication: • SmPC section 4.4 (Special warnings and precautions for use) Routine risk minimization activities recommending specific clinical measures to address the risk: • A recommendation for regular screening of UC patients who are at increased risk for dysplasia or colon carcinoma, or who have a prior history of dysplasia or colon carcinoma is provided in SmPC section 4.4. Other routine risk minimization measures beyond the Product Information: • Legal status: Restricted medical prescription

V.2. Additional Risk Minimization Measures

Table Part V.2: Description of Additional Risk Minimization Measures	
Additional Risk Minimization Activity 1: Patient Reminder Card	
Objectives:	The objectives of the patient reminder card are to serve as a reminder to record the dates and outcomes of specific tests and to facilitate patient sharing of special information about ongoing treatment with REMICADE with treating HCPs. The patient reminder card addresses the following important identified risks: • Serious infection/sepsis • BCG breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE In addition to providing guidance for all patients regarding active infection, TB, and hepatitis B, the patient reminder card includes information for mothers regarding vaccination of infants exposed to infliximab in utero or during breast-feeding, including when to seek the attention of an HCP.
Rationale for the additional risk minimization activity:	The patient reminder card contains important information about the risk of infection in patients treated with REMICADE and in infants exposed to infliximab in utero or during breast-feeding, including when to seek the attention of an HCP. The patient reminder card facilitates the sharing of important information between patients and HCPs and is considered an essential tool to ensure the safe use of REMICADE.
Target audience and planned distribution path:	Patients. The patient reminder card is provided as part of the product packaging. Physicians who prescribe REMICADE are expected to provide and explain the patient reminder card to all their patients treated with REMICADE and to review the content with them.
Plans to evaluate the effectiveness of the interventions and criteria for	There are no regulatory commitments regarding measuring the effectiveness of the patient reminder card.

Table Part V.2: Description of Additional Risk Minimization Measures	
success:	
Additional Risk Minimization Activity 2: Direct Healthcare Professional Communication	
Objectives:	The overall objective of the DHPC is to inform HCPs of important updated recommendations regarding the administration of live vaccines to infants exposed to infliximab in utero or during breast-feeding. The DHPC addresses the following important identified risks: • Serious infection/sepsis • BCG breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE
Rationale for the additional risk minimization activity:	The REMICADE SmPC, PL, and patient reminder card have been updated to reflect the current evidence regarding live vaccination of infants exposed to infliximab in utero or during breast-feeding. Because the updated recommendations represent new information for the prescriber, a DHPC is considered necessary so that the risk of BCG breakthrough infection in these infants is minimized.
Target audience and planned distribution path:	Prescribers of infliximab: including but not limited to rheumatologists, adult and pediatric gastroenterologists, dermatologists, pediatricians. Exact target audience to be defined and agreed at national level. Professional societies and national associations to be defined and agreed at national level. These should preferably include national associations for the above-mentioned specialists, and also for general practitioners, specialists in obstetrics and HCP or related HCP organizations who are responsible for national immunization programs for children. Distribution path to be defined and agreed at national level.
Plans to evaluate the effectiveness of the interventions and criteria for success:	There are no regulatory commitments regarding measuring the effectiveness of the DHPC.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infection/sepsis	Routine risk minimization measures: • SmPC section 4.3 (Contraindications) • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • SmPC section 4.6 (Fertility, pregnancy and lactation) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Additional risk minimization measures: • Patient reminder card • DHPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003)
BCG breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE	Routine risk minimization measures: • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • SmPC section 4.6 (Fertility, pregnancy and lactation) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Additional risk minimization measures: • Patient reminder card (BCG only) • DHPC (BCG only)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Demyelinating disorders	Routine risk minimization measures: • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003)
Malignancy	Routine risk minimization measures: • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.8 (Undesirable effects) • PL section 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003)
Colon carcinoma/dysplasia (in pediatric UC)	Routine risk minimization measures: • SmPC section 4.4 (Special warnings and precautions for use) Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for REMICADE® (Infliximab)

This is a summary of the risk management plan (RMP) for REMICADE. The RMP details important risks of REMICADE, how these risks can be minimized, and how more information will be obtained about REMICADE's risks and uncertainties (missing information).

REMICADE's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how REMICADE should be used.

This summary of the RMP for REMICADE should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of REMICADE's RMP.

I. The Medicine and What it is Used For

REMICADE is authorized for the treatment of rheumatoid arthritis, Crohn's disease (adult and pediatric), ulcerative colitis (adult and pediatric), ankylosing spondylitis, psoriatic arthritis, and psoriasis (see SmPC for the full indication). It contains infliximab as the active substance, and it is given by the intravenous route of administration.

Further information about the evaluation of REMICADE's benefits can be found in REMICADE's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000240/human_med_001023.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of REMICADE, together with measures to minimize such risks and the proposed studies for learning more about REMICADE's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can include:

- Specific information, such as warnings, precautions, and advice on correct use included in the PL addressed to patients and the SmPC addressed to healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - ie, the amount of medicine included in a single pack which is chosen to ensure that the medicine is used correctly;
- The medicine's legal status - ie, the way a medicine is supplied to the patient (eg, with or without a prescription).

Together, these measures constitute routine risk minimization measures.

In the case of REMICADE, these measures are supplemented with the additional risk minimization measures mentioned under relevant important risks (see section II.B, below).

In addition to risk minimization measures, information about adverse reactions is collected continuously and regularly analyzed, including in Periodic Safety Update Reports (PSURs) so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of REMICADE are risks that need special risk management activities to further investigate or minimize the risk so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of REMICADE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Serious infection/sepsis Bacille Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE Demyelinating disorders Malignancy
Important potential risks	Colon carcinoma/dysplasia (in pediatric ulcerative colitis)
Missing information	None

II.B. Summary of Important Risks

Important Identified Risk: Serious Infection/Sepsis	
Evidence for linking the risk to the medicine	REMICADE acts by inhibiting the activity of TNFα and reduces the immune response and inflammation in the body. Patients may therefore get infections more easily when receiving treatment with REMICADE. These infections may be serious and may, in rare cases, be life threatening. Serious infections/sepsis, including opportunistic infections, TB, and hepatitis B reactivation, have been reported in patients treated with REMICADE in clinical trials and in the postmarketing setting. These findings are consistent with published medical literature and experience with other medicines that also act by inhibiting TNF. Serious infection/sepsis is considered an important identified risk because the impact of this risk on the individual patient can be potentially significant and the risk needs to be carefully weighed against the benefit conferred by the use of the medicine. REMICADE is contraindicated in patients with TB or other severe infections, such as sepsis, abscesses, and opportunistic infections (section 4.3 of the SmPC).
Risk factors and risk groups	**Serious Infection/Sepsis** Because REMICADE suppresses the activity of TNFα, which mediates inflammation and regulates immune responses, patients treated with REMICADE are more susceptible to serious infections. Elderly patients In clinical trials, the incidence of serious infection in REMICADE-treated patients 65 years of age and older was greater than that seen in those under 65 years of age. In addition, there is a greater incidence of infections in the elderly population in general. Children In clinical trials, more children who received REMICADE developed infections than adults who received REMICADE. **Opportunistic Infections** The risk of developing opportunistic infections increases dramatically with progressive impairment of the immune system. Patients with chronic infection or a history of recurrent infection, including those who use other immunosuppressive medications, such as methotrexate, are at a greater risk of developing an opportunistic infection during REMICADE therapy. Patients who have resided in or traveled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, and blastomycosis are widespread, are also at increased risk of developing an opportunistic infection during REMICADE therapy.

Important Identified Risk: Serious Infection/Sepsis	
	Tuberculosis The most common risk factors for the development of TB include conditions that weaken the immune system, such as advanced age, human immunodeficiency virus (HIV) infection, alcohol abuse, malignancy, use of corticosteroids or other immunosuppressive therapy, connective tissue disease, renal failure, diabetes, and pregnancy. Other risk factors for the development of TB include contact with a person(s) with active TB infection and having been born in, or lived in, or traveled to countries where the incidence of TB is high. Exposure to TB may occur through various health care settings (eg, hospitals and nursing homes) or high-density institutions (eg, prisons). **Hepatitis B Reactivation** Approximately 14% to 50% of immunosuppressed patients who are chronic carriers of HBV will experience acute reactivations during the natural history of their disease. Thus, risk factors for HBV reactivation in patients with a history of HBV infection include the concomitant use of medications that suppress the immune system (eg, chemotherapy, corticosteroids, methotrexate, azathioprine, TNFα inhibitors). Other risk factors that may contribute to HBV reactivation include HIV infection, transplantation (especially bone marrow), and withdrawal from immunosuppressive therapies.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.3 (Contraindications) • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • SmPC section 4.6 (Fertility, pregnancy and lactation) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Additional risk minimization measures: • Patient reminder card • DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Bacille Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE	
Evidence for linking the risk to the medicine	REMICADE crosses the placenta. REMICADE acts by inhibiting the activity of TNFα and reduces the immune response. If REMICADE is given during pregnancy, it may cause some rare side-effects in the baby for up to 12 months after birth such as specific types of infection after the baby receives a live vaccine or has low white blood cell count. Cases of BCG breakthrough infection and agranulocytosis have been reported in postmarketing reports in babies whose mothers used REMICADE while pregnant. These findings are consistent with published medical literature. BCG breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE is considered an important identified risk because the impact of this risk on an infant exposed to REMICADE in utero is significant.
Risk factors and risk groups	Infants exposed to REMICADE in utero and who receive BCG vaccine within 12 months after birth are at risk for developing disseminated BCG infection. Infants exposed in utero to REMICADE are also at increased risk of developing agranulocytosis.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • SmPC section 4.6 (Fertility, pregnancy and lactation) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Additional risk minimization measures: • Patient reminder card (BCG only) • DHPC (BCG only)

Important Identified Risk: Demyelinating disorders	
Evidence for linking the risk to the medicine	Serious nervous system disorders such as transverse myelitis, multiple sclerosis-like disease, optic neuritis, and Guillain-Barré syndrome are rare side effects of REMICADE. In clinical trials, demyelinating disorders have been reported in patients treated with REMICADE. Reports have been noted in the postmarketing setting and are consistent with published medical literature and experience with other medicines that also act by inhibiting TNF. Demyelinating disorders are considered an important identified risk because of the consistency of evidence across multiple sources, including data from other products in the same class.
Risk factors and risk groups	Multiple Sclerosis (MS) and other autoimmune diseases have been linked to genetic and environmental factors. First-degree relatives of MS patients are at greater risk to develop MS than the general population. Whites, particularly of northern European descent, are also more likely to develop MS. Several studies have suggested an association between smoking and MS. Obesity in early life and Epstein-Barr virus have also been identified as risk factors for MS.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Malignancy	
Evidence for linking the risk to the medicine	TNF blockers, including REMICADE, decrease the activity of the immune system. This may increase the risk of cancer. Certain cancers have been seen more commonly in TNFα treated patients than expected. Although this has not been seen with all cancer types, it is possible that REMICADE may have some effect on other cancers. Malignancies, including the subtypes of lymphoma, hepatosplenic T-cell lymphoma (HSTCL), leukemia, melanoma, Merkel cell carcinoma, cervical cancer, Kaposi's sarcoma, and pediatric malignancy, have been reported in clinical trials with REMICADE, the postmarketing setting, published medical literature, or epidemiological studies. Some children and teenage patients who have received TNF blockers such as REMICADE have developed cancers, including unusual types such as HSTCL, which sometimes resulted in death. Most of the patients were receiving concomitant immunosuppressants, such as methotrexate, azathioprine, or 6-mercaptopurine.
Risk factors and risk groups	Because disease severity, cumulative disease activity, and disease duration may also contribute to an increased risk of malignancy in patients with immune-mediated diseases, it is difficult to distinguish the individual contribution of immunosuppressive medications, including those like REMICADE that inhibit TNFα, from other risk factors for the development of malignancy. This is further complicated by the fact that patients with severe disease are more likely to have been treated with one or more immunosuppressive medications. A risk for the development of malignancies other than the types noted specifically above in patients treated with TNF blockers cannot be excluded.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.8 (Undesirable effects) • PL section 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Colon carcinoma/dysplasia (in pediatric ulcerative colitis)	
Evidence for linking the risk to the medicine	Colorectal cancer is known to occur at a higher rate in patients with chronic ulcerative colitis than in the general population. Tumor necrosis factor blocking agents, including REMICADE, decrease the activity of the immune system and as a result, there may be an increased risk of intestinal cancer if abnormal growth in the intestine develops in patients with ulcerative colitis who are treated with REMICADE. Therefore, colon carcinoma/dysplasia (in pediatric ulcerative colitis) is considered an important potential risk that needs to be carefully weighed against the benefit conferred by use of the medication.
Risk factors and risk groups	Patients with long-standing ulcerative colitis or primary sclerosing cholangitis, or who had a prior history of dysplasia or colon carcinoma are at a higher risk for developing colon cancer or dysplasia. Other risk factors for development of colorectal dysplasia and cancer in patients with ulcerative colitis include extent of disease, family history of colorectal cancer, young age at diagnosis, and the presence of backwash ileitis (ileal inflammation in the context of ulcerative colitis).
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 (Special warnings and precautions for use) Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) See section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of REMICADE.

II.C.2. Other Studies in Postauthorization Development Plan

Study	Purpose of the Study
DEVELOP (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003)	To obtain long-term safety and clinical status information on pediatric patients (under 17 years of age) with inflammatory bowel disease (ie, Crohn's disease, ulcerative colitis, or indeterminate colitis) who were treated with REMICADE and/or other medical therapies for inflammatory bowel disease. Data from the 3 studies will be pooled, analyzed, and presented in the DEVELOP report. To address the safety concerns of: Serious infection/sepsis Demyelinating disorders Malignancy Colon carcinoma/dysplasia (in pediatric ulcerative colitis)

PART VII: ANNEXES

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Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Additional Risk Minimization Activities (if applicable)

Approved Key Messages of the Additional Risk Minimization Measures

Patient Reminder Card

Prescribing HCPs should provide and explain the patient reminder card to all patients treated with REMICADE. Direction to HCPs regarding the provision of the patient reminder card is given in section 4.2 of the SmPC.

The patient reminder card includes the following key messages:

- A reminder to patients to show the patient reminder card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using REMICADE
- A statement that the brand name and batch number should be recorded
- Provision to record the type, date, and result of TB screenings
- That treatment with REMICADE may increase the risks of serious infections/sepsis, opportunistic infections, TB, hepatitis B reactivation, and BCG breakthrough infection in infants with in utero or breast-feeding exposure to infliximab, and when to seek attention from a HCP
- Contact details of the prescriber

Direct Healthcare Professional Communication

The DHPC includes the following key messages:

- Infants exposed to infliximab in utero (i.e., during pregnancy)
    - Infliximab has been detected in infant serum up to 12 months after birth. After in utero exposure, infants may be at increased risk of infection, including serious disseminated infection that can become fatal.
    - Live vaccines (e.g., BCG vaccine) should not be given to infants after in utero exposure to infliximab for 12 months after birth.
    - If infant infliximab serum levels are undetectable or if infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant.
- Infants exposed to infliximab via breast milk
    - Infliximab has been detected at low levels in human milk. It has also been detected in infant serum after exposure to infliximab via breast milk.
    - Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable.

Direct Healthcare Professional Communication recipients in all EU countries where infliximab is marketed:

- Prescribers of infliximab; including but not limited to rheumatologists, adult and pediatric gastroenterologists, dermatologists, pediatricians. Exact target audience to be defined and agreed at national level.
- Professional societies and national associations to be defined and agreed at national level. These should preferably include national associations for the above-mentioned specialists, and also for general practitioners, specialists in obstetrics and HCP or related HCP organizations who are responsible for national immunization programs for children.