Summary of the Risk Management Plan

Summary of the Risk Management Plan for Kromeya (adalimumab)

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

Kromeya's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Kromeya should be used.

This summary of the RMP for Kromeya 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 Kromeya's RMP.

I. The Medicine and What it is used for

Kromeya is proposed to be authorized for Rheumatoid Arthritis (RA), Crohn's Disease (CD), Psoriasis, Ulcerative Colitis (UC), and Uveitis in adults. As well, Kromeya is proposed to be authorized for Polyarticular Juvenile Idiopathic Arthritis (pJIA), Enthesitis-Related Arthritis, Pediatric Crohn's Disease, Pediatric Psoriasis and Paediatric Uveitis(see SmPC for the full indication). It contains adalimumab as the active substance and is administered as clear solution for injection (vial), clear solution for injection in pre-filled syringe and clear solution for injection in pre-filled pen.

Further information about the evaluation of Kromeya’s benefits can be found in Kromeya’s EPAR, including in its plain-language summary, available on the EMA website: https://www.ema.europa.eu/en/medicines/human/EPAR/idacio

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

Important risks of Kromeya, together with measures to minimize such risks and the proposed studies for learning more about Kromeya’s risks, are outlined in this section.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Kromeya, these measures are supplemented with *additional risk minimization* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

If important information that may affect the safe use of Kromeya is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Kromeya 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 Kromeya. 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 (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB • Reactivation of hepatitis • Pancreatitis • Lymphoma • HSTCL • Leukemia • NMSC • Melanoma • Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin) • Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barre syndrome [GBS], and optic neuritis [ON]) • Immune reactions (including lupus-like reactions and allergic reactions) • Sarcoidosis

List of important risks and missing information	
	• CHF • MI • CVA • Interstitial lung disease (ILD) • Pulmonary embolism • Cutaneous vasculitis • Stevens-Johnson syndrome (SJS) • Erythema multiforme • Worsening and new onset of Ps • Hematologic disorders • Intestinal perforation • Intestinal stricture in CD • Liver failure and Other Liver Events • Elevated ALT levels (• Autoimmune Hepatitis (AIH) • Medication errors and maladministration
Important potential risks	• Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, and melanoma) • Vasculitis (non-cutaneous) • Progressive multifocal leukoencephalopathy (PML) • Reversible posterior leukoencephalopathy syndrome (RPLS) • Amyotrophic lateral sclerosis (ALS) • Adenocarcinoma of colon in UC patients • Infections in infants exposed to adalimumab in utero • Medication errors with pediatric via • Off-label use
Missing information	• Patients with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications; • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD and pedERA;

List of important risks and missing information	
	• Pregnant and lactating women • Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and IJA • Long-term safety data in the treatment of adults with HS. • Long-term safety data in the treatment of adults with uveitis

II.B Summary of Important Risks

Table 1 Important Identified Risk: Serious Infections Including Diverticulitis and Opportunistic Infections, e.g., Invasive Fungal Infections, Parasitic Infections, Legionellosis, and TB

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, the overall subject incidence of AEs in the SOC "Infections and Infestations" was 50.7% in the Kromeya arm, 37.8% in the Humira® arm and 48.5% in the Humira®/Kromeya switch arm. There were 7 SAEs of infection: respiratory tract infection viral, peritonsillar abscess and sinusitis in the Kromeya arm, arthritis bacterial and pneumonia in the Humira® arm, and appendicitis and staphylococcal abscess in Humira®/Kromeya switch arm. The most commonly reported AEs of infection were nasopharyngitis (18.6%, 16.0% and 16.8%), pharyngitis (5.4%, 1.7 %, and 3.0%) and upper respiratory tract infection (5.4%, 5.0% and 5.0%). There was 1 report of tuberculosis (TB) in Kromeya arm, and there were no reports of invasive fungal infections.

The table below represents data derived from Humira® studies:

Identified or potential risk	Serious Infections, Including Diverticulitis and Opportunistic Infections, e.g., Invasive Fungal Infections, Parasitic Infections, Legionellosis, and TB
Risk groups or risk factors	Risk factors for infection, in general, may include risk factors for serious infectious events with anti-TNF agents include disease inherent and individual patient characteristics. Advanced age, disease activity, comorbidities (eg, diabetes, chronic obstructive pulmonary disease) and baseline corticosteroid use significantly increase the risk of serious infectious events (Doran et al, 2002).
Evidence source	Humira® SmPC, referenced published literature and Kromeya clinical studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.3, 4.4, 4.8): Section 4.3: Contraindications for active TB or other severe infections such as sepsis, and opportunistic infections. Section 4.4: Warnings regarding active TB and serious infections such as sepsis due to bacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis. Warning regarding a higher risk of infections in the elderly population 65 years. Section 4.8: Diverticulitis is listed as an adverse reaction. In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risks of serious infections associated with the use of: • Patient Alert Card • HCP Educational Material
Additional pharmacovigilance activities	This safety concern will be monitored in the proposed category 3 studies, as feasible.

Table 2 Important Identified Risk: Reactivation of Hepatitis B

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there were no reports of hepatitis B reactivation in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Reactivation of Hepatitis B
Risk groups or risk factors	Risk factors of HBV infection include unprotected sex, sharing needles during intravenous (IV) drug use, sharing a household with someone who has a chronic HBV infection, occupational exposure (e.g., hospital workers), receiving hemodialysis for end-stage kidney (renal) disease, traveling to regions with high infection rates of HBV, such as Africa, Central and Southeast Asia, and Eastern Europe (Mayo Clinic 2011).
Evidence source	Humira® SmPC Aug 2017, referenced published literature and Kromeya clinical studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warning regarding hepatitis B reactivation is included in the Special warnings and precautions for use section. Section 4.8: The reactivation of hepatitis B is also listed as an adverse reaction identified in post marketing surveillance in the Undesirable effects section (Section 4.8) of the SmPC. The SmPC recommends testing for HBV before initiating treatment with Humira®. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 3 Important Identified Risk: Pancreatitis

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, the overall subject incidence of pancreatitis AEs was 0.8% (1 subject, non-serious AE) in the Humira® arm. There were no reports of pancreatitis in the Kromeya arm or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Pancreatitis
Risk groups or risk factors	Most common factors associated with an increased risk of pancreatitis include gallstones, alcohol consumption, trauma, ischemia, mechanical obstruction, infections, autoimmunity, and certain drugs (Moores 2012).
Evidence source	Humira® SmPC Aug 2017, Humira® USPI May 2017, referenced published literature and Kromeya clinical studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.8: Pancreatitis is listed as an uncommon adverse reaction seen in clinical trials. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 4 Important Identified Risk: Lymphoma

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there were no reports of lymphoma in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Lymphoma
Risk groups or risk factors	Factors associated with an increased risk of NHL include weakened immune system (e.g., heritable disease, certain drugs used after an organ transplant), infection (e.g., HIV, Epstein-Barr virus, H. pylori, human T-cell lymphoma/leukemia virus type I (HTLV-I), and hepatitis C), and age (over 60 years) (National Cancer Institute 2008). Factors associated with an increased risk of HL include weakened immune system (e.g., heritable disease, certain drugs used after an organ transplant), viral infection (e.g., HIV, Epstein-Barr virus), and age (among teens and adults aged 15 to 35 years and adults aged 55 years or older) (National Cancer Institute 2008). A prospective observational cohort study of 19,486 patients with IBD, including 7,727 patients with UC or unclassified IBD, found an increased risk for developing lymphoproliferative disorders among patients receiving thiopurines compared to patients who had never received these drugs (hazard ratio: 5.28; 95% CI: 2.01 - 13.9) (Beaugerie 2009).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya clinical studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warning regarding lymphoma and malignancies in the adult and pediatric population. Section 4.8: Information on incidence rates from clinical trials. In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Alert Card • HCP Educational Material

Table 5 Important Identified Risk: Hepatosplenic T-Cell Lymphoma

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there were no reports of HSTCL in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Hepatosplenic T-Cell Lymphoma
Risk groups or risk factors	Risk factors for lymphoma, in general, can be found in **Error! Reference source not found.**. Past and concomitant thiopurine therapy appears to contribute to the risk in patients with IBD. Other risks in Important Identify Risk: Lymphoma may or may not be applicable to HSTCL which is rare (Kotlyar 2011, Parakkal 2011).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya clinical studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warning regarding hepatosplenic T-cell lymphoma and malignancies in the adult and pediatric population. Section 4.8: Information on incidence rates from post marketing is included. The SmPC also highlights that some of the cases of HSTCL occurred with concomitant use of azathioprine or 6-mercaptopurine, and that the potential risk combination of azathioprine or 6-mercaptopurine and Kromeya should be carefully considered. In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Alert Card • HCP Educational Material

Table 6 Important Identified Risk: Leukemia

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54 there were no reports of leukemia in the Kromeya arm, Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Leukemia
Risk groups or risk factors	Factors associated with an increased risk of leukemia include radiation, tobacco smoking, benzene exposure, prior chemotherapies (e.g., alkylating agents), genetic diseases including Down syndrome, blood disorders (e.g., myelodysplastic syndrome), HLTV-I, and a family history of leukemia (National Cancer Institute 2014).
Evidence source	Humira® SmPC, Aug 2017, Humira® USPI May 2017 and Kromeya studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Warning regarding the risk of leukemia and malignancies in the adult and pediatric population In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Alert Card • HCP Educational Material

Table 7 Important Identified Risk: Non-Melanoma Skin Cancer

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there were no reports of NMSC in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Non-Melanoma Skin Cancer
Risk groups or risk factors	Factors associated with an increased risk of skin cancer include radiation (e.g., sunlight, tanning, therapy), personal or family history of melanoma, fair skin, certain drugs (e.g., antibiotics, hormones, antidepressants, thiopurines (Peyrin-Biroulet 2011)), medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic (National Cancer Institute 2011). Additional risk factors that increase squamous cell cancer risk are HPV infection and actinic keratosis (National Cancer Institute 2011).
Evidence source	Humira® SmPC, Aug 2017 and Kromeya studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warning regarding the risk of NMSC and malignancies in the adult and pediatric population. Section 4.8: Incidence rates for NMSC from clinical trials are included. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Identified risk	Non-Melanoma Skin Cancer
	To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Alert Card • HCP Educational Material

Table 8 Important Identified Risk: Melanoma

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there were no reports of melanoma in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Melanoma
Risk groups or risk factors	Factors associated with an increased risk of melanoma include UV radiation (e.g., sunlight, tanning), personal history of melanoma, family history of melanoma, fair skin, certain drugs (e.g., antibiotics, hormones, antidepressants), medical conditions that suppress the immune system or are treated with drugs that suppress the immune system, dysplastic nevus, and having many common moles (National Cancer Institute 2011).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature reports and Kromeya studies
Risk minimization measures	Section 4.4: Warning regarding malignancies in the adult and pediatric population. Section 4.8: Melanoma is listed as an adverse reaction identified in clinical trials. In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Alert Card • HCP Educational Material

Table 9 Important Identified Risk: Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin)

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there were no reports of MCC in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin)
Risk groups or risk factors	Factors associated with an increased risk of MCC include advanced age, immunosuppression (e.g., organ transplant, HIV), other cancers (e.g., squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and hematological neoplasias) and UV light exposure (Becker 2010).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature reports and Kromeya studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warning regarding Merkel cell carcinoma (neuroendocrine carcinoma of the skin). Section 4.8: MCC is also listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Alert Card • HCP Educational Material
Additional pharmacovigilance activities	This safety concern will be monitored in the proposed category 3 studies, as feasible.

Table 10 Important Identified Risk: Demyelinating Disorders (Including Multiple Sclerosis, Guillain- Barre Syndrome, and Optic Neuritis)

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there were no reports of demyelinating disorders in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Demyelinating Disorders
Risk groups or risk factors	Factors associated with an increased risk of MS include genetic predisposition (e.g., HLA-DR2 (HLA-DRBl *15), ethnic origin (being white), female sex, Epstein-Barr infection, smoking, latitude/vitamin D, and early exposure to environmental risk factors (Ramagopalan 2010). Factors associated with an increased risk of GBS include male sex, Campylobacter jejuni infection, some vaccines, and increased age (Sejvar 2011). Subjects with intermediate uveitis have a high prevalence of demyelination (Zein 2004, Llorenc 2012).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warnings on demyelinating disorders are included. Further details for the uveitis patient population are also included. Section 4.8: Demyelinating disorders are also listed as adverse reaction identified in post marketing surveillance in order to inform patients of these risks, corresponding Text is also present in the package leaflet. To educate prescribers and patients about 1) the risk of demyelinating disorders associated with the use of, and 2) the underlying risk of demyelinating disorders associated with uveitis, particularly intermediate uveitis: • Patient Alert Card • HCP Educational Material

Table 11 Important Identified Risk: Immune Reactions - Lupus-Like Reactions

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there were no reports of lupus like reactions in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Lupus-Like Reactions
Risk groups or risk factors	No epidemiological data available.
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warnings regarding lupus-like reactions and serious allergic reactions are included. Section 4.8: Lupus-like syndrome and anaphylaxis are also listed as adverse reactions identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 12 Important Identified Risk: Immune Reactions - Allergic Reactions

In the pivotal adult study EMR200588-002 in psoriasis patients through Week 54, the subject incidence of AEs under the SMQ "hypersensitivity" was 4.5% (10 of 221 subjects) in the Kromeya arm, 3.4% (4 of 119 subjects) in the Humira® arm, and 5.0% (5 of 101 subjects) in the Humira®/Kromeya switch arm. The overall incidence rate of AEs under the SMQ "anaphylactic reaction" was 1.0% (1 subject of 101) in the Humira®/Kromeya switch arm, and none in the Kromeya or Humira® arms. Of these, there was one SAE report of anaphylactic shock (due to bee sting) in the Humira®/Kromeya switch arm, one event of erythema multiforme (1 of 221 subjects) and one event of hypersensitivity vasculitis (1 of 221 subjects) in the Kromeya arm.

The table below represents data derived from Humira® studies:

Identified risk	Allergic Reactions
Risk groups or risk factors	No epidemiological data available.
Evidence source	Humira® SmPC, Aug 2017 and Kromeya studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warnings regarding lupus-like reactions and serious allergic reactions are included. Section 4.8: Lupus-like syndrome and anaphylaxis are also listed as adverse reactions identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 13 Important Identified Risk: Sarcoidosis

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there was no report of sarcoidosis in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Sarcoidosis
Risk groups or risk factors	Factors associated with an increased risk of sarcoidosis include genetic predisposition and family history of sarcoidosis, female sex, and age between 20 to 40 years. In the USA, lifetime risk of sarcoidosis among blacks is higher than whites. Sarcoidosis is more common among persons of Scandinavian, Irish, German and West Indian descent, while sarcoidosis is relatively rare in Japan, Spain, and Portugal (O'Regan 2012).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Sarcoidosis is listed as an uncommon adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 14 Important Identified Risk: Congestive Heart Failure

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there was no report of congestive cardiac failure in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Congestive Heart Failure
Risk groups or risk factors	Factors associated with an increased risk of CHF include being male, being black, increased age, hypertension, antecedent MI and diabetes mellitus. Healthy lifestyle factors (i.e., normal weight, not smoking, regular exercise, moderate alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables) were associated with a lower risk of CHF (Roger 2012).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.3, 4.4 and 4.8): Section 4.3: Moderate to severe CHF as contraindication to Humira® use is contained in the Contraindication section. Section 4.4: Warning regarding including worsening and new onset CHF is included. It advises that Kromeya should be used with caution patients with mild heart failure with instructions to stop adalimumab in patients who develop new or worsening of symptoms of CHF. Section 4.8: CHF is also listed as an adverse reaction identified in clinical studies. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Objective and justification of why needed: To educate prescribers and patients about the risk of CHF associated with the use of: • Patient Alert Card • HCP Educational Material

Table 15 Important Identified Risk: Myocardial Infarction

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, acute myocardial infarction was reported for one subject (incidence rate: 0.5%) in the Kromeya arm and myocardial infarction was reported for one subject (incidence rate: 1.0%) in the Humira®/Kromeya switch arm. Both events of myocardial infarction were SAEs.

The table below represents data derived from Humira® studies:

Identified risk	Myocardial Infarction
Risk groups or risk factors	Factors associated with an increased risk of MI include increased age, high blood pressure, smoking/tobacco use, high blood cholesterol and other lipids, physical inactivity, dietary factors, abdominal obesity, diabetes mellitus, personal history of CHD, and end-stage renal disease and chronic kidney disease (Roger 2012).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies
Risk minimization measures	Section 4.8: Myocardial infarction is listed as an adverse reaction identified in patients taking adalimumab in originator's post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 16 Important Identified Risk: Cerebrovascular Accident

In the pivotal adult study of Kromeya in patients with psoriasis, through Week 54, there was no report of a cerebrovascular accident (CVA) in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Cerebrovascular Accident
Risk groups or risk factors	Factors associated with an increased risk of CVA include increased age, high blood pressure, disorders of heart rhythm (including atrial fibrillation), smoking/tobacco use, high blood cholesterol and other lipids, physical inactivity, diabetes mellitus, and end-stage renal disease and chronic kidney disease (Roger 2012).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Cerebrovascular accident is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 17 Important Identified Risk: Interstitial Lung Disease

In the pivotal adult study of Kromeya in psoriasis patients, through Week 54, there was no report of ILD in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Interstitial Lung Disease
Frequency	Cases of ILD were reported uncommonly (< 1/1000 to < 1/100} in clinical trials (Humira® SmPC, Aug 2017)
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Interstitial lung disease is listed as an adverse reaction identified in clinical studies. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 18 Important Identified Risk: Pulmonary Embolism

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there was no report of pulmonary embolism in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Pulmonary Embolism
Risk groups or risk factors	Venous thromboembolism (including pulmonary embolism) risk factors include increasing age, surgery, trauma/fracture, hospital or nursing home confinement, active cancer, central vein catheterization or transvenous pacemaker, prior superficial vein thrombosis, varicose veins and neurological disease with leg paresis, and among women, physical inactivity, oral contraceptives, pregnancy/postpartum, and hormone therapy (Roger 2012).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Pulmonary embolism is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 19 Important Identified Risk: Cutaneous Vasculitis

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there was no report of cutaneous vasculitis in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies.

Identified risk	Cutaneous Vasculitis
Risk groups or risk factors	Factors associated with an increased risk of cutaneous vasculitis are largely unknown, but may include infection (e.g., hepatitis B virus [HBV] with polyarteritis nodosa, and hepatitis C virus [HCV] with mixed cryoglobulinemia), certain drugs (e.g., penicillins, sulfonamides, quinolones, hydantoins), chemical substances (e.g., insecticides, herbicides, petroleum derivatives), inflammatory diseases (e.g., systemic lupus erythematosus [SLE], RA, Sjogren syndrome, CD, UC, mixed cryoglobulinemia, hypergammaglobulinemic purpura of Waldenstrom), and malignancy (solid and hematologic neoplasms) (Pulido-Perez 2012, Fiorentino 2003).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies.
Risk minimization measures	Text in SmPC Text in SmPC (refer to SmPC section 4.8): Section 4.8: Cutaneous vasculitis is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 20 Important Identified Risk: Stevens - Johnson syndrome

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there was no report of SJS in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Stevens-Johnson Syndrome
Risk groups or risk factors	Risk factors for SJS include infection (e.g., HIV), genetic susceptibility (e.g., HLA-B*l502 among Han Chinese patients who are exposed to carbamazepine, HLA-B*5801 among Han Chinese patients who are exposed to allopurinol), and drug exposure (e.g., allopurinol, sulfonamide antibiotics, aminopenicillins, cephalosporins, quinolones, chlormezanone, carbamazepine, phenytoin, phenobarbital, valproic acid, NSAID of the oxicam-type, and corticosteroids) (Harr 2010).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8): Section 4.8: SJS is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 21 Important Identified Risk: Erythema Multiforme

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there was one report of erythema multiforme (diagnosis not medically confirmed by specialist, as subject was lost to follow up) in the Kromeya arm, and none in the Humira® arm or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Erythema Multiforme (EM)
Risk groups or risk factors	Risk factors for EM include herpes simplex virus, other infections (e.g., fungal, mycoplasma pneumonia), and medications (e.g., barbiturates, hyadantoins, NSAIDS, penicillins, phenothiazines, and sulfonamides (Schneider 2012).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Erythema multiforme is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 22 Important Identified Risk: Worsening and New Onset of Psoriasis

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there was no report of worsening or new onset psoriasis in the Kromeya arm, the Humira® arm or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Worsening and New Onset of Psoriasis
Risk groups or risk factors	High BMI, tobacco smoke, stressful life events, and Genetic predisposition (e.g., HLA-Cw*06) may be risk factors for psoriasis (Kumar 2012, Li 2009).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Worsening and New Onset of Psoriasis is listed as an adverse reaction identified in post marketing surveillance Text in PIL: Worsening and new onset of Ps is addressed in section 4.8: Table 2: Worsening and New Onset of Psoriasis (including palmoplantar pustular psoriasis) is listed as an adverse drug reaction with a frequency of 'common' (includes spontaneous data). No text in relation to these risks is present in the package leaflet.

Table 23 Important Identified Risk: Hematologic Disorders

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, anemia (0.9%, 0.0%, 1.0%), eosinophilia (1.4%, 0.0%, 2.0%), lymphocytosis (0.9%, 0.0%, 0.0%), lymphopenia (0.5%, 0.0%, 0.0%), and neutropenia (0.0%, 0.8%, 0.0%) were reported in the respective treatment arms (Kromeya, Humira®, Humira®/Kromeya). Of these events, the single event of neutropenia in the Humira® arm was considered an SAE.

The table below represents data derived from Humira® studies:

Identified risk	Hematologic Disorders including Pancytopenia
Risk groups or risk factors	Factors associated with an increased risk of febrile neutropenia among patients with cancer receiving chemotherapy include older age, poor performance status, comorbidities (such as renal disease, cardiovascular disease, and liver disease), chemotherapy, advanced disease of cancer, and certain genetic factors (Lyman 2014).
Evidence source	Humira® SmPC, Aug 2017, referenced published literature and Kromeya studies
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Warning regarding hematologic reactions including medically significant cytopenias is included. It advises that discontinuation of Kromeya therapy should be considered in patients with confirmed significant hematologic abnormalities. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 24 Important Identified Risk: Intestinal Perforation

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there was no report of intestinal perforation in the Kromeya arm, the Humira® arm or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Intestinal Perforation
Risk groups or risk factors	NSAIDs, corticosteroids, and opioid analgesics may be associated with perforated colonic diverticular disease (Morris 2003). Use of NSAIDs and steroids has also been associated with perforation of the small or large bowel (Langman 1985, Lanas 1997). Additionally, gastrointestinal perforation may be a result of appendicitis, cancer, Crohn's disease, diverticulitis, gallbladder disease, peptic ulcer disease, ulcerative colitis, and abdominal surgery (NCBI NLM PubMed Health: Gastrointestinal Perforation 2012).
Evidence source	Humira®-SmPC Aug 2017, referenced published literature and Kromeya clinical studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Intestinal perforation is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 25 Important Identified Risk: Intestinal Stricture in CD

In the pivotal adult study EMR200588-002 in Psoriasis patients, through Week 54, there was no report of intestinal stricture in CD in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Intestinal Stricture in CD
Risk groups or risk factors	For Humira®-indicated populations, the risk factors of intestinal stricture are not well described.
Evidence source	Humira®-SmPC Aug 2017, referenced published literature and Kromeya clinical studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Warning regarding small bowel obstruction and intestinal stricture is included. No text in relation to this risk is present in the package leaflet.

Table 26 Important Identified Risk: Liver Failure and Other Liver Events

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, the overall incidence rate of AEs of hepatobiliary disorders was 1.4% (3 subjects) in the Kromeya arm, 0.8% (1 subject) in the Humira® arm and 1.0% (1 subject) in the Humira®/Kromeya switch arm. There was one SAE (cholecystitis chronic) in the Kromeya arm and none in the Humira® arm or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Liver Failure and Other Liver Events
Risk groups or risk factors	Factors associated with an increased risk of liver failure include drug toxicity (e.g., acetaminophen), chronic hepatitis (e.g., hepatitis C viral infection, hepatitis B viral infection, autoimmune hepatitis), long-term alcohol use, disease of the bile ducts, hemochromatosis, Wilson's disease, and nonalcoholic steatohepatitis (National Institute of Diabetes and Digestive and Kidney Diseases: National Digestive Diseases Information Clearinghouse 2013).
Evidence source	Humira®-SmPC Aug 2017, referenced published literature and Kromeya clinical studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8) Section 4.8: Liver failure is listed as an adverse reaction identified in post marketing surveillance Hepatitis is listed as an adverse reaction with a frequency of 'rare.' In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 27 Important Identified Risk: Elevated ALT Levels

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, the incidence rate of the PT alanine aminotransferase increased was 3.2% in the Kromeya arm, 3.4% in the Humira® arm, and 3.0% in the Humira®/Kromeya switch arm. None of these events were considered as SAEs.

The table below represents data derived from Humira® studies:

Identified risk	Elevated ALT Levels
Risk groups or risk factors	Elevations in ALT are a marker of liver injury or muscle injury. ALT elevations may be indicative of autoimmune hepatitis, hepatitis B/C infection, exposure to some drugs or toxins, exposure to ethanol, fatty liver disease, tumors, congestive heart failure, and hemochromatosis, copper overload of Wilson's disease or alpha l-antitrypsin deficiency, and serious muscle injury (Hashem 1999).
Evidence source	Humira®-SmPC Aug 2017, referenced published literature and Kromeya clinical studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8): Section 4.8: The risk of elevated ALT levels and elevated liver enzymes is listed as an adverse reaction identified in clinical studies. In order to inform patients of these risks, corresponding text is also present in the package leaflet.
Additional pharmacovigilance activities	This safety concern will be monitored in the proposed category 3 studies, as feasible.

Table 28 Important Identified Risk: Autoimmune Hepatitis

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, there were no reports of AIH in the Kromeya arm, the Humira® arm, or the Humira®/Kromeya switch arm.

The table below represents data derived from Humira® studies:

Identified risk	Autoimmune Hepatitis
Risk groups or risk factors	Factors associated with an increased risk of AIH are largely unknown, but may include female sex, presence of an autoimmune disease, and genetic predisposition. Potential environmental risk factors include certain viruses (e.g., measles virus, hepatitis viruses, cytomegalovirus and Epstein-Barr virus), and medicines (herbal products, antibiotics such as minocycline or oxafloxacin, and statins) (Gossard 2012).
Evidence source	Humira®-SmPC Aug 2017, referenced published literature and Kromeya clinical studies.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8) Section 4.8: AIH is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.
Additional pharmacovigilance activities	This safety concern will be monitored in the proposed category 3 studies, as feasible.

Table 29 Important Identified Risk: Medication errors and maladministration

Identified risk	Medication errors and maladministration
Risk groups or risk factors	Sometimes patients can have trouble using the Humira pen. This could cause patients to be under dosed or miss a dose, which may make Humira less effective.
Evidence source	Not available
Risk minimization measures	Text in the SmPC: None. Instructions for preparing and giving an injection of adalimumab are outlined in the Package Leaflet.

Table 30 Important Potential Risk: Other Malignancies (Except Lymphoma, HSTCL, Leukemia, NMSC, and Melanoma)

Potential risk	Other Malignancies
Risk groups or risk factors	Malignancies are a heterogeneous group with varied risk factors. Risk factors for relatively common cancers are presented for illustration. Factors associated with an increased risk of breast cancer include combination hormone therapy, obesity in postmenopausal women, alcohol consumption, and genetic susceptibility. Strenuous exercise, early pregnancy, and breastfeeding may lower the risk of breast cancer (National Cancer Institute 2013). Kidney cancer risk may be increased through smoking, obesity, hypertension, and a family history of kidney cancer or conditions with a predisposition to kidney disease (e.g., Von Ripple-Lindau syndrome) (National Cancer Institute 2011). Established risk factors for lung cancer include cigarette smoking (including passive smoking), radon exposure, and exposure to lung carcinogens (e.g., asbestos) (National Cancer Institute 2013). Factors associated with an increased risk of prostate cancer include increased age, race (high risk among blacks and of intermediate levels among whites), and a family history of prostate cancer (National Cancer Institute 2013).
Evidence source	Referenced published literature
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8): Section 4.4: Warning regarding malignancies and malignancies in the pediatric population in the warning section and information on rates from clinical trials are included. Section 4.8: Warning regarding malignancies and malignancies in the pediatric population in the warning section and information on rates from clinical trials are included. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 31 Important Potential Risk: Vasculitis (Non-Cutaneous)

Potential risk	Vasculitis (Non-Cutaneous)
Risk groups or risk factors	Risk factors for vasculitis include smoking, chronic infection, hypersensitivity to medicines, autoimmune disorders (e.g., SLE, RA, scleroderma), and hematologic cancers (e.g., lymphoma, leukemia) (National Heart, Lung, and Blood Institute. Accessed on 11 January 2013).
Evidence source	Referenced published literature
Risk minimization measures	Text in SmPC (refer to SmPC section 4.8): Section 4.8 contains vasculitis as uncommon.

Table 32 Important Potential Risk: Progressive Multifocal Leukoencephalopathy

Potential risk	Progressive Multifocal Leukoencephalopathy
Risk groups or risk factors	PML occurs predominantly among severely immunosuppressed patients. A descriptive analysis of PML cases identified through claims found approximately 40% of patients were aged 40 to 49 years and 75% were male (Eng 2006). Currently, over 80% of PML cases are diagnosed in patients with HIVIAIDS (Weber 2008). Prior to the era of HIV and AIDS, more than 60% of PML cases were seen in patients with lymphoproliferative disorders, with the highest incidence reported in patients with chronic lymphocytic leukemia (Carson 2009). Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, systemic lupus erythematosus (SLE) and other rheumatic diseases (Carson 2009, Calabrese 2007, Bartt 2006, Govindappa 2007).
Evidence source	Referenced published literature
Risk minimization measures	Text in SmPC: None Other routine risk minimization measures: Prescription only medicine.

Table 33 Important Potential Risk: Reversible Posterior Leukoencephalopathy Syndrome

Potential risk	Reversible Posterior Leukoencephalopathy Syndrome
Risk groups or risk factors	Suspected etiologies in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Comorbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%) (Lee 2008).
Evidence source	Humira®-SmPC Aug 2017, Referenced published literature.
Risk minimization measures	Text in SmPC: None Other routine risk minimization measures: Prescription only medicine.

Table 34 Important Potential Risk: Amyotrophic Lateral Sclerosis

Potential risk	Amyotrophic Lateral Sclerosis
Risk groups or risk factors	Genetic predisposition and smoking are the most important risk factors for ALS. Other factors associated with disease include age at menopause (females), dietary factors, electrical injury, family history of non-ALS neurodegenerative disease (e.g., Parkinson's or Alzheimer's disease), geographical residence (rural, suburban or urban), Gulf war service (Male veterans), maternal age, number of births (in females) and birth order, loss of child, occupation, physical activity, playing football professionally, previous poliomyelitis infection, race/ethnicity, smoking, toxin exposure (agricultural chemicals, lead), trauma (e.g., head injury), and years of education (Wijesekera 2009).
Evidence source	Referenced published literature, Humira®-SmPC Aug 2017,
Risk minimization measures	Text in SmPC: None Other routine risk minimization measures: Prescription only medicine.

Table 35 Important Potential Risk: Adenocarcinoma of Colon in Ulcerative Colitis Patients

Potential risk	Adenocarcinoma of Colon in Ulcerative Colitis Patients
Risk groups or risk factors	Factors associated with an increased risk of colorectal cancer include age greater than 50 years, presence of colorectal polyps, genetic predisposition, personal or family history of some cancers, duration of UC, extent and severity of UC, comorbid primary sclerosing cholangitis (Van Assche 2013), diet, and cigarette smoking (National Cancer Institute 2006).
Evidence source	Referenced published literature, Humira®-SmPC Aug 2017,
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Recommendation that all patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis 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.
Additional pharmacovigilance activities	This safety concern will be monitored in the proposed category 3 studies, as feasible.

Table 36 Important Potential Risk: Infections in Infants Exposed to Adalimumab in Utero

Potential risk	Infections in Infants Exposed to Adalimumab in Utero
Risk groups or risk factors	Infants exposed to adalimumab in utero.
Evidence source	Referenced published literature. Literature report that indicates adalimumab actively crosses the placenta and can be detectable in the serum of infants exposed in utero for at least 3 months from birth (Mahadevan 2011) and information reports of the presence of another monoclonal antibody (infliximab) in infants from mothers who were on the drug (Vasiliauskas 2006).
Risk minimization measures	Text in SmPC (refer to SmPC section 4.6): Section 4.6: Information regarding the risk of infections in infants exposed to adalimumab in utero is listed. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 37 Important potential Risk: Medication errors with pediatric vial

Potential risk	Medication errors with pediatric vial
Risk groups or risk factors	Improper use of this product may cause the patient to receive the wrong dose of adalimumab.
Evidence source	Not available
Risk minimization measures	Text in the SmPC: None Detailed usage description of the single use pediatric vial outlined in the Patient Leaflet and the vial is clearly labelled for single use only.

Table 38 Important potential Risk: Off label use

Potential risk	Off-label use
Risk groups or risk factors	Sometimes, physicians may prescribe adalimumab for uses that are not yet approved
Evidence source	Not available
Risk minimization measures	Text in SmPC: None Other routine risk minimization measures: Prescription only medicine.

Table 39 **Missing Information: Patients with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications.**

Missing information	Patients with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Warnings regarding patients with immune-compromised conditions are included. There is currently no information on patients with a history of clinically significant drug or alcohol abuse listed in the SmPC. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 40 **Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with pedCD and pedERA.**

Missing information	Long-term safety information in the treatment of children aged from 6 years to less than 18 years with pedCD and pedERA.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.2): Section 4.2: Statements that the safety and efficacy of in these populations is yet to be established In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 41 Missing information: Pregnant and lactating women

Missing information	Pregnant and lactating women
Risk minimization measures	Text in SmPC (refer to SmPC section 4.6): Section 4.6: Limited clinical data on exposed pregnancies are available and, therefore, administration of adalimumab is not recommended during pregnancy. Contraception is recommended to women while on Kromeya therapy and for a least 5 months after last treatment. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 42 Missing Information: Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and JIA

Missing information	Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and JIA
Risk minimization measures	None

Table 43 Missing Information: Monitoring to better understand the effects of adalimumab in longer-term treatment of HS.

Missing information	Monitoring to better understand the effects of adalimumab in longer-term treatment of HS.
Risk minimization measures	Text in SmPC (refer to SmPC section 4.2): Section 4.2: Statements that the long-term safety and efficacy of Kromeya in this population will be periodically re-evaluated. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

Table 44 Missing Information: Long term safety data in the treatment of adults with uveitis

Missing information	Long term safety data in the treatment of adults with uveitis
Risk minimization measures	Text in SmPC (refer to SmPC section 4.2): Section 4.2: Statements that the long-term safety and efficacy of Kromeya in this population will be periodically re-evaluated. In order to inform patients of these risks, corresponding text is also present in the package leaflet.

II.C Post-authorization Development Plan

The safety profile of Kromeya as observed in clinical trials is similar to that of Humira®. Humira® has been marketed for over 12 years and the safety profile has been consistent to date. The long-term safety assessments of Humira® in clinical trial exposure of 23458 patients treated with Humira® for diseases including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, and Crohn's disease continue to be consistent with that of the TNF antagonist class of drugs, and no new safety signals have been reported in these assessments (Burmester et al 2013). In view of the structural and functional similarities between MSB and Humira® the safety profile of Kromeya is expected to be the same as that of Humira® in all other indications not studied. Continued monitoring of the safety data and identification of any new signal is proposed to be followed through the safety assessments of spontaneous adverse drug reaction reports and communicated via the submission of periodic aggregate reports.

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 invented name.

II.C.2 Other Studies in the Post-Authorization Development Plan

Observational registry (RABBIT) Study #1-A prospective, observational cohort study (sample size of at least 300 subjects foreseen) whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumor necrosis factor-inhibitor therapies in the treatment of RA.

Objective: The purpose of the study is to contribute to the overall evidence base in support of adalimumab, in particular the estimation of incidence rates of adverse events of special interest for adalimumab as identified in the summary of safety concerns in the risk management plan.

II.C.2.2

Observational registry (IBD UK) Study #2-A prospective, observational cohort study (sample size of at least 300 subjects foreseen) to facilitate continuous improvement in IBD patient care and access to care across the UK, improve understanding of long term outcomes for IBD patients from care and Support IBD research.

Objective: The purpose of the study is to contribute to the overall evidence base in support of adalimumab, in particular the estimation of incidence rates of adverse events of special interest for adalimumab as identified in the summary of safety concerns in the risk management plan.