Summary of risk management plan for Hulio® (adalimumab)

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

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

This summary of the RMP for Hulio® 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 Hulio®'s RMP.

I. The medicine and what it is used for

Hulio® is authorised for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis, psoriatic arthritis, plaque psoriasis in adults and children, hidradenitis suppurativa, Crohn's disease in adults and children, ulcerative colitis, and non-infectious uveitis in adults and children (see SmPC for the full indication). It contains adalimumab as the active substance and it is given by subcutaneous injection.

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

http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004429/human_med_002302.jsp.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;

Important advice on the medicine's packaging;

The authorised 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 minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 Hulio® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Hulio® are risks that need special risk management activities to further investigate or minimise 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 Hulio®. 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 tuberculosis [TB]) Reactivation of hepatitis B Pancreatitis Lymphoma Hepatosplenic T-cell Lymphoma (HSTCL) Leukaemia Non-melanoma skin cancer (NMSC) Melanoma Merkel cell carcinoma (MCC) (neuroendocrine carcinoma of the skin)

List of important risks and missing information	
	Demyelinating disorders (including multiple sclerosis [MS], Guillain- Barré syndrome [GBS], and optic neuritis) Immune reactions (including lupus-like reactions and allergic reactions) Sarcoidosis Congestive heart failure (CHF) Myocardial infarction (MI) Cerebrovascular accident (CVA) Interstitial lung disease (ILD) Pulmonary embolism (PE) Cutaneous vasculitis Stevens-Johnson syndrome (SJS) Erythema multiforme (EM) Worsening and new onset of psoriasis (Ps) Haematologic disorders Intestinal perforation Intestinal stricture in CD Liver failure and other liver events Elevated alanine transaminase (ALT) levels Autoimmune hepatitis Medication errors and maladministration
Important potential risks	Other malignancies (except lymphoma, hepatosplenic T-cell lymphoma [HSTCL], leukaemia, non-melanoma skin cancer [NMSC], and melanoma) Vasculitis (non-cutaneous) Progressive multifocal leukoencephalopathy (PML) Reversible posterior leukoencephalopathy syndrome (RPLS) Amyotrophic lateral sclerosis (ALS) Colon cancer in ulcerative colitis (UC) patients Infections in infants exposed to Hulio® in utero Medication errors with paediatric vial Off-label use
Missing information	Subjects 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

List of important risks and missing information	
	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 to <18 years with Crohn's disease (CD) and paediatric enthesitis-related arthritis (pedERA) Pregnant and lactating women Remission-withdrawal-retreatment data for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (nr-axSpA) and episodic treatment in psoriasis, Crohn's disease, ulcerative colitis and juvenile idiopathic arthritis (Ps, CD, UC, and JIA) Long-term safety information in the treatment of adults with hidradenitis suppurativa (HS) Long-term safety information in the treatment of adults and children with uveitis

II.B Summary of important risks

Important identified risk 1: Serious infections including diverticulitis and opportunistic infection, e.g., invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, respiratory tract infections have been reported to occur very commonly (≥ 1/10). In the clinical studies conducted with Hulio® to date, the most common treatment-related infections included bronchitis, nasopharyngitis and urinary tract infection, although the number of patients experiencing a serious infection was small (19 subjects [2.9%] receiving Hulio®). Serious infections have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Standard-dose and high-dose biological drugs (with or without traditional disease-modifying anti-rheumatic drugs [DMARDs]) have been shown to be associated with a statistically significant increase in serious infections in methotrexate-naïve rheumatoid

Important identified risk 1: Serious infections including diverticulitis and opportunistic infection, e.g., invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB)	
	arthritis patients compared with traditional DMARDs; the absolute risk increase of serious infections with biologic therapy was identified as 6 per 1000 for standard-dose biologic and 17 per 1000 for high-dose biologic therapy. Other risks associated with serious infections include: very young people and elderly people; concomitant immunosuppressive therapies, including steroids, chemotherapy drugs or radiation; history of previous serious or recurrent infections; compromised circulation (e.g. longstanding diabetes); compromised skin integrity (e.g. large burns or severe trauma); and splenectomy or dysfunctional spleen.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3 where patients with active tuberculosis or other severe infections are contraindicated* *SmPC section 4.4 where a warning is given not to initiate treatment in patients with active infections, to closely monitor patients for infections, and to discontinue Hulio® if a patient develops a new serious infection or sepsis* *SmPC section 4.8 where a description of serious infections observed in adalimumab clinical trials is provided* *SmPC section 4.8 listed as adverse reactions* *PL section 2 where patients with active tuberculosis or other severe infections are contraindicated* *PL section 2 where a warning is given for the patient not to use if they have a severe infection, and that they will be monitored closely for infections and TB* *PL section 4 listed as side effects* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

Important identified risk 1: Serious infections including diverticulitis and opportunistic infection, e.g., invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB)	
	Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE) *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 2: Reactivation of Hepatitis B	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, reactivation of hepatitis B has been reported to occur rarely (≥ 1/10,000 to < 1/1,000). Although there have been no treatment-related cases of hepatitis B reactivation in the clinical studies conducted with Hulio® to date, reactivation of hepatitis B has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	The WHO fact sheet updated July 2016 specifies the following risk groups: people who frequently require blood or blood products, dialysis patients, recipients of solid organ transplantations; people interned in prisons; persons who inject drugs; household and sexual contacts of people with chronic hepatitis B virus infection; people with multiple sexual partners; health-care workers and others who may be exposed to blood and blood products through their work; and travellers to endemic areas, who have not been vaccinated.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given to test patients for HBV infection before initiating treatment with Hulio®, to closely monitor patients who are carriers of HBV, and to stop treatment if HBV reactivation develops* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that the doctor will test them for HBV*

Important identified risk 2: Reactivation of Hepatitis B	
	PL section 4 listed as a side effect *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 3: Pancreatitis	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, pancreatitis has been reported to occur uncommonly (≥ 1/1,000 to < 1/100). Although there have been no treatment-related cases of acute pancreatitis in the clinical studies conducted with Hulio® to date, pancreatitis has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Gallbladder disease (gallstones) and excess alcohol consumption account for most cases of pancreatitis with less common causes including: injury/trauma, ischaemia, viral infections (Coxsackie B, hepatitis and mumps), and certain drugs (thiazides, valproate, azathioprine, L-asparaginase, corticosteroids).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 4: Lymphoma	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, lymphoma has been reported to occur uncommonly (≥ 1/1,000 to < 1/100). Although there have been no treatment-related cases of lymphoma in the clinical studies conducted with Hulio® to date, lymphoma has been classed

Important identified risk 4: Lymphoma	
	as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of Hodgkin's lymphoma include immunosuppression, viral infection (human immunodeficiency virus [HIV], Epstein-Barr virus), mononucleosis and cigarette smoking. Factors associated with an increased risk of non-Hodgkin's lymphoma include a weakened immune system (e.g. congenital and acquired immunodeficiency states or autoimmune disorders), chromosomal translocations and molecular rearrangements, infection (e.g. HIV, Epstein-Barr virus, Hepatitis C, Human T cell leukaemia virus type 1 [HTLV-1] and Helicobacter pylori), environmental factors (e.g. pesticides, herbicides, solvents, organic chemicals, wood preservatives, dusts, hair dye, chemotherapy and radiation exposure). http://patient.info/doctor/hodgkins-lymphoma-pro.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about possible development of lymphomas in patients (including children) treated with a TNF antagonist* *SmPC section 4.8 where a description of lymphomas observed in adalimumab clinical trialsis provided* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE)*

Important identified risk 4: Lymphoma	
	British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK) See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 5: Hepatosplenic T-cell Lymphoma (HSTCL)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, the occurrence of HSTCL is reported to be not known. Although there have been no treatment-related cases of HSTCL in the clinical studies conducted with Hulio® to date, HSTCL has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors for lymphoma, in general, include a weakened immune system (e.g. congenital and acquired immunodeficiency states or autoimmune disorders), chromosomal translocations and molecular rearrangements, infection (e.g. HIV, Epstein-Barr virus, Hepatitis C, Human T cell leukaemia virus type 1 [HTLV-1] and Helicobacter pylori), environmental factors (e.g. pesticides, herbicides, solvents, organic chemicals, wood preservatives, dusts, hair dye, chemotherapy and radiation exposure). Past and concomitant thiopurine therapy appears to contribute to the risk in patients with irritable bowel disease (IBD).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about possible development of HSTCL in patients treated with adalimumab and that the combination of azathioprine or 6-mercaptopurine and Hulio® should be carefully considered* *SmPC section 4.8 where a description of HSTCL observed in adalimumab clinical trials is provided* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures:

Important identified risk 5: Hepatosplenic T-cell Lymphoma (HSTCL)	
	Patient Alert Card *HCP Educational Material*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 6: Leukaemia	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, leukaemia has been reported to occur rarely (≥ 1/10,000 to < 1/1,000). Although there have been no treatment-related cases of leukaemia in the clinical studies conducted with Hulio® to date, leukaemia has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of leukaemia include haematological disorders (e.g. myelodysplastic syndrome), radiation, congenital disorders (e.g. Down's syndrome), exposure to benzene, prior chemotherapy treatment (e.g. alkylating agents), and a family history of leukaemia.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about possible development of leukaemia in patients treated with a TNF antagonist* *SmPC section 4.8 where a description of leukaemia observed in adalimumab clinical trials is provided* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can increase the risk of getting leukaemia* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures:

Important identified risk 6: Leukaemia	
	Patient Alert Card *HCP Educational Material*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 7: Non melanoma skin cancer (NMSC)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, skin cancer excluding melanoma has been reported to occur commonly (≥ 1/100 to < 1/10). Of the treatment-related treatment-emergent adverse events, one case (0.2%) of basal cell carcinoma (BCC) was reported in the clinical studies conducted with Hulio®. NMSC has been classed as an identified risk for Hulio® in accordance with the reference product.

Important identified risk 7: Non melanoma skin cancer (NMSC)	
Risk factors and risk groups	Factors associated with an increased risk of skin cancer include exposure to sunlight (i.e. ultraviolet radiation, which is also emitted from tanning machines), fair skin, a personal or family history of skin cancer, actinic keratosis, damaged skin (burns, scars, long-standing sores, persistent inflammation), exposure to X-rays or certain chemicals (such as arsenic or creosote), a weakened immune system (e.g. due to immunosuppressant medication), some rare inherited disorders, (e.g. albinism, xeroderma pigmentosa, Gorlin's syndrome and Bazex syndrome). http://patient.info/health/skin-cancer-non-melanoma Among patients with rheumatoid arthritis use of tumour necrosis factor (TNF) inhibitors and prednisone have been shown to be associated with an increased risk of NMSC. Also, it was showed that TNF-α antagonist therapy in veterans with rheumatoid arthritis may be associated with an increased risk of NMSC, compared with therapy with non-biologic DMARDs, whilst another article concluded that disease-related factors like phototherapy may be important contributing factors to NMSC diagnosed in psoriasis patients treated with TNF inhibitors when compared with rheumatoid arthritis patients.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about possible development of other malignancies in patients treated with a TNF antagonist* *SmPC section 4.8 listed as an adverse reaction* *SmPC section 4.8 where a description of NMSC observed in adalimumab clinical trials is provided* *PL section 2 where a warning is given that Hulio® can increase the risk of getting non-melanoma skin cancer* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*

Important identified risk 7: Non melanoma skin cancer (NMSC)	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 8: Melanoma	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, melanoma has been reported to occur uncommonly (≥ 1/1,000 to < 1/100). Although there have been no treatment-related cases of melanoma in the clinical studies conducted with FKB327 to date, melanoma has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Factors associated with increased risk of melanoma include personal and/or family history of melanoma, having many common naevi (moles), ultraviolet radiation (i.e. exposure to sunlight, previous use of tanning machines), solar keratosis, past pesticide exposure.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about possible development of other malignancies in patients treated with a TNF antagonist* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer* *PL section 2 where a warning is given for the patient to talk to their doctor if new skin lesions appear during or after treatment* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*

Important identified risk 8: Melanoma	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 9: Merkel cell carcinoma (MCC)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, occurrence of MCC is reported to be not known. Although there have been no treatment-related cases of MCC in the clinical studies conducted with Hulio® to date, MCC has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of MCC include advanced age (the mean age of patients at the time of initial diagnosis is 70 years), immunosuppression (e.g. in patients with organ transplants and HIV infections, other cancers (e.g. squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and haematological neoplasias), and exposure to UV light.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about the possible development of other malignancies in patients treated with a TNF antagonist* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*

Important identified risk 9: Merkel cell carcinoma (MCC)	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 10: Demyelinating disorders (including multiple sclerosis [MS], Guillain- Barré syndrome [GBS], and optic neuritis)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, demyelinating disorders have been reported to occur rarely (≥ 1/10,000 to < 1/1,000). There have been no treatment-related cases coded as a recognised demyelinating disorder, although one treatment-related adverse event of hypoaesthesia was reported in the clinical studies conducted with Hulio®. Demyelinating disorders have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors associated with an increased risk for MS are a combination of genetic susceptibility (HLA-DR15 haplotype) and environmental exposures (including latitude, vitamin D deficiency, season of birth, Epstein Barr virus infection, and smoking behaviour). These factors appear to act synergistically and the risk of MS is increased in individuals exposed to more than one factor. Being Caucasian and female increases risk, as does having a family relative with MS Risk factors for GBS include male sex, prior infection (e.g. Campylobacter jejuni, Epstein Barr virus, cytomegalovirus, mycoplasma, HIV, and more recently Zika virus), vaccines, malignancies (e.g. lymphomas, especially Hodgkin's disease). Risk factors for optic neuritis include female sex, race (more frequent in white Caucasians, genetic mutations (as per MS),

Important identified risk 10: Demyelinating disorders (including multiple sclerosis [MS], Guillain- Barré syndrome [GBS], and optic neuritis)	
	bacterial/viral infections, sarcoidosis/lupus and some drugs (e.g. quinine and some antibiotics).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disease* *SmPC section 4.4 where a warning is given to exercise caution in considering the use of Hulio® in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders, and to consider discontinuation if these disorders develop* *SmPC section 4.4 where guidance is given to perform neurologic evaluation in patients with non-infectious intermediate uveitis prior to and during treatment* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given for the patient to talk to their doctor if experiencing symptoms such as weakness, numbness or tingling of the limbs* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 11: Immune reactions (including lupus-like reactions and allergic reactions)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, hypersensitivity and allergies (including seasonal allergy) have been reported to occur commonly (≥ 1/100 to < 1/10). Anaphylaxis and lupus-like

Important identified risk 11: Immune reactions (including lupus-like reactions and allergic reactions)	
	syndrome have been reported to occur rarely (≥ 1/10,000 to < 1/1,000). The overall incidence of hypersensitivity reaction or anaphylaxis reported as adverse events in the clinical studies conducted with Hulio® was very low (19 cases [2.9%]), with rash, allergic dermatitis and urticaria being the most frequently reported AEs. Immune reactions have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	No data is available for lupus-like reactions or allergic reactions, although general risks for systemic lupus erythematosus include: certain human leukocyte antigen DRB1 types e.g. DR3 and DR2; patients who have a defective C4 complement gene (C4A null allele); and environmental factors including ultraviolet light, viruses (eg, the Epstein-Barr virus) and some drugs (e.g.chlorpromazine, methyldopa, hydralazine, isoniazid, d-penicillamine and minocycline).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3 where patients with hypersensitivity to the active substance or to any of the excipients are contraindicated* *PL section 2 where patients with allergies to adalimumab or any of the other ingredients are contraindicated* *SmPC section 4.4 where instruction is given to discontinue treatment immediately and initiate appropriate therapy if an anaphylactic reaction or other serious allergic reaction occurs* *SmPC section 4.4 where a warning is given to stop further treatment with Hulio® if a patient develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against double-stranded DNA* *SmPC section 4.8 listed as an adverse reaction* *PL sections 2 and 4 where warnings are given for the patient not to further use Hulio® if they experience allergic reactions and to seek urgent medical attention* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures:

Important identified risk 11: Immune reactions (including lupus-like reactions and allergic reactions)	
	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 12: Sarcoidosis	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, sarcoidosis has been reported to occur uncommonly (≥ 1/1,000 to < 1/100). Although there have been no treatment-related cases of sarcoidosis in the clinical studies conducted with Hulio® to date, sarcoidosis has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of sarcoidosis include age (mid-20s to mid-40s), female sex, people of African and Scandinavian descent (lowest rates are reported in Japan), some exposures to dusty or mouldy environments, family history (3.6 9.6% of cases).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 13: Congestive heart failure (CHF)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, CHF has been reported to occur uncommonly (≥ 1/1,000 to < 1/100). Although, there have been no treatment-related cases of CHF in the clinical studies conducted

Important identified risk 13: Congestive heart failure (CHF)	
	with Hulio® to date, CHF has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of CHF include coronary/congenital heart disease, hypertension, and diabetes. In general, an unhealthy lifestyle (e.g. smoking, unbalanced/unhealthy diet, smoking, lack of physical exercise, excessive alcohol consumption) increases the risk. http://www.nhs.uk/Conditions/Heart-failure (accessed 06Feb2017), However, another article showed that the relative impact of the above risk factors appear to be significantly less in RA subjects compared to non-RA subjects, supporting the hypothesis that systemic inflammation is a major cardiovascular risk factor for in RA.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3 where patients with moderate to severe heart failure (NYHA class III/IV) are contraindicated* *SmPC section 4.4 where a warning is given to discontinue treatment with Hulio® in patients who develop new or worsening symptoms of congestive heart failure* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given for the patient not to use if they have moderate or severe heart failure* *PL section 2 where a warning is given for the patient to talk to their doctor if they have mild heart failure or have, or have previously had, a serious heart condition before starting treatment, or if they develop new or worsening symptoms of heart failure* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

Important identified risk 13: Congestive heart failure (CHF)	
	Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE) *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 14: Myocardial infarction (MI)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, MI has been reported to occur uncommonly (≥ 1/1,000 to < 1/100). There were 2 serious cases (0.4%) of MI (one of which was acute) in the clinical studies conducted with Hulio®. MI has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of MI include over 50 years of age (becoming more common with increasing age), smoking, high blood pressure, being overweight, high cholesterol, physical inactivity, poor diet, diabetes, family history of heart disease and end-stage renal disease and chronic kidney disease.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 15: Cerebrovascular accident (CVA)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, CVA has been reported to occur uncommonly (≥ 1/1,000 to < 1/100). Although there have been no treatment-related cases of CVA in the clinical studies conducted with Hulio® to date, CVA has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors for CVA include hypertension, smoking, diabetes mellitus, heart disease (valvular, ischaemic, atrial fibrillation), peripheral arterial disease, post-transient ischaemic attack, polycythaemia vera, carotid artery occlusion, combined oral contraceptive pill, hyperlipidaemia, excess alcohol and clotting disorders.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 16: Interstitial lung disease (ILD)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, ILD has been reported to occur uncommonly (≥ 1/1,000 to < 1/100). In the clinical studies conducted with Hulio® to date, of the treatment-related treatment-emergent AEs, one case (0.2%) of ILD was reported in the Hulio® treatment group. ILD has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of ILD in rheumatoid arthritis patients include history of smoking, increased age, male gender. In general, other factors associated with ILD include inhaled agents (e.g. silica, asbestos, heavy metals or mouldy foliage), environmental factors (e.g. pigeon breeding and

Important identified risk 16: Interstitial lung disease (ILD)	
	contaminated ventilation systems), chronic viral infections (e.g. hepatitis C and Epstein-Barr viruses), gastro-oesophageal reflux disease with micro-aspiration. Genetic predisposition may also be important (e.g. human leukocyte antigen (HLA) B54/ B40 and α-1 protease inhibitor).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 17: Pulmonary embolism (PE)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, PE has been reported to occur uncommonly (≥ 1/1,000 to < 1/100). Although there have been no treatment-related cases of PE in the clinical studies conducted with Hulio® to date, PE has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Clots form when one or more of the following factors are present: increased blood coagulability, reduced mobility, or blood vessel abnormalities. Risk factors for venous thromboembolism (including PE) include age over 60 years, fracture of lower extremities, joint replacement surgery, major general surgery, major trauma, active cancer, heart or respiratory failure, dehydration, obesity, pregnancy, history of venous thromboembolism, hormone replacement therapy and oral contraceptive use.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)*

Important identified risk 17: Pulmonary embolism (PE)	
	Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 18: Cutaneous vasculitis	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, cutaneous vasculitis has been reported to occur rarely (≥ 1/10,000 to < 1/1,000). Although there have been no treatment-related cases of cutaneous vasculitis in the clinical studies conducted with Hulio® to date, cutaneous vasculitis has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors for cutaneous vasculitis include smoking (RR=2.94; 95% CI 1.68 to 5.13), early rheumatoid arthritis disability (Steinbrocker class III IV at diagnosis) (RR=2.45; 95% CI 1.51 to 4.00), and increased age. Other factors in general include infection (e.g. Henoch-Schönlein purpura, septic vasculitis, upper respiratory tract flares of granulomatosis with polyangiitis [Wegener's granulomatosis], and polyarteritis nodosa [PAN]), other inflammatory diseases, drug-induced (e.g. sulfonamides, beta-lactams, quinolones, non-steroidal anti-inflammatory drug, oral contraceptives, thiazides, anti-influenza vaccines, and chemicals such as insecticides and petroleum products).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 19: Stevens-Johnson syndrome (SJS)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, SJS has been reported to occur rarely (≥ 1/10,000 to < 1/1,000). Although there have been no treatment-related cases of SJS in the clinical studies conducted with Hulio® to date, SJS has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Approximately 75% of SJS are caused by medications and 25% by infections and 'other' (as yet unknown) factors. Lamotrigine (an antiepileptic) and nevirapine (an anti-HIV drug) and other drugs (e.g. allopurinol, anti-infective sulphonamides, carbamazepine, phenytoin, phenobarbital and oxicam-NSAIDs) are considered high risk as well as a genetic predisposition (e.g. HLA-B1502 allele in the Han-Chinese population).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 20: Erythema multiforme (EM)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, EM has been reported to occur rarely (≥ 1/10,000 to < 1/1,000). Although there have been no treatment-related cases of EM in the clinical studies conducted with Hulio® to date, EM has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors for erythema multiforme include herpes simplex virus (HSV), other infections (e.g. mycoplasma pneumonia, fungal), medications (e.g. barbiturates, penicillins, phenothiazines, sulphonamides, anticonvulsants NSAIDs), vaccinations (e.g. diphtheria-tetanus, hepatitis B, smallpox), genetic susceptibility (e.g. association with HLA-B35, HLA-B62, HLA-DR53).

Important identified risk 20: Erythema multiforme (EM)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 21: Worsening and new onset of Psoriasis (Ps)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, worsening and new onset of Ps has been reported to occur commonly (≥ 1/100 to < 1/10). Although there have been no treatment-related cases of worsening and new onset of Ps in the clinical studies conducted with Hulio® (*studies were conducted in RA patients*), worsening and new onset of Ps has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	High BMI, environmental tobacco smoke exposure at home, and stressful life events may influence the development of paediatric Ps. The risk of Ps in adults was higher in urban dwellers, patients who were divorced and those exposed to environmental tobacco smoke at home, with alcohol consumption, family history of Ps and change in work conditions also shown to be risk factors, as well as genetic predisposition (e.g. HLA-Cw6, which is found in about 4-16% of healthy controls and in about 20% to over 50% of Ps cases, depending on the population being studied).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 22: Haematologic disorders	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, leukopenia (including neutropenia and agranulocytosis) and anaemia have been reported to occur very commonly (≥ 1/10), leukocytosis and thrombocytopenia have been reported to occur commonly (≥ 1/100 to < 1/10), idiopathic thrombocytopenic purpura has been reported to occur uncommonly (≥ 1/1,000 to < 1/100), and pancytopenia has been reported to occur rarely (≥ 1/10,000 to < 1/1,000). Although there have been only a few nonserious cases of anaemia and neutropenia (0.8% each) and leukopenia (0.3%) in the clinical studies conducted with Hulio® to date, haematological disorders have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors for anaemia include: iron deficiency from an inadequate diet or poor absorption, iron deficiency due to medical condition (e.g. celiac disease, heavy menstrual periods, stomach ulcers, gastrointestinal surgery), various chronic conditions (e.g. chronic kidney disease, cancer, ulcerative colitis, rheumatoid arthritis), pregnancy, and inherited haematological disorders. Risk factors for neutropenia include nutritional deficiencies (e.g. deficiencies of iron, vitamin B12, folate), infections (e.g. malaria, helminth infections, HIV), bone marrow infiltration with malignancy, and immunosuppressant therapy.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that adverse events of the haematologic system have been reported in patients treated with adalimumab* *SmPC section 4.4 where a warning is given to consider discontinuation of Hulio® therapy in patients with confirmed significant haematologic abnormalities* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can cause low blood-cell counts*

Important identified risk 22: Haematologic disorders	
	PL section 2 where a warning is given for the patient to seek urgent medical attention if they develop pale complexion, dizziness, persistent fever, bruise or bleed very easily *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 23: Intestinal perforation	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, intestinal perforation has been reported to occur rarely (≥ 1/10,000 to < 1/1,000). Although there have been no treatment-related cases of intestinal perforation in the clinical studies conducted with Hulio® to date, intestinal perforation has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Illnesses associated with intestinal perforation include appendicitis, diverticulitis, stomach ulcer, gallstones/gallbladder infection, Crohn's disease or ulcerative colitis, and cancer. In addition, trauma, abdominal surgery, ingestion of foreign objects, and use of NSAIDs/opioid analgesics/corticosteroids have also been associated with intestinal perforation. Smoking and excessive use of alcohol may also increase risk of intestinal perforation.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 24: Intestinal stricture in Crohn's disease (CD)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. Although there have been no treatment-related cases of intestinal stricture in CD in the clinical studies conducted with Hulio® (*studies were conducted in RA patients*), intestinal stricture in CD patients has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Genetic factors are associated with strictures e.g. carrying of nucleotide oligomerisation domain 2 (NOD2) variants and Janus-associated kinase 2 (JAK2). CD patients with NOD2 /caspase-recruitment domain 15 (CARD15) mutations on both chromosomes have a 10-fold greater risk of developing strictures compared with those carrying the single mutation. In Asians, the genetic marker TNF superfamily 15 (TNFSF15) and a serological marker anti-Saccharomyces cerevisiae antibodies (ASCA) IgA are also related to CD complications. Other common risk factors include age of diagnosis less than 40 years, perianal disease and the need for steroids during the first flare, history of smoking, deep mucosal ulcerations in the small bowel, prior appendectomy, and antimicrobial antibodies.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that failure to respond to treatment for CD may indicate the presence of fixed fibrotic stricture, although available data suggest that adalimumab does not worsen or cause strictures* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 25: Liver failure and other liver events	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased have been reported to occur

Important identified risk 25: Liver failure and other liver events	
	uncommonly (≥ 1/100 to < 1/10), whilst hepatitis has been reported to occur rarely (≥ 1/10,000 to < 1/1,000). Although there have been no treatment-related cases of liver failure or other liver events in the clinical studies conducted with Hulio® to date, liver failure or other liver events have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of liver failure include toxins (e.g. alcohol abuse, paracetamol poisoning, drug toxicity, chemical poisoning, plants/plant products), viral infections (hepatitis, adenovirus, Epstein-Barr virus, cytomegalovirus and viral haemorrhagic fevers), hepatocellular carcinoma or metastatic carcinoma, and metabolic diseases (e.g. Wilson's disease).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 2 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important identified risk 26: Elevated alanine transaminase (ALT) levels	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, elevated liver enzymes have been reported to occur very commonly (≥ 1/10). In the FKB327-002/003 clinical trials, treatment-related elevated ALT levels were experienced by 6 (0.9%) patients receiving Hulio®. Elevated ALT levels have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	ALT elevations are indicative of liver injury such as incurred by autoimmune hepatitis, alcoholic hepatitis, exposure to drugs (eg, phenytoin, carbamazepine, isoniazid, statins, methotrexate, paracetamol overdose, amiodarone), acute viral hepatitis (eg, HAV, HBV and HCV and cytomegalovirus infection), neoplasms,

Important identified risk 26: Elevated alanine transaminase (ALT) levels	
	haemochromatosis, metabolic disorders (eg, glycogen storage disorders, Wilson's disease), ischaemic liver injury (eg, severe hypotension, fatty liver disease), as well as non-hepatic causes such as coeliac disease, haemolysis and hyperthyroidism.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 2 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 27: Autoimmune hepatitis (AIH)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, AIH has been reported to occur rarely (≥ 1/10,000 to < 1/1,000). Although there have been no treatment-related cases of AIH in the clinical studies conducted with Hulio® to date, autoimmune hepatitis has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk for AIH include female gender, other autoimmune diseases, and genetic predisposition (e.g. the complement allele C4AQO and the HLA haplotypes B8, B14, DR3, DR4, and Dw3). Immune serum markers are often present and include antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver-kidney microsomal-1 (anti-LKM-1) antibody, antibodies against soluble liver antigen (anti-SLA), anti-mitochondrial antibody (AMA) and antiphospholipid antibodies.

Important identified risk 27: Autoimmune hepatitis (AIH)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 2 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 28: Medication errors and maladministration	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. The incidence of medication errors has been low for Humira®. Only one medication error has been reported in the Hulio® clinical studies to date, where a subject did not receive the full dose due to an administration error involving the healthcare professional (HCP) using the pre-filled pen. Medication error and maladministration have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors include inconsistent oversight and minimal knowledge of the injection device (whether pre-filled pen, pre-filled syringe, or vial) and/or procedure. Risk factors include minimal knowledge of the injection procedure at the injecting physician's facility, inadequate training of the patient/carer in the injection procedure by the physician/nursing team, and inadequate oversight of the patient's self-injection process by the physician/nursing team.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 where guidance is given that Hulio® treatment should be initiated and supervised by specialist physicians*

Important identified risk 28: Medication errors and maladministration	
	experienced in the diagnosis and treatment of conditions for which Hulio® is indicated *SmPC section 4.2 where guidance is given on the recommended posology and method of administration* *SmPC section 6.4 where guidance is given on the special precautions for storage* *PL section 3 where instructions are given on how to use Hulio®* *PL section 3 where instruction is given for the patient to tell their doctor or pharmacist if they have accidentally injected more or less Hulio® than recommended or forgotten a scheduled dose* *PL section 5 where guidance is given on the storage conditions for Hulio®* *PL section 7 where instructions for preparing and giving an injection of Hulio® are detailed* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 1: Other malignancies (except lymphoma, hepatosplenic T-cell lymphoma [HSTCL], leukaemia, non-melanoma skin cancer [NMSC[, and melanoma)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. In all clinical trials with adalimumab (non-registry and registry trials), 1.1% subjects reported malignancies other than lymphoma, HSTCL, leukaemia, NMSC, and melanoma. There has been one case (0.2%) breast cancer and one case (0.2%) cervix carcinoma in the FKB327 treatment group but none in Humira treatment group in the clinical studies conducted with Hulio® to date. Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma) have been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Sustained inflammatory activity seems to be the primary risk factor for malignancies in autoimmune diseases such as RA as well as the common aetiology between RA and malignancy, such as

Important potential risk 1: Other malignancies (except lymphoma, hepatosplenic T-cell lymphoma [HSTCL], leukaemia, non-melanoma skin cancer [NMSC[, and melanoma)	
	genetic factors, smoking-related tissue necrosis and viral infection (e.g. Epstein-Barr virus, retroviruses). However, it is difficult to separate disease-related mechanisms from the potential oncogenic properties of immunosuppressive drugs used in these autoimmune-inflammatory diseases. An analysis of the British Society for Rheumatology Biologics Register (BSRBR)-RA, showed that after an average follow-up of 5 years, patients with rheumatoid arthritis and prior malignancy selected to receive treatment with TNF inhibitors in the UK do not have an increased risk of recurrence or development of new incident malignancy.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about the possible development of other malignancies in patients (including children and adolescents) treated with a TNF antagonist* *SmPC section 4.8 listed as adverse reactions* *PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer especially if the patient has COPD or is a heavy smoker* *PL section 2 where a warning is given for the patient to talk to their doctor if they have COPD or are a heavy smoker and to discuss whether treatment with Hulio® is appropriate* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC-OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk 2: Vasculitis (non-cutaneous)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. In all rheumatoid arthritis trials with adalimumab, the rate of vasculitis was determined as 0.2 events per 100 patient-years of exposure. Although there have been no treatment-related cases of non-cutaneous vasculitis in the clinical studies conducted with Hulio® to date, vasculitis (non-cutaneous) has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors for vasculitis include a genetic predisposition, infection (eg, Henoch-Schönlein purpura, septic vasculitis, upper respiratory tract flares of granulomatosis with polyangiitis, polyarteritis nodosa), inflammatory disease (eg, SLE, RA, IBD), medications (eg, sulfonamides, beta-lactams, quinolones, NSAIDs, oral contraceptives, thiazides, anti-influenza vaccines), chemicals such as insecticides and petroleum products, neoplastic disorders, and smoking
Risk minimisation measures	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 3: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. There have been no reports of PML in all clinical trials with adalimumab. Similarly, there have been no treatment-related cases of PML in the clinical studies conducted with Hulio® to date. PML has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	PML primarily affects individuals with chronically and severely suppressed immune systems and is associated primarily with HIV patients, haematological malignancies, or relapsing–remitting multiple sclerosis patients treated with natalizumab.

Important potential risk 3: Progressive multifocal leukoencephalopathy (PML)	
	PML is also associated with other conditions such as organ transplantation, solid malignancies, sarcoidosis, autoimmune disorders (e.g. lupus, RA), and congenital immune deficiencies; these populations individually contribute a relatively small number of cases and together account for less than 10% of all reported PML cases.
Risk minimisation measures	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 4: Reversible posterior leukoencephalopathy syndrome (RPLS)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. There have been no reports of RPLS in all clinical trials with adalimumab. Similarly, there have been no treatment-related cases of RPLS in the clinical studies conducted with Hulio® to date. RPLS has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Suspected aetiologies 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%).
Risk minimisation measures	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 5: Amyotrophic lateral sclerosis (ALS)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. In all RA trials with adalimumab, the rate of ALS was determined as < 0.1 event per 100 patient-years of exposure. Although there have been no treatment-related cases of ALS in the clinical studies conducted with Hulio® to date, ALS has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Whites, males, non-Hispanics, those aged >60 years, and those with a family history of the disease are more likely to develop ALS. Previous exposure to heavy metals (e.g., lead and chromium), pesticides, and β-N-methylamino-L-alanine (BMAA) produced by cyanobacteria also have been associated with an increased risk for ALS. Other possible risk factors include military service, nutritional intake, use of statins, exposure to viral agents, vigorous physical activity, and trauma.
Risk minimisation measures	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 6: Colon cancer in ulcerative colitis (UC) patients	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. There was only one case of colon cancer in UC patients treated in Humira® UC trials (a rate of < 0.1 event of colon cancer per 100 patient-years of exposure). There have been no treatment-related cases of colon cancer in UC patients in the clinical studies conducted with Hulio® (*studies were conducted in rheumatoid arthritis patients*). However, colon cancer has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors for colon cancer include extent and duration of UC, primary sclerosing cholangitis, a family history of sporadic colorectal cancer, severity of histologic bowel inflammation, and in some studies, young age at onset of colitis. The standardised incidence rate (SIR) for colorectal cancer was 8.6 (95% CI, 3.8 –

Important potential risk 6: Colon cancer in ulcerative colitis (UC) patients	
	19.5) in those of young age and 4.8 (95% CI, 3.9 –5.9) in those with extensive colitis. Men with UC had a greater risk of colorectal cancer (SIR, 2.6; 95% CI, 2.2–3.0) than women (SIR, 1.9; 95% CI, 1.5–2.3).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that the risk for developing dysplasia or colon cancer in UC patients is unknown* *SmPC section 4.4 where instruction is given to screen UC patients for dysplasia at regular intervals before therapy and throughout their disease course (including use of colonoscopy and biopsies) if they are at increased risk or have a prior history of dysplasia or colon carcinoma* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 7: Infections in infants exposed to Hulio® in utero	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. There have been no reports of infections in infants exposed to adalimumab in utero during clinical trials. Similarly, there have been no reports of infants exposed to Hulio® in utero in the clinical studies conducted with Hulio® to date. Infections in infants exposed to Hulio® in utero has been classed as a potential risk in accordance with the reference product.
Risk factors and risk groups	Infants exposed to adalimumab in utero.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6 where a recommendationis given not to administer live vaccines to infants exposed to adalimumab in utero for 5 months following the mother's last adalimumab injection during pregnancy*

Important potential risk 7: Infections in infants exposed to Hulio® in utero	
	PL section 2 where instruction is given for the patient to tell their baby's doctors and/or other HCPs about their Hulio® use during pregnancy before the baby receives any vaccinations *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 8: Medication errors with paediatric vial	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. The incidence of medication errors has been low for Humira®. Medication errors have not been reported in the Hulio® clinical studies with the exception of one case, where a subject did not receive the full dose due to an administration error involving the healthcare professional (HCP) using the pre-filled pen, but not the vial. Medication error with the paediatric vial has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors include minimal knowledge of the injection procedure at the injecting physician's facility, inadequate training of the patient/carer in the injection procedure by the physician/nursing team, and inadequate oversight of the patient's self-injection process by the physician/nursing team.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 where guidance is given that Hulio® treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Hulio® is indicated* *SmPC section 4.2 where guidance is given on the recommended posology and method of administration* *SmPC section 6.4 where guidance is given on the special precautions for storage* *PL section 3 where instructions are given on how to use Hulio®*

Important potential risk 8: Medication errors with paediatric vial	
	PL section 5 where guidance is given on the storage conditions for Hulio® *PL section 7 where instructions are detailed for preparing and giving an injection of Hulio®* *PL section 3 where instructions are given for the patient carer to tell the doctor or pharmacist if they have accidentally injected the child with more or less Hulio® than recommended or forgotten a scheduled dose* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 9: Off-label use	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. Evidence for off-label use is limited to that found in the literature where similar TNF-α antagonists have been used off-label to treat immunologic-based infertility, Behçets disease, refractory diabetic macular oedema, age-related macular degeneration, sarcoidosis, and vasculitis. To date, no new safety signal for Humira® has been identified in these reports. There has been no off-label use of Hulio® to date as it is not yet authorised. However, off-label use has been classed as potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Hulio® could be used off-label in patients with conditions in which TNF-α plays a role and where current therapy is ineffective.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.1 and 4.2 where clear specifications of authorised indications and posology, respectively, are provided* *PL sections 1 and 3where clear specifications of authorised indications and posology, respectively are provided* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*

Important potential risk 9: Off-label use	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Missing information 1: Subjects with immune-compromised conditions may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given for physicians to exercise caution when considering the use of Hulio® in patients with underlying conditions which may predispose them to infections, including the use of concomitant immunosuppressive medications* *PL section 2 where a warning is given for the patient to tell their doctor before using Hulio® if they are suffering from another condition which makes them more susceptible to getting infections* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*

Missing information 2: Long-term safety information in the treatment of children aged from 6 to <18 years with Crohn's disease (CD) and paediatric enthesitis-related arthritis (pedERA)	
Risk minimisation measures	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*

Missing information 3: Pregnant and lactating women	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6 where women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and not to breast-feed for at least five months after the last Hulio® treatment* *PL section 2 where advice is given for the patient to use adequate contraception and not to breast-feed while using Hulio® and for at least 5 months after the last Hulio® dose* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*

Missing information 4: Remission-withdrawal-retreatment data for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (nr-axSpA) and episodic treatment in psoriasis, Crohn's disease, ulcerative colitis and juvenile idiopathic arthritis (Ps, CD, UC, and JIA)	
Risk minimisation measures	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*

Missing information 5: Long-term safety information in the treatment of adults with hidradenitis suppurativa (HS)	
Risk minimisation measures	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*

Missing information 6: Long-term safety information in the treatment of adults and children with uveitis	
Risk minimisation measures	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Hulio®.

II.C.2 Other studies in post-authorisation development plan

FKB327-003: An Open-label Extension Study to Compare the Long term Efficacy, Safety, Immunogenicity and Pharmacokinetics of FKB327 and Humira® in Patients with Rheumatoid Arthritis on Concomitant Methotrexate (ARABESC-OLE).

Purpose of the study:

Primary:

- To compare the safety of long-term treatment with FKB327 and Humira® in patients with RA.

Secondary:

- To compare the efficacy of long-term treatment with FKB327 and Humira® in patients with RA.
- To compare the proportions of patients developing anti-drug antibodies (ADAs) on long-term treatment with FKB327 and Humira® in patients with RA.
- To compare the PK of long-term treatment with FKB327 and Humira in patients with RA.
- To evaluate safety, changes in efficacy, and changes in PK and immunogenicity in patients who were switched from Humira® in the preceding FKB327-002 double-blind study to FKB327 in the FKB327-003 OLE study, and of patients who were switched from FKB327 to Humira®, respectively.
- To evaluate safety, changes in efficacy, and changes in PK and immunogenicity in patients who were switched from FKB327 in the preceding FKB327-002 double-blind study to Humira® in the FKB327-003 OLE study, and then switched back to FKB327 in the second part of the FKB327-003 OLE study (from Week 30; double switch).

Safety surveillance of Hulio® (FKB327) (adalimumab) using the rheumatoid arthritis BSRBR-RA registry in the United Kingdom (UK): long term, prospective, observational study.

Purpose of the study:

This observational post-authorisation safety study aims to characterise the safety profile of the adalimumab biosimilar formulation Hulio®, and to describe the effectiveness and response to

the treatment in RA patients in a real-life environment, using already existing data from the British Society for Rheumatology Biologics Registry (BSRBR-RA). In particular, this registry will address the long-term safety in RA with emphasis on TB/other serious infection, malignancies, elevated ALT levels, autoimmune hepatitis, and CHF/MI.