Simponi

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
II/0117/G	This was an application for a group of variations. Grouped application consisting of: C.I.13: Submission of the final report from study UC Nordic (MK-8259-013) listed as a category 3 study in the RMP. This is a Non-interventional Observational Longitudinal Post Authorization Safety Study (PASS) of SIMPONI in Treatment of Ulcerative Colitis using	30/11/2023	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	Nordic National Health Registries. C.I.13: Submission of the final report from study ENEIDA (MK-8259-042) listed as a category 3 study in the RMP. This is a Post-Authorization Safety Study (PASS) of Golimumab in UC Using the Spanish ENEIDA Registry. The RMP version 27.1 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/1560/ 202304	Periodic Safety Update EU Single assessment - golimumab	30/11/2023	n/a		PRAC Recommendation - maintenance
IB/0118	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/11/2023		SmPC, Labelling and PL	
II/0115	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	31/08/2023	n/a		
II/0113	Submission of the final report from study CNTO148UCO1001 (PURSUIT PEDS PK) listed as a category 3 study in the RMP. This is a phase 1b open-label study to assess the safety and	06/07/2023	n/a		Study CNTO148UCO1001 was a Phase 1b open label study to assess the safety and pharmacokinetics of subcutaneously administered golimumab in paediatric subjects aged 2 to 17 years with moderately to severely

	pharmacokinetics of subcutaneously administered golimumab, a human anti-TNFα antibody, in pediatric subjects with moderately to severely active ulcerative colitis. The RMP version 26.1 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				active ulcerative colitis (UC). Thirty-five (35) patients were included and around 29% of the patients were between 2-11 years old and around 43% of the patients had a weight <45 kg (including 5 patients with a weight<30kg). The serum golimumab concentrations appeared to be relatively comparable between paediatrics with UC with a body weight ≥45 kg and adults with UC when compared within the same body weight categories. There seemed to be a trend towards lower mean serum concentration in paediatrics weighing < 45 kg (who received the BSA-adjusted dose regimen) as compared to those weighing ≥ 45 kg and compared to the reference adults UC population (who received the flat fixed dose regimen). The overall safety profile in this small paediatric UC study was consistent with the known safety profile of golimumab with no new safety concerns identified.
II/0109	Update of the Package Leaflet in order to update the Instructions for Use (IFU) for the pre-filled pen. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/06/2023		PL	
II/0111	Update of section 4.6 of the SmPC in order to update information on pregnancy based on final results from PASS study CNTO148ART4001 listed as a category 3 study in the RMP; this is an observational prospective cohort study to collect and analyse information pertaining to pregnancy outcomes of women exposed to golimumab during pregnancy. The package leaflet is updated accordingly. The RMP	12/05/2023		SmPC and PL	There is a moderate amount (approximately 400) of prospectively collected pregnancies exposed to golimumab resulting in live birth with known outcomes, including 220 pregnancies exposed during the first trimester. In a population-based study from Northern Europe including 131 pregnancies (and 134 infants), there were 6/134 (4.5%) events of major congenital anomalies following in utero exposure to Simponi vs 599/10,823 (5.5%) events for non-

	version 25.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				biologic systemic therapy compared to 4.6% in the general population of the study. Confounder-adjusted odds ratios were OR 0.79 (95% CI 0.35-1.81) for Simponi vs. non-biologic systemic therapy and OR 0.95 (95% CI 0.42-2.16) for Simponi vs. the general population, respectively. Due to its inhibition of TNF, golimumab administered during pregnancy could affect normal immune responses in the newborn. Studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The available clinical experience is limited. Golimumab should only be used during pregnancy if clearly needed.
IB/0114	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	21/04/2023	n/a		
II/0112	Submission of the final report from study PO4480 (RABBIT) listed as a category 3 study in the RMP. This is an observational prospective cohort study to evaluate the long-term safety of treatment with biologics in rheumatoid arthritis. The RMP (version 24.2) has also been updated. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/03/2023	n/a		The objectives of the RABBIT study were 1) to compare crude, unadjusted incidence rates of pre-defined outcomes in patients with RA exposed to Simponi, other biologic (b) or conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs) and 2) to compare risks of pre-defined outcomes in adjusted analyses. The outcomes are in alignment with the safety concerns specified for Simponi in the current EU risk management plan, except for cardiovascular events and all-cause mortality, which were analysed as outcomes of interest. The results of the RABBIT cohort 2 report on Simponi showed a lower risk for serious infections in patients treated with Simponi compared to patients of comparator groups I (other bDMARDs) and III (nonbionaïve

					csDMARDs), but not for comparator group II (bionaïve csDMARDs). No significant risk increase was shown for Simponi vs. all investigated comparator groups for the outcomes of myocardial infarction, overall malignancies, first malignancies, non-melanoma skin cancer and all-cause mortality. Overall, the results suggest that the use of Simponi for the treatment of RA patients in daily rheumatologic care is a safe and generally well-tolerated option.
II/0107	Update to section 5.1 of the SmPC to add the results of the final report from study MK-8259-038 (Go-BACK) in order to fulfil MEA/30.2. This is a phase 4, randomised, double-blind, parallel-group, withdrawal, post-authorisation efficacy study (PAES) of golimumab in adult participants, aged 18 to 45 years, with active non-radiographic axial spondyloarthritis. In addition, the MAH took the opportunity to update the list of local representatives. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/02/2023		SmPC and PL	The efficacy and safety of continued golimumab treatment (full or reduced dosing frequency) compared with treatment withdrawal was assessed in adult patients (18-45 years of age) with active nr-axSpA who demonstrated sustained remission during 10 months of monthly treatment with open label Simponi (GO-BACK). Eligible patients (who achieved a clinical response by Month 4 and an inactive disease status (ASDAS <1.3) at both Months 7 and 10) entering the double-blind withdrawal phase were randomised to continued monthly treatment with Simponi (full-treatment regimen, N = 63), every 2-month treatment with Simponi (reduced treatment regimen, N = 63) or monthly placebo treatment (treatment withdrawal, N = 62) for up to approximately 12 months. The primary efficacy endpoint was the proportion of patients without a flare of disease activity. Patients who experienced a flare, i.e., had an ASDAS collected at 2 consecutive assessments that both showed either an absolute score of ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (end of open-label period), reinitiated monthly Simponi in an open-label retreatment phase to characterise clinical response.

					Among the 188 patients with inactive disease who received at least one dose of double-blind treatment, a significantly (p<0.001) greater proportion of patients did not experience a disease flare when continuing Simponi with either the full-treatment (84.1%), or reduced treatment (68.3%) regimens compared with treatment withdrawal (33.9%). In the placebo group, flares started approximately 2 months after Simponi was withdrawn, with the majority of flares occurring within 4 months of treatment withdrawal. For more information, please refer to the Summary of Product Characteristics.
IB/0110	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/12/2022	n/a		
IA/0108/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	11/11/2022	n/a		
IB/0106	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	23/05/2022	n/a		

IB/0105	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/05/2022	n/a		
IB/0104	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	05/01/2022	n/a		
N/0103	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/10/2021		PL	
N/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/06/2021		PL	
IA/0101/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites	23/03/2021	n/a		
IB/0100	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	11/02/2021	n/a		
IA/0099	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	18/12/2020	n/a		

IB/0098	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	18/12/2020	n/a		
PSUSA/1560/202004	Periodic Safety Update EU Single assessment - golimumab	26/11/2020	n/a		PRAC Recommendation - maintenance
IA/0097/G	This was an application for a group of variations. A.z - Administrative change - Other variation A.7 - Administrative change - Deletion of manufacturing sites B.IV.z - Quality change - Change in Medical Devices - Other variation	16/11/2020	n/a		
II/0095	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	12/11/2020	n/a		
IAIN/0096	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/10/2020	22/03/2021	SmPC, Annex II and PL	
II/0093	B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method	22/10/2020	n/a		
IAIN/0092	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2020	22/03/2021	SmPC, Annex II, Labelling and PL	

IAIN/0091	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	11/10/2019	n/a		
IA/0090	A.7 - Administrative change - Deletion of manufacturing sites	11/09/2019	n/a		
IB/0089/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	23/08/2019	28/02/2020	SmPC, Labelling and PL	
II/0085	Submission of the final report from study (CNTO148ART4002) listed as a category 3 study in the RMP. This is an observational phase 4 study using the Optum Research Database (ORD) to estimate the long-term safety profile in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) who are initiating Simponi treatment and/or other types of biologic and non-biologic treatments. In addition, the RMP (version 20.0) is updated to reflect the final study report from study CNTO148ART4002 and to revise	14/06/2019	28/02/2020	SmPC, Annex II and Labelling	The final report for the golimumab safety and surveillance program using the Optum Research Database (ORD) (study CNTO148ART4002) describes a prospective, observational, inception cohort study using a large US health insurance claims database to estimate the long-term safety profile in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) who are initiating Simponi treatment and/or other types of biologic and non-biologic treatments. Based on the information in this report, no specific safety concerns in patients with RA, PsA, or AS treated with Simponi relative to those patients

	the list of safety concerns in accordance with the GVP Module V guideline (rev. 2). The Annexes II and IIIA of the product information are updated to remove congestive heart failure and to add breakthrough infection after administration of live vaccine in infants exposed to golimumab in utero from the patient reminder card and labelling. In addition, the MAH took the opportunity to make some editorial changes in the SmPC. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				treated with a non-biologic medication were noted. Results of the current safety evaluation are consistent with reports of Simponi safety and are generally comparable with observations from other studies in patients with rheumatic disease. Overall, no new safety signals arose from this study warranting updates to the product information, but some methodological issues remain. There are some uncertainties with regards to “Serious depression including suicidality” and this should remain as an important potential risk in the risk management plan (RMP) and the risk should be reviewed in the next PSUR. The list of safety concerns in the RMP is also updated in accordance with Guideline on good pharmacovigilance practices (GVP) Module V, revision 2. With this update, congestive heart failure is removed from the list of important identified risk in the Simponi RMP, this results in an amendment of the Annex II condition and Annex IIIA (labelling); namely to remove “congestive heart failure” from the patient reminder card. Breakthrough infection after administration of live vaccine in infants exposed to golimumab in utero is added in the patient reminder card as this was a missing information.
II/0087/G	This was an application for a group of variations. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	26/04/2019	28/02/2020	SmPC, Labelling and PL	

	B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IAIN/0088	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/03/2019	28/02/2020	SmPC and PL	
X/0083/G	This was an application for a group of variations. Extension of application to add a new strength of 45 mg/0.45 mL solution for injection for paediatric use. C.I.6.a - Extension of indication to include paediatric patients from the age of 2 years and older for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) with Simponi 50 mg solution for injection in pre-filled pen and pre-filled syringe. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. The labelling and package leaflet are also updated accordingly. C.I.11.z - To update the RMP to version 18.0 to delete the following safety concerns: vasculitis, psoriasis (new onset or worsening of pre-existing), and sarcoidosis/sarcoid like reaction as the result of the CHMP in the outcome of variation Type II/068. C.I.11.z - To update the RMP to version 18.0 to change the due date of the category 3 study MK-8259-050 as the result of the CHMP outcome of MEA033.	13/12/2018	18/02/2019	SmPC, Labelling and PL	Please refer to the published assessment report Simponi EMEA/H/C/000992/X/0083/G: EPAR – Assessment Report

	In addition, the marketing authorisation holder took the opportunity to: - update the Product Information in line with the latest QRD template (version 10); - implement the recommendations as stated in the revised Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' with regards to the excipient Sorbitol (E420); - add a statement in section 4.4 of the SmPC to record the name and the batch number of the administered product, in line with Good Pharmacovigilance Practice (GVP) Module PII: Biological medicinal products. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IA/0086	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	18/12/2018	n/a		

II/0084	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	06/09/2018	18/02/2019	SmPC, Annex II, Labelling and PL	The educational programme for prescribing HCPs was based on the SmPC and did not provide additional clinical value beyond the information already provided in the SmPC or current routine clinical practice. Consequently this educational programme for prescribing HCPs as an additional risk minimisation measure is removed. The educational programme consists of a patient reminder card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professional(s) treating the patient about on-going treatment with the product. The patient reminder card shall contain the following key messages: • A reminder to patients to show the patient reminder card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using Simponi. • A statement that the brand name and batch number should be recorded. • Provision to record the type, date, and result of TB screenings. • That treatment with Simponi may increase the risks of serious infection, opportunistic infections, tuberculosis, hepatitis B reactivation, and congestive heart failure; and when to seek attention from a HCP. • Contact details of the prescriber.
II/0082/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of	05/07/2018	n/a		

	the AS - Minor change in the manufacturing process of the AS B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS				
II/0079	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/05/2018	02/07/2018	SmPC and PL	Pharmacokinetic data from pivotal C0524T18 study supports a dose optimisation posology for patients with ulcerative colitis with body weight less than 80 kg and who have had an inadequate response. Patients who have an adequate response after the initial dose of 200 mg, followed by 100 mg at week 2 should receive 50 mg at week 6 and every 4 weeks thereafter. Patients who have an inadequate response may benefit from continuing with 100 mg at week 6 and every 4 weeks thereafter. The results of this study supporting this dosing regimen were reflected in section 5.1 of the SmPC.
II/0078/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/03/2018	02/07/2018	SmPC and PL	A cumulative review of the MAH's global safety database for the event of agranulocytosis retrieved 8 cases that were either confounded by other factors or provided insufficient information. However, considering the seriousness, potentially life threatening nature of the event and the fact that agranulocytosis is a rare condition that is often drug-related, section 4.4 and 4.8 of the SmPC were updated to include agranulocytosis to inform prescribers of this potential risk. This was further supported further by the established hematologic effects of golimumab and the labelling of agranulocytosis as adverse drug reactions for others anti-tumor necrosis factor (anti-TNF) agents as a class.

					The Adverse Event (AE) term neutropenia has been explicitly added to the tabulated list of ADRs and grouped under the clinical concept of leukopenia in Section 4.8 Undesirable effects. Based on the inclusion of neutropenia under the concept of leukopenia, the frequency of the grouped terms was recalculated resulting in an updated frequency to common for leukopenia (including neutropenia).
IA/0081/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	21/12/2017	n/a		
PSUSA/1560/ 201704	Periodic Safety Update EU Single assessment - golimumab	30/11/2017	n/a		PRAC Recommendation - maintenance
II/0075/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	09/06/2017	n/a		

	B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS				
II/0074/G	This was an application for a group of variations. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	18/05/2017	n/a		
IA/0076/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	03/05/2017	11/09/2017	Annex II and PL	
II/0072	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	02/02/2017	11/09/2017	SmPC and PL	

	data				
IB/0073	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	15/12/2016	n/a		
II/0071/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.f.1.b.4 - Stability of FP - Extension of the shelf life of the finished product - Based on extrapolation of stability data not in accordance with ICH/VICH guidelines	08/12/2016	11/09/2017	SmPC	
II/0067	Update of the SmPC sections 4.8 and 5.1 as a result of new data from the Phase 3 extension studies of Simponi in ulcerative colitis and non-radiographic axial spondyloarthritis (C0524T18 and P07642, respectively). Moreover, the updated RMP version 17 has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/10/2016	11/09/2017	SmPC	In this variation the MAH updated the Product Information with the data from two extension studies in non-radiographic axial spondyloarthritis and ulcerative colitis. Non-radiographic axial spondyloarthritis Approximately 93% of patients who were receiving Simponi at the beginning of the open label extension (week 16) remained on treatment through the end of the study (week 52). The improvements in signs and symptoms, spinal mobility, physical function, quality of life, and productivity observed at week 16 among patients treated with Simponi 50 mg continued in those remaining in the study at week 52. Ulcerative colitis Patients who completed the maintenance study through week 54 continued treatment in a study extension, with efficacy evaluated through week 216. Efficacy evaluation in

					the study extension was based among others on changes in corticosteroid use. Among patients who entered the study extension, the proportion of subjects who remained corticosteroid free was generally maintained through week 216. Of patients that continued in the study extension and had evaluable samples through week 228, antibodies to golimumab were detected in 4% (23/604) of golimumab treated patients. Eighty-two percent (18/22) of antibody-positive patients had neutralizing antibodies in vitro.
IA/0070	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	20/09/2016	n/a		
II/0069/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.c - Change in the batch size (including batch	28/07/2016	n/a		

	size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product or a new bioequivalence study B.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur. B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
II/0063	Extension of indication to add a new indication for Simponi in the treatment of polyarticular juvenile idiopathic arthritis in combination with methotrexate in children with a body weight of at least 40 kg, who have responded inadequately to previous therapy with methotrexate; consequently, SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 have been revised to include new efficacy, PK and safety information. The Package Leaflet and RMP have been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/05/2016	24/06/2016	SmPC, Labelling and PL	Please refer to the scientific discussion Simponi EMEA/H/C/00993/II/0063.
II/0068/G	This was an application for a group of variations.	26/05/2016	n/a		

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0065/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information based on review of all available safety data. The Package Leaflet and RMP are updated accordingly. Additionally, the due date of Nordic National Register Study has been updated in the RMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	19/11/2015	24/06/2016	SmPC and PL	In this variation the MAH updated the safety information of the Simponi PI to highlight the risks of invasive fungal infections; clarify that leukaemia has been observed in clinical trials in addition to the post marketing setting; and that cases of congestive heart failure (CHF) with fatal outcomes have been observed in patients receiving Simponi.
IA/0066	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished	16/10/2015	n/a		

	product - Tightening of in-process limits				
II/0061	Extension of Indication to include a new indication for the treatment of non radiographic axial spondyloarthritis (nr Axial SpA) for Simponi (Golimumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/05/2015	22/06/2015	SmPC and PL	Please refer to the scientific discussion Simponi-H-C-992-II-61.
IB/0064	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	24/04/2015	22/06/2015	SmPC	
PSUV/0058	Periodic Safety Update	20/11/2014	15/01/2015	SmPC and PL	Please refer to Simponi PSUV 0058 EPAR: Scientific conclusions and grounds recommendingthe variation to the terms of the marketing authorisation
IB/0062	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/12/2014	n/a		
II/0060	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/09/2014	n/a		

II/0059	Update of section 4.8 of the SmPC in order to add 'Bullous Skin Reactions' as an adverse drug reaction, identified during routine signal detection activities. In addition, information related to immunogenicity has been updated in section 5.1 of the SmPC to include wording agreed but inadvertently omitted during a previous procedure. The Package Leaflet is updated accordingly. Moreover, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	15/01/2015	SmPC and PL	During routine signal detection activities, an elevated signal score for dermatitis bullous was identified for golimumab. Following a thorough review of all cases section 4.8 of the SmPC has been updated in order to add 'Bullous Skin Reactions' as an adverse drug reaction with a frequency of uncommon, based on incidence in clinical trials. The PL has been updated accordingly, by adding Skin blisters to the list of uncommon side effects. In addition, information related to immunogenicity has been updated in section 5.1 of the SmPC, as this text was inadvertently omitted during a previous procedure.
IA/0057/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	10/07/2014	n/a		
II/0055	Update of sections 4.8 and 5.1 of the SmPC in order to reflect the safety and efficacy data (Week 256 for efficacy and Week 268 for safety) for studies C0524T05,C0524T06, C0524T11, C0524T08, and C0524T09. The package leaflet is updated accordingly.	26/06/2014	15/01/2015	SmPC and PL	The marketing authorization holder (MAH) committed to conduct long-term extensions of the subcutaneous (SC) Phase 3 RA (C0524T05, C0524T06, and C0524T11), PsA (C0524T08), and AS (C0524T09) clinical studies and to submit the final clinical study reports (CSRs). With this variation to the MAH provided the final (268-

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				week) CSRs for these 5 clinical studies and proposed to update sections 4.8 and 5.1 of the SmPC to reflect the new data. For safety, in addition to the 268-week data from the 5 studies, safety data from 2 other clinical trials have been added to the integrated database as support for the changes in section 4.8 of the SmPC. A revised RMP was also submitted. Interim data (week 52 and week 104) for RA studies C0524T05 and C0524T06 as well as for the PsA study C0524T08 had been evaluated previously. Overall, data from all studies through Week 268 support a sustained beneficial effect and a safety profile similar for other anti-TNFα agents.
R/0056	Renewal of the marketing authorisation.	25/04/2014	19/06/2014	SmPC, Labelling and PL	Based on the review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and, therefore, considered that the benefit risk of Simponi continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation with unlimited validity.
II/0053/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	22/05/2014	15/01/2015	Annex II and PL	

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.a.4.a - Change to in-process tests or limits				

	applied during the manufacture of the AS - Tightening of in-process limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
N/0054	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/03/2014	19/06/2014	Labelling and PL	
IB/0052	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	19/12/2013	n/a		
IAIN/0051	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the	22/11/2013	19/06/2014	PL	

	product information				
IB/0048/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	23/10/2013	n/a		
IB/0050	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/10/2013	19/06/2014	SmPC, Annex II, Labelling and PL	
II/0039	Extension of Indication to include new indication/population for Simponi for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6 mercaptopurine (6 MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated accordingly. Editorial changes have been made to the labelling. Following the update of the RMP, the MAH has taken	25/07/2013	19/09/2013	SmPC and PL	Please refer to Scientific Discussion Simponi/H/C/992/II/39 for further information.

	the opportunity to update the information regarding the educational material in Annex II. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
X/0040	Annex I_2.(c) Change or addition of a new strength/potency	27/06/2013	03/09/2013	SmPC, Labelling and PL	
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
II/0046	Update of section 4.8 of the SmPC in order to change the frequency of “interstitial lung disease” from Rare to Uncommon. The Package Leaflet was proposed to be updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	19/09/2013	SmPC and PL	The review of interstitial lung disease (ILD) in relation to golimumab contains many reports with important confounding factors. These include therapies with other drugs known to cause ILD and lung toxicity, such as MTX, as well as disease states (RA, UC) that have a pulmonary involvement have a high rate of association with ILD, making a definitive assessment challenging. However, there are several cases with a close temporal relationship to the start of golimumab therapy that make a causal association between golimumab therapy and the development of ILD at least a reasonable possibility. To support this finding as a class effect, other TNF inhibitors also have ILD as an ADR within their labelling. Based on this review, ILD is an ADR for golimumab. Although the post-marketing reporting frequency is 2 cases per 10,000 PY and the CIOMS frequency category is Rare, the clinical trial frequency for ILD (including pneumonitis and pulmonary fibrosis) is 3 cases per 1,000 subjects and the

					CIOMS frequency category is Uncommon. Therefore, the most conservative estimate of frequency for this ADR should be Uncommon.
WS/0400	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.5 of the SmPC in order to add information regarding administration of live vaccines and therapeutic infectious agents concurrently with Remicade and Simponi. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	27/06/2013	25/07/2013	SmPC and PL	The MAH's proposal to revise the PI was prompted by a single post-marketing case of Bacillus Calmette-Guerin (BCG) disseminated Mycobacterium bovis infection after concurrent use of infliximab for the treatment of ulcerative colitis and use of BCG by bladder instillation for the treatment of bladder cancer. A clear causal association between infliximab and the onset of disseminated BCG infection could not be determined due to confounding factors but could not be excluded. Upon analysis, the MAH concluded that this case represented a situation similar to receiving a live vaccine because BCG is a live attenuated form of Mycobacterium bacillus. The risks of infection and complications from infections following administration of a live vaccine have been reported to be much higher in patients whose immune systems have been compromised than in the healthy population. The MAH therefore proposed to update the product information to change the section heading of the Vaccination section to reflect the need to consider other therapeutic infectious agents, not just vaccines and to add a warning to not administer therapeutic infectious agents concurrently with Remicade or Simponi. This was agreed by the CHMP.
II/0044	Update of section 4.4 of the SmPC in order to add a warning regarding the occurrence of active tuberculosis in patients treated with Simponi during and after treatment with latent tuberculosis. The	21/03/2013	25/07/2013	SmPC, Annex II and PL	The review conducted by the MAH has shown that the risk of reactivation of TB remains a concern, in particular as this has occurred also after prophylactic treatment of TB. In the 6th PSUR, 40 cases of TB were reported. Of these, 7 cases

	Package Leaflet is updated accordingly. Changes were also made to the package leaflet to clarify the instructions for administration section of the pre-filled pen/syringe. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8.3. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				reported at least 1 screening result that was suggestive of TB. Five of these cases reported use of TB prophylaxis prior to starting golimumab. In addition, 3 subjects, where screening results were negative or not reported, received prophylaxis which may indicate clinical suspicion of latent TB. Thus, a total of 8 subjects developed TB on golimumab treatment, despite having received prophylactic treatment. One of the cases, occurring within a clinical study, was fatal. It is acknowledged that it is not proven that all the cases were reactivations and not a second primary disease. However it seems unlikely that a second community acquired infection, i.e. new exposure was the reason in all cases. In the fatal case this explanation is particularly improbable, since it was a disseminated infection and no known TB exposure. The product information has therefore been updated to raise awareness that cases of active tuberculosis have occurred in patients treated with Simponi during and after treatment for latent tuberculosis. Patients receiving Simponi should be monitored closely for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.
II/0037/G	This was an application for a group of variations. Changes in the manufacturing process of the active substance, changes to in-process limits applied during the manufacture of the active substance, changes in the specification limits of the active substance, change in test procedure for the active	21/03/2013	n/a		

	substance, changes in the specification parameters and limits of the finished product, changes in test procedure for the finished product. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test				

	procedure				
II/0031/G	This was an application for a group of variations. Changes to quality control testing arrangements for the active substance. Addition of a biological test method in the manufacturing process of the active substance. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	21/03/2013	n/a		
WS/0314	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/10/2012	19/11/2012	SmPC and PL	
WS/0312	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	18/10/2012	19/11/2012	SmPC and PL	The cumulative review of registries, clinical trials and postmarketing cases of MCC (or neuroendocrine carcinoma of the skin) coincident with infliximab or golimumab use

	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and safety information regarding cases of melanoma and Merkel cell carcinoma (MCC). The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				identified 19 reports for infliximab and none for golimumab. All 19 reports were postmarketing cases. No MCC cases were observed in registries and clinical trials. Of the 19 reports there were 2 fatalities reported in patients either taking multiple immunosuppressants concomitantly with infliximab or with limited information regarding medical history. Of the 19 reports, most of them had confounding factors (i.e. one or more risk factors for MCC such as prior immunosuppressant history, concomitant immunosuppressant therapies, and/or a history of malignancy) limiting the causality assessment with infliximab. Based on this review, MCC is considered causally associated with the use of infliximab, and a drug class effect to TNF inhibitors. Key factors supporting this conclusion include the biological plausibility based on immunosuppression by TNF-α inhibitors, the apparent sensitivity of MCC to immunosuppression, and the elevated reporting rate compared with the background rate of this type of cancer, all which suggest an association of MCC with this drug class. MCC is therefore added to section 4.8, with a frequency category of “Not known” for both infliximab and golimumab, as the frequemcy of the event cannot be estimated from the available data. The severity and seriousness of the event of MCC also justify its addition to section 4.4 to warn the physicians that cases of MCC have been reported in patients treated with TNF blocker therapy and to recommend periodic skin examination, particularly for patients with risk factors for skin cancer.. The cumulative review of melanoma cases, coincident with infliximab or golimumab use, from registries, clinical trials and postmarketing identified 385 reports for infliximab and 14 for golimumab. For infliximab, there were 2 reports from

					clinical trials, 333 from postmarketing and 50 from registries. For golimumab there were 6 clinical trials reports, 7 postmarketing and 1 registry reports. In the FDA AERS database, there were significant numbers of cases of melanoma events with all of the TNF-α blockers. In more than 50% of the cases there were associated risk factors limiting the causality assessment with the drugs. Based on the overall data, it remains unclear whether a causal relationship exists between infliximab or golimumab use and the development of melanoma, however the possible contribution of infliximab or golimumab use to the risk cannot be excluded. Based on the data, the frequency category of melanoma is “rare” (□1/10,000 and <1/1,000) for both infliximab and golimumab.
II/0035	Update of section 4.8 of the SmPC in order to add skin exfoliation as a new adverse reaction. The Package Leaflet is updated in accordance. Editorial changes have also been made to section 3 and 4 of the Package Leaflet. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	19/07/2012	10/09/2012	SmPC and PL	The MAH had provided a review of reports of skin exfoliation. No cases with the diagnosis erythema multiforme, Steven Johnson Syndrome or Toxic Epidermal Necrolysis, representing severe skin reactions were retrieved. In clinical trials, two serious cases (dermatitis exfoliative and skin exfoliation) were reported in patients who received golimumab with concomitant therapy. In the postmarketing setting, six nonserious cases of skin exfoliation were reported: 3 cases of nonserious psoriatic-like desquamation, 2 cases with skin lesions likely due to other etiology, and one case of skin exfoliation with concomitant methotrexate use. All cases reported a plausible temporal relationship between exposure to golimumab and skin exfoliation. It was concluded that the development of skin exfoliation is reasonably likely to be causally associated with the use of golimumab and that the term skin exfoliation should be added to section 4.8 of the

					SmPC. The frequency ‘rare’ was based on the two cases reported from clinical studies, in relation to in total 5,100 patients treated in these studies.
IG/0213	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		
IA/0036/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites	20/07/2012	n/a		
IB/0034	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	28/02/2012	n/a		
II/0027	Update of section 4.8 of the SmPC with nausea as new adverse event as requested by CHMP. The Package Leaflet was proposed to be updated in accordance. Furthermore, the MAH proposed this opportunity to introduce editorial changes and bring the PI in line with the latest QRD template version 8.0. The list of local representatives in the PL was also updated.	15/12/2011	06/02/2012	SmPC, Annex II, Labelling and PL	In response to a CHMP request, the MAH had performed a cumulative review to evaluate whether nausea and vomiting are associated with the use of golimumab. Based on this data the CHMP concluded that the product information should be updated to include nausea as an adverse drug reaction as there is at least a reasonable possibility for a causal relationship.

	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				
IA/0032/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	15/12/2011	n/a		
II/0026	Update of 4.8 with 3 year data on infections, serious infections, malignancies, demyelinating disorders and liver enzyme elevations. The PIL is not affected by this update. However, a correction to section 2 in PIL (allergic reactions) is made and the list of local representatives is being updated.	21/07/2011	05/09/2011	SmPC and PL	The MAH has updated section 4.8 of the SmPC with the most recent safety data from ongoing long-term extensions of clinical studies which have been assessed previously. The description of selected adverse drug reactions, namely infections, malignancies, neurological events, and liver effects, has been updated with data from clinical trial extensions covering approximately 3 years (Week 160) of

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				follow-up.
IG/0090/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	08/07/2011	n/a		
II/0025	Update of section 4.8 of the SmPC with regard to neurological events (demyelination). Furthermore, a cross-reference to section 4.8 has been added in 4.4. The PIL is not affected. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	27/05/2011	SmPC	A review of demyelination events was conducted by the MAH to evaluate the occurrence of demyelinating disorders in the 100 mg group relative to 50 mg group of golimumab clinical trials. As of January 2010, five cases of demyelination were observed in studies with golimumab. Overall, in the controlled and uncontrolled portions of the Phase 2 RA and the Phase 3 RA, PsA, and AS trials, a greater incidence of demyelination was observed in the golimumab 100 mg treatment group compared with the golimumab 50 mg group.
II/0024	Update of section 4.8 of the SmPC regarding the frequency of leukaemia and inclusion of sarcoidosis, the latter in response to a CHMP request. The Package Leaflet is updated accordingly. Minor correction in the list of local representatives in section 6 of the PIL.	14/04/2011	27/05/2011	SmPC and PL	The MAH has updated the product information regarding the frequency of leukemia as an ADR following a report of leukemia from a golimumab clinical trial subject. Furthermore, following a request from CHMP based on the report on the cumulative review of non-necrotizing granulomatous disease (including sarcoidosis) with golimumab as well as the entire class of anti-TNF agents,

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				"sarcoidosis" has been added as a rare Immune system disorder ADR.
II/0021	Update of sections 4.1 and 5.1 to add the reduction in rate of progression of joint damage in psoriatic arthritis (PsA). Furthermore, update of section 5.1 regarding maintenance of the effects in signs and symptoms and physical function in PsA patients. The Package Leaflet is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	14/04/2011	27/05/2011	SmPC and PL	Please refer to the Scientific Discussion Simponi/H/C/000992/II/21 for further information.
II/0023/G	This was an application for a group of variations. Changes to the control of the drug substance and drug product B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	14/04/2011	20/04/2011		

	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
II/0013	Update of section 4.4, 4.5 and 4.6 of the SmPC regarding possible transplacental transfer of golimumab/neonatal vaccination. The package leaflet is updated accordingly. Annex II is also updated with the latest version number of the RMP. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/03/2011	20/04/2011	SmPC, Annex II and PL	The MAH proposes changes to the PI, mainly based on information available for infliximab. This is endorsed, since possible placental transfer as shown for infliximab, and its potential consequences for the newborn infant are as relevant for golimumab. The data for infliximab has been assessed within another variation procedure (EMEA/H/C/240/II/0145).
II/0018	Update of section 4.8 of the SmPC regarding vasculitis. The package leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/01/2011	21/02/2011	SmPC and PL	The MAH has reviewed reports from clinical trials, medical affairs, solicited and unsolicited data for cases of vasculitis and concluded that vasculitis is possibly associated with the use of golimumab. The addition of systemic vasculitis and cutaneous vasculitis in section 4.8 of the SmPC and corresponding changes to section 4 of the Package Leaflet is endorsed by CHMP. The benefit-risk profile of golimumab is still considered favourable.
WS/0066	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4. of the SmPC to add a recommendation for routine hepatitis B virus (HBV) testing as well as a recommendation to consult with a hepatitis B expert for patient tested positive for	16/12/2010	27/01/2011	SmPC and PL	The Marketing Authorization Holder (MAH) of Remicade and Simponi performed an assessment of guidelines and literature on the management of patients with HBV infection. As a result of a review of recently-issued guidelines and the medical literature regarding HBV testing of patients prior to initiating or receiving immunosuppressive therapy, the product information for infliximab (Remicade) and golimumab (Simponi) have been

	HBV infection. The corresponding section of the package leaflet is updated accordingly. Furthermore, the list of local representatives in the PIL has been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				revised to indicate the following: 1. Patients should be tested for HBV before initiating treatment with infliximab or golimumab, and 2. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.
II/0015	Update of section 4.4 and 4.8 of the SmPC with additional safety information regarding serious hypersensitivity reactions following a request from the CHMP. The Package Leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	27/01/2011	SmPC and PL	Nonserious hypersensitivity reactions were already described in the Simponi SmPC. A cumulative review of clinical trial and postmarketing reports of serious systemic hypersensitivity including anaphylaxis revealed seven cases that were received by the MAH in conjunction with Simponi administration. Four of the six cases that occurred in the post-marketing setting were medically confirmed and included in the last PSUR. In its assessment, the CHMP requested further monitoring and evaluation of serious systemic hypersensitivity cases as well as an update of the SmPC. Furthermore, the Risk Management Plan (RMP) will also be updated to include severe hypersensitivity reactions as an identified risk instead of a potential risk.
II/0014	Update of section 4.4 and 4.8 of the SmPC to add safety information regarding demyelinating disorders. In the addition, the MAH has updated section 4.4 regarding congestive heart failure. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	27/01/2011	SmPC	Cumulatively, seven demyelinating events have been reported in subjects who received golimumab in clinical trials, six of which were considered serious. Six of the seven events were representative of central demyelination and one was representative of peripheral demyelination. In addition, one spontaneous report pertaining to demyelination (MS) was received. With this variation, the wording in section 4.4 has been further modified to state that prescribers should exercise

					caution in considering the use of TNF blockers, including Simponi, in patients with central or peripheral nervous system demyelinating disorders, and discontinuation of Simponi should be considered if these disorders develop. In section 4.8, the ADR of demyelinating disorders was modified to include central and peripheral disorders. In addition, the MAH has aligned the warning statement regarding congestive heart failure (CHF) in section 4.4 of the SmPC with the information already included in section 4.8.
II/0008	Update of section 4.1 of the SmPC to extend the indication in rheumatoid arthritis (RA) to include adult patients not previously treated with MTX; and addition of an indication for reduction in the rate of progression of joint damage in all RA populations. Related changes are made in section 5.1. The PIL has been updated accordingly. In addition, the MAH has introduced changes related to the revised SmPC guideline and implementation of the most recent QRD template. Annex II has been modified to delete the DDPS version number and update the RMP version. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	16/12/2010	27/01/2011	SmPC, Annex II and PL	Please refer to the Scientific Discussion "Simponi/H/C/000992/II/008" for further information.
IB/0020/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	27/01/2011	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IA/0022/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	19/01/2011	n/a	SmPC, Annex II, Labelling and PL	
IB/0019	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	02/12/2010	n/a		
IA/0017	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a	30/11/2010	n/a	Annex II	

	DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH				
IA/0016/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	15/11/2010	n/a		
II/0009	Update of section 5.1 of the SmPC related to maintenance of effect on signs and symptoms, physical function, and health-related quality of life and updated immunogenicity data. C.I.4 - Variations related to significant modifications	23/09/2010	25/10/2010	SmPC	The MAH has proposed changes to section 5.1 of the SmPC of Simponi to add information on the maintenance of treatment effect in patients with rheumatoid arthritis (RA). The revisions are based on long-term data from study C0524T06 in patients with inadequate response to DMARD up to week 104. For the 50 mg + MTX dose group 54%

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				(48/89) of subjects remained on the dose throughout the 2 years period. The ACR20/50/70 responses for these patients at week 104 have been added to section 5.1 of the SmPC, as well as information on maintenance of DAS28 responses, improvement in HAQ and SF-36 physical component. The update of the information on immunogenicity data was supported appropriately by summarised data from all Phase 3 studies with golimumab in rheumatologic indications. The overall risk-benefit assessment for Simponi was not changed by this variation and remains positive.
II/0010	Based on pharmacokinetic data from the Phase 1 study C0524T14 the MAH has updated section 5.2 Pharmacokinetic properties with regard to the concomitant use of golimumab and methotrexate (MTX). In this study, concomitant use of MTX reduced golimumab apparent total systemic clearance (CL/F) by approximately 36% after 6-month treatment with SC golimumab in subjects with RA. While the number of evaluable patients in study C0524T14 was limited, the proposed estimate is in agreement with the previous text on the effect of MTX on the clearance of subcutaneously administered golimumab which was based on a population pharmacokinetic analysis of a larger number of subjects. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/06/2010	28/07/2010	SmPC and PL	

IG/0007	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	04/06/2010	n/a	Annex II	
II/0005	Change to the manufacturing process of the drug substance Change(s) to the manufacturing process for the active substance	20/05/2010	02/06/2010		
II/0006	Change to the drug substance manufacturing process Change(s) to the manufacturing process for the active substance	18/03/2010	24/03/2010		
II/0004	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Update of DDPS (Pharmacovigilance)	18/02/2010	23/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (version 005) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
II/0003	Update of the SmPC in sections 4.4 and 4.8 with reagrd to malignancies and lymphoproliferative disorders as well as concurrent administration of TNF-antagonists and anakinra and on switching between biological DMARDS. Corresponding changes were introduced in the package leaflet as appropriate. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	23/03/2010	SmPC and PL	A previous safety analysis of clinical and post-marketing data of TNF-blocking agents revealed a potential safety signal involving the occurrence of malignancies in paediatric patients, leukaemia, and psoriasis-like lesions associated with this class of products. In order to better reflect these safety concepts appropriately in the product information for Simponi, an addditional review was undertaken by the MAH to assess the individual cases available to the MAH. From the data presented by the MAH on leukaemias and paediatric malignancies, it is agreed that there are a number of uncertainties regarding whether

					there is a causal association between anti-TNF agents and leukaemias or paediatric malignancies or not. Nevertheless, given the mechanism of action of these agents, the possible risks for the development of such malignancies with use of agents of this class cannot be excluded. Thus, the amendments to the warning in section 4.4 have been introduced addressing the potential risk for the development of paediatric malignancies and leukaemia in patients treated with TNF-antagonists. The MAH also conducted an independent class evaluation of TNF product labelling in major regions such as the US and EU, as well as a TNF medical literature review. As a result, the MAH has added safety information to the Simponi product information regarding the concomitant use of anakinra and abatacept with TNF-blockers and precautionary text regarding the switching between biological disease-modifying antirheumatic drugs (DMARDs).
II/0002	Revision of the SmPC, section 5.1 Clinical Efficacy, rheumatoid arthritis, regarding data from study C9524T11 (GO-AFTER) after re-analysis following exclusion of 16 patients from a single trial site from the efficacy analysis. Addition of names of local representatives of the MAH in section 6 of the PIL. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	23/03/2010	SmPC and PL	After concerns were raised about documentation and data collection practices at one single clinical trial site of study C0524T11, selected key efficacy parameters at Week 24 such as primary endpoint, major secondary endpoints, and other key secondary endpoints were re-analyzed by the MAH excluding the data from this site. Safety and pharmacokinetic (PK) data were left unchanged. Overall the conclusions regarding the statistical significance of the results in the C0524T11 study were unchanged with the following 2 exceptions: " The difference between the golimumab 50 mg

					group and the placebo group in improvement from baseline in HAQ score at Week 24 for subjects who discontinued prior anti-TNF? therapy(s) due to lack of efficacy changed from being significant (p=0.045) to not significant (p=0.067). " The number of subjects in the golimumab 100 mg group who had an ACR 90 response changed from being statistically significant (p = 0.042) to statistically not significant (p = 0.077). In addition, the removal of the efficacy data collected at this site changed the p-value for the primary endpoint (ACR 20 response of the golimumab 50 mg group) from p<0.001 to p=0.001; however, the primary endpoint remained statistically significant. The reanalysis of efficacy data did not critically change the overall results for key efficacy parameters (such as the co-primary endpoint, percentage of patients achieving an ACR 20 response at week 14). Accordingly, the risk/benefit analysis for the approved indication remains favourable and the applicant's proposed SmPC changes in section 5.1 are agreed with.
IA/0001	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	15/12/2009	n/a		