Protocol Information

Title	Post-Marketing Observational Cohort Study of Patients with Inflammatory Bowel Disease (IBD) Treated with Inflectra (infliximab) in Usual Clinical Practice (CONNECT-IBD)
Protocol version identifier	V2.0
Date of last version of protocol	23 February 2015
Active substance	Infliximab
Medicinal product	Inflectra (infliximab), Remicade (infliximab)
Product reference	EMEA/H/C/002778
Marketing authorisation holder (MAH)	Hospira, UK Ltd.
Research question and objectives	Primary study objectives: • To characterise the population and drug utilisation patterns of patients treated with Inflectra for Crohn's Disease (CD) or Ulcerative Colitis (UC) in the context of standard of care Remicade • To assess the safety of Inflectra up to a 2-year follow up period in the treatment of patients with CD or UC in the context of standard of care Remicade Secondary study objective: • To assess the effectiveness of Inflectra in the treatment of patients with CD or UC in the context of standard of care Remicade Exploratory objectives: • To evaluate the immunogenicity profile of Inflectra in the treatment of patients with CD or UC • To evaluate patient-reported outcomes (PRO) including quality of life (QoL), work productivity and healthcare resource use (HRU) in patients treated with Inflectra for CD or UC
Countries of study	Approximately 200 sites in 15 countries in which Inflectra and Remicade are available for prescription
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Abbreviation	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
ARDS	Acute Respiratory Distress Syndrome
AV	Atrioventricular
CD	Crohn's Disease
CRF	Case Report Form
CSR	Clinical study report
DIC	Disseminated Intravascular Coagulation
DVT	Deep vein thrombosis
EDC	Electronic Data Capture
EMA	European Medicines Agency
E-mail	Electronic mail
GCP	Good Clinical Practice
GI	Gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HBI	Harvey Bradshaw Index
HBV	Hepatitis B Virus
HCP	Healthcare provider
HRU	Healthcare Resource Utilisation
HSTCL	Hepatosplenic T-cell Lymphoma
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification

(continued)

Abbreviation	Definition
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KOL	Key Opinion Leader
mAb	Monoclonal Antibody
MAH	Marketing Authorisation Holder
PRCA	Pure Red Cell Aplasia
PRO	Patient-Reported Outcome
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCT	Randomised Clinical Trial
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SIDS	Sudden Infant Death Syndrome
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumour necrosis factor
UC	Ulcerative Colitis
WPAI	Work Productivity and Activity Impairment

3 ABSTRACT

Protocol Title

Post-Marketing Observational Cohort Study of Patients with Inflammatory Bowel Disease Treated with Inflectra (infliximab) in Usual Clinical Practice (CONNECT-IBD).

Rationale and Background

Remicade (infliximab, Janssen Biotech, Inc.), an IgG_1 chimeric human-murine monoclonal antibody (mAb), was authorised for approval in Europe in August 1999. Since then it has been utilised in many thousands of patients for the treatment of 2 major types of inflammatory bowel disease (IBD), Crohn's Disease (CD) and ulcerative colitis (UC). In September 2013, Inflectra (infliximab), a mAb biosimilar to reference Remicade, was approved by the European Medicines Agency (EMA) based on an extensive biosimilar comparability exercise, which demonstrated that quality, as well as the clinical efficacy, pharmacokinetics and safety profile of Inflectra are highly comparable to that of Remicade. Marketing authorisation of Inflectra included all approved indications for Remicade including the extrapolated indications of moderate to severe CD and UC. This study is designed to characterise the patient population currently receiving Inflectra in the context of standard of care (SOC) utilisation of Remicade, and to document the safety and effectiveness of Inflectra, also in the context of SOC Remicade, in the treatment of patients with CD or UC in real-world clinical practice.

Research Objective

Primary study objectives:

- To characterise the population and drug utilisation patterns of patients treated with Inflectra for CD or UC in the context of SOC Remicade
- To assess the safety of Inflectra up to a 2-year follow-up period in the treatment of patients with CD or UC in the context of SOC Remicade

Secondary study objective:

- To assess effectiveness[1] of Inflectra in the treatment of patients with CD or UC in the context of SOC Remicade

Exploratory objectives:

- To evaluate the immunogenicity profile of Inflectra in the treatment of patients with CD or UC
- To evaluate patient-reported outcomes (PRO) including quality of life (QoL), work productivity and healthcare resource utilisation (HRU) in patients treated with Inflectra for CD or UC

Study Design

This study is a multi-national, multi-centre, observational cohort study of patients with CD or UC, who are treated with Inflectra (or Remicade for the smaller SOC cohort). The decision to treat with Inflectra (or Remicade) will be made at the usual care discretion of the physician independent of and before the decision to enrol patients in the study. In order to characterise the population and drug utilisation patterns associated with the use of Inflectra in CD and UC, as well as its safety and effectiveness in the context of contemporaneous SOC Remicade, the study plans to enrol approximately 3,300 patients in a mix of academic and community sites in approximately 15 countries where Inflectra and Remicade are authorised for the treatment of CD or UC. In order to meaningfully describe expected subgroups in this heterogeneous patient population under treatment, approximately 2,500 of the patients enrolled will be included in the Inflectra cohort. All patients are expected to be enrolled over an approximate 24-month period, with each patient followed for up to 2 years. Enrolled patients who permanently discontinue infliximab (Inflectra or Remicade) treatment will be encouraged to remain in the study and be followed for the remainder of the study period using a simplified case report form (CRF).

There will be no study visits mandated per the study protocol. Patients' visit schedules will follow local SOC, typically coinciding with the schedule of infusions of Inflectra or

Remicade, with additional visits as needed at the treating physician's discretion. Data for the study will be entered into an electronic data capture (EDC) system at enrolment and then approximately every 3 months thereafter up to 2 years.

For the exploratory objective of assessing the immunogenicity profile of Inflectra, patients treated with Inflectra will be provided with a separate consent form to obtain authorisation for collecting blood samples taken during their routine pre-treatment and follow-up work-ups for Inflectra therapy for trough level and immunogenicity analyses. Participation in this exploratory analysis will be optional.

Population

The target study population will include patients with CD or UC, who are being treated with, or initiating treatment with, Inflectra (or Remicade for the SOC cohort) at the time of study enrolment. This would include the following treatment subgroups:

- Biologic-naïve patients initiating Inflectra (or Remicade);
- Patients currently being treated with Inflectra (or Remicade);
- Patients who are considered stable by the Investigator under Remicade therapy for CD or UC, who switch to Inflectra;
- Patients switching to Inflectra (or Remicade) from an alternative biologic therapy (e.g. adalimumab) due to non-responsiveness to or intolerance;
- Patients re-initiating infliximab (Inflectra or Remicade) after having successfully completed and exited a previous course of infliximab therapy in the past.

Patients with fistulating disease or stomas, and those receiving combination therapy will be included.

Study Outcomes/Assessments

Primary Outcomes:

- Patients' demographic characteristics
- Clinical and diagnostic characteristics
  - Relevant medical history of CD or UC including prior treatments
- Inflectra treatment
  - Inflectra switches and reasons for switch

- Dose and frequency, augmentation/reduction and reasons of changes

- Co-therapy(ies) related to the management of CD or UC
- Serious adverse events (SAEs) or adverse events of special interest (AESI) during the 24-month follow-up period.

Secondary Outcomes:

- Clinical assessment of disease activity
  - Data relating to the Harvey Bradshaw Index (HBI) for patients with CD
  - Data relating to the Partial Mayo Scoring System for Assessment of UC Activity (the abbreviated version excluding the endoscopy sub-score)
  - Data relating to the Montreal classification index for CD
  - Data relating to the Montreal classification index for UC:
    - classification by extent
    - classification by severity
  - Data relating to the fistula drainage assessment index for CD
- Laboratory results related to the treatment or assessment of CD or UC
- Imaging results related to the treatment or assessment of CD or UC

Exploratory Outcomes:

- Immunogenicity-related or pharmacokinetic assessments of patients receiving Inflectra
- QoL as measured by the short Inflammatory Bowel Disease Questionnaire (SIBDQ)
- Changes in work productivity and activity impairment measured by the Work Productivity and Activity Impairment Questionnaire – Specific Health Problem V2.0 (WPAI: SHP V2.0)
- Healthcare resource utilisation (HRU) related to the management of CD or UC, SAEs or AESI

Data Sources

CRFs will be designed to gather the data needed for the study that is collected as part of local SOC of the study patients. Clinical information recorded in the patients' medical charts will

be abstracted and entered into the EDC system. As well, patients will complete the paper-based PRO questionnaires.

Sample Size

The study will enrol approximately 3,300 patients with CD or UC, who are either already being treated or initiating treatment with Inflectra or Remicade. The study is designed primarily to characterise the use of Inflectra in patients with CD or UC.

Data Analysis

Considering this study is not designed to test specific hypotheses, the statistical analysis will be descriptive in nature. Given the expected heterogeneity of patients commonly seen in observational studies, patients will be stratified (e.g., UC vs. CD, by subgroup, by country) based on final data available for analysis. Data permitting, *post hoc* inferential analysis may be used to examine the impact of risk factors or predictors on outcomes of interest, as appropriate. Detailed procedures of all analyses will be described in the Statistical Analysis Plan (SAP).

Limitations of the Research Methods

Loss to Follow-up

All patients will be followed for up to 2 years. If a patient misses more than 1 usual care visit, the site will attempt to communicate with the patient and document the patient's reason for not returning. Sites will be requested to attempt to contact patients at various times of the day and evening, and on different days of the week. If the patient cannot be contacted after the due diligence process, the treating physician will attempt to contact the patient's designated secondary contacts, including the patient's general practitioner and next of kin or out-of-household contacts to obtain information on the patient's whereabouts and vital status. If the patient's care has been transferred to another healthcare professional (HCP), the treating physician at the enrolling site will be responsible for obtaining the required follow-up information from the new treating physician. Patients who do not return for at least 2 scheduled visits, and for whom no information is available will be considered lost to follow-up.

Study Limitations

Recognising that this is an observational study, there are some limitations or potential biases inherent in this study design: survivor bias, selection bias and the risk of systematic longer follow-up period in the Remicade patient group (given the higher probability of current use). The observational study will include patients who initiated Inflectra or Remicade prior to implementation of the study ("prevalent exposure"). One limitation of this approach is that patients who initiate treatment and discontinue shortly thereafter would not be included and could differ in demographic and clinical characteristics from those who become enrolled ("survivor bias"). A further limitation of this approach is that Remicade patients are more likely to be prevalent patients, while a higher proportion of Inflectra patients will be biologic-naïve at the time of study entry. This may have implications on HRU as biologic-naïve patients may present with less advanced disease.

Given the historic availability of Remicade safety and effectiveness information, the observation groups of the study will include different numbers of patients. Therefore, the estimation of the true incidence of AEs will be supported by different statistical powers, according to those subgroup sizes. The width of the confidence intervals around the estimated incidence rates will differ between subgroups (wider with Remicade). Consequently, the findings may be difficult to compare or the comparison may not be clinically meaningful. Events may occur in the Inflectra observation group, but the comparison groups may be too small to determine if the differences across the subgroups are significant. Historically available information for Remicade may be utilised to provide additional context. However, the findings from this study will be descriptive and not inferential in nature, due to the study nature and design.

4 PROTOCOL AMENDMENT: SUMMARY OF CHANGES

Preceding Protocol Version/Date	Change section/Page	Description of Protocol Amendment	New Protocol Version/Date
Version 1.0 04 November 2014	1. Throughout document	1. Inflammatory Bowel Disease (IBD) is specified as Crohn's Disease (CD) or Ulcerative Colitis (UC)	Version 2.0 23 February 2015
	2. List of abbreviations, Page 6	1. Short Inflammatory Bowel Disease Questionnaire (SIBDQ) was added	
	3. Throughout document pertaining to protocol title	1. Infliximab was added in brackets next to Inflectra for consistency reasons	
	4. Abstract, Pages 9-12	1. The sentence 'Patients with fistulating disease or stomas and those receiving combination therapy will be included' was added to population section 2. 'In the six months prior to enrolment for biologic naïve patients or in the 12 months prior to enrolment for biologic experienced patients' wording was removed from study outcomes section 3. 'Data relating to the Montreal classification index for CD' 'Data relating to the Montreal classification index for UC: classification by extent classification by severity' 'Data relating to the fistula drainage assessment index for CD' were added as additional clinical assessments to the secondary outcomes section 4. QoL will be measured by short Inflammatory Bowel Disease Questionnaire (SIBDQ) under exploratory outcomes section 5. The wording 'For all patients with "prevalent exposure," data collection will include information on any AESI and SAE experienced during Inflectra or Remicade treatment prior to study enrolment, so that any AESI that occur shortly after treatment initiation will not be under-represented in the study population. A safety analysis will compare AESIs and SAEs experienced during Inflectra or Remicade treatment prior to enrolment with events after enrolment' was removed from study limitations section	
	5. Secondary study objectives, Page 18	1. The following sentence was added "Effectiveness is a measure of the extent to which a specific intervention, procedure, regimen, or service when deployed in the field in routine circumstances, does what it is intended to do for a specified population. 'Effectiveness' should be distinguished from 'efficacy', which is a measure of the extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions" to clearly define effectiveness as opposed to efficacy.	
	6. Figure 1, Page 20	1. The study design schematic was updated to reflect protocol changes	
	7. Enrolment, Page 21	1. Enrolment process wording changed to 'Patients will be recruited for the study during the course of	

		usual care at each investigative site. Patients deemed potentially eligible for the study by their physician will be invited to participate. At the time of study invitation, consenting patients may be enrolled if they are eligible to be included in either the Inflectra or the Remicade cohort and meet study inclusion and exclusion criteria (Sections 7.2.3.1 and 7.2.3.2)'	
	8. Patient Eligibility, Page 22	1. Changed as described in 4.1	
	9. Inclusion criteria, Page 22	1. Inclusion criterion 1: 'At least 18 years of age at the time of initial confirmed diagnosis of IBD' was changed to 'at least 12 years at the time of initial confirmed diagnosis of CD and UC and at least 18 years at the time of enrolment to the study' 2. Inclusion criterion 2: The following sentence was added 'Patients with stomas or surgery/pouch will also be included" to indicate additional patient subgroups included'	
	10. Primary outcomes, Page 23	1. Changed as described in 4.2	
	11. Secondary Outcomes, Page 23	1. Changed as described in 4.3	
	12. Exploratory Outcomes, Page 23	2. Changed as described in 4.4	
	13. Study data Collection Schedule Table, Page 25	1. Changed to include additional clinical assessments	
	14. Study limitations, Page 30	1. Changed as described in 4.5	
	15. Adverse Events of Special Interest (AESI) Table 3, Page 39	1. 'Infusion reaction associated with shortened infusion duration [RA [RA)' was deleted	
	16. References, Page 44	1. Change of reference to describe SIBDQ	
	17. Appendices, Page 51-58	1. Appendix 3 added to describe the 'Montreal Classification' of Crohn's Disease clinical assessment 2. Appendix 4 added to describe the 'Montreal Classification' of Ulcerative colitis clinical assessment 3. Appendix 5 added to describe the 'Fistula drainage assessment' of Crohn's Disease clinical assessment 4. Appendix 8 added to include a detailed description of protocol updates	
	18. Sponsor Signatures Page	1. Jeff White, Senior Clinical Manager, is replacing Susan Reid, Director	
	19. Throughout document	1. Minor changes to language for clarity	

Detailed changes of the protocol updates can be found on Appendix 8.

5 RATIONALE AND BACKGROUND

Remicade (infliximab, Janssen Biotech, Inc.), an IgG_1 chimeric human-murine monoclonal antibody (mAb), was authorised for approval in Europe in August 1999. Since then, it has been utilised in many thousands of patients for the treatment of 2 major types of inflammatory bowel disease (IBD), Crohn's Disease (CD) and ulcerative colitis (UC). Infliximab was designed to bind to tumour necrosis factor-α (TNF-α), and prevent it from binding to its endogenous receptors[2]. Since its original characterization, infliximab has been shown to act through a multitude of additional mechanisms of action beyond TNF-neutralization in inflammatory bowel disease.

In September 2013, Inflectra (infliximab), a mAb biosimilar to reference Remicade, was approved by the European Medicines Agency (EMA) based on an extensive biosimilar comparability exercise, which demonstrated that quality, as well as the clinical efficacy, pharmacokinetics and safety profile of Inflectra are highly similar to that of Remicade. Inflectra is an IgG_1 chimeric human-murine mAb biosimilar to Remicade produced in the same type of cell-line as Remicade. In addition to extensive non-clinical comparability testing of molecular structure and function, including those mechanisms of action thought to be important in CD or UC, the approval of Inflectra in Europe was also based on the results of 2 large, double-blind, randomised clinical trials (RCTs): a phase I-type Programme evaluating the Autoimmune disease investigational drug CT-P13 in ankylosing spondylitis (PLANETAS) in 250 patients with ankylosing spondylitis,[3] and a phase III-type study Programme evaluating the Autoimmune disease investigational drug CT-P13 in rheumatoid arthritis (PLANETRA) in 606 patients with rheumatoid arthritis[4]. These 2 studies demonstrated that the pharmacokinetics and clinical efficacy of Inflectra were equivalent based on pre-specified criteria to that of Remicade, and that the two treatments were well tolerated with comparable immunogenicity and safety profiles. Based on the totality of evidence submitted demonstrating that Inflectra was highly similar to Remicade, the European Medicines Agency (EMA) granted licensure for Inflectra equivalent to the license for Remicade. This marketing authorisation included several extrapolated indications, including those for the treatment of CD and UC.

A summary of key findings presented in the Inflectra European Public Assessment Report of the non-clinical evidence supporting extrapolation to the CD or UC indications:

- Comparable binding to soluble transmembrane bound TNF-α compared to Remicade
- Comparable binding to FcγRIa, FcγRIIa, FcγRIIb and FcRn, C1q compared to Remicade
- Reduced binding (~20% by SPR vs. Remicade) to rFcγRIIIa and rFcγRIIIb in vitro
    - Difference in the level of afucosylated glycans, Man5 and G0 for CT-P13: total 5.46 - 6.26% vs. Man5, G0 and G2 for Remicade: total 11.91 - 14.61%
- Ex vivo testing in representative physiological environments, demonstrated that differences in binding to FcγRIIIa and in ADCC activity, were abolished in the presence of:
    - serum of a CD patient
    - peripheral blood mononuclear cells preparations (vs. isolated NK cells)
    - whole blood
- The EMA's interpretation was that the difference in binding affinity was overcome by competition from plasma IgGs, soluble factors, immune complexes and presence of mixed cell populations expressing multiple FcRs. At inflammatory sites, the vascular permeability is increased, which allows for many blood components to enter the extra vascular space. "A range of arguments and experiments enable to conclude with a high level of probability that the quality differences detected in the level of afucosylation and binding to FcγRIIIa are not clinically relevant."
- "In conclusion, by using a range of experimental models that are considered representative of the pathophysiological conditions and putative mechanisms of action of infliximab, the Applicant has provided convincing evidence that the difference detected in the amount of afucosylated species has no clinically relevant impact on the efficacy and safety of CT-P13, in particular in IBD. Additional in vitro data from human intestinal cells are further supporting extrapolation of the clinical data to IBD."

This study is designed to capture data from real-world clinical practice to characterise the population, document drug utilisation patterns, safety and effectiveness of Inflectra in the context of standard of care (SOC) utilisation of Remicade, in patients with CD or UC.

6 RESEARCH QUESTION AND OBJECTIVES

6.1 Primary Study Objective

- To characterise the population and drug utilisation patterns of patients treated with Inflectra for CD or UC in the context of standard of care (SOC) Remicade
- To assess the safety of Inflectra up to a 2-year follow up period in the treatment of patients with CD or UC in the context of standard of care (SOC) Remicade

6.2 Secondary Study Objective

- To assess the effectiveness[1] of Inflectra in the treatment of patients with CD or UC in the context of standard of care (SOC) Remicade. Effectiveness is a measure of the extent to which a specific intervention, procedure, regimen, or service when deployed in the field in routine circumstances, does what it is intended to do for a specified population. 'Effectiveness' should be distinguished from 'efficacy', which is a measure of the extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions.

6.3 Exploratory Study Objectives

- To evaluate immunogenicity profile of Inflectra in the treatment of patients with CD or UC
- To evaluate patient-reported outcomes (PRO) including quality of life (QoL), work productivity and healthcare resource utilisation (HRU) in patients treated with Inflectra for CD or UC

7 RESEARCH METHODS

7.1 Study Design

This study is a multi-national, multi-centre, observational cohort study of patients with CD or UC, who are treated with Inflectra (or Remicade for the smaller SOC cohort). The decision to treat with Inflectra (or Remicade) will be made at the usual care discretion of the physician independent of and before the decision to enrol patients in the study. In order to characterise the population and drug utilisation patterns associated with the use of Inflectra in Crohn's disease and ulcerative colitis, as well as its safety and effectiveness in the context of contemporaneous SOC Remicade, the study plans to enrol approximately 3,300 patients in a mix of academic and community sites in approximately 15 countries where Inflectra and Remicade are authorised for the treatment of CD or UC. In order to meaningfully describe expected subgroups in this heterogeneous patient population under treatment, approximately 2,500 of the patients enrolled will be included in the Inflectra cohort. All patients are expected to be enrolled over an approximate 24-month period, with each patient followed for up to 2 years. Enrolled patients who permanently discontinue infliximab (Inflectra or Remicade) treatment will be encouraged to remain in the study and be followed for the remainder of the study period using a simplified case report form (CRF).

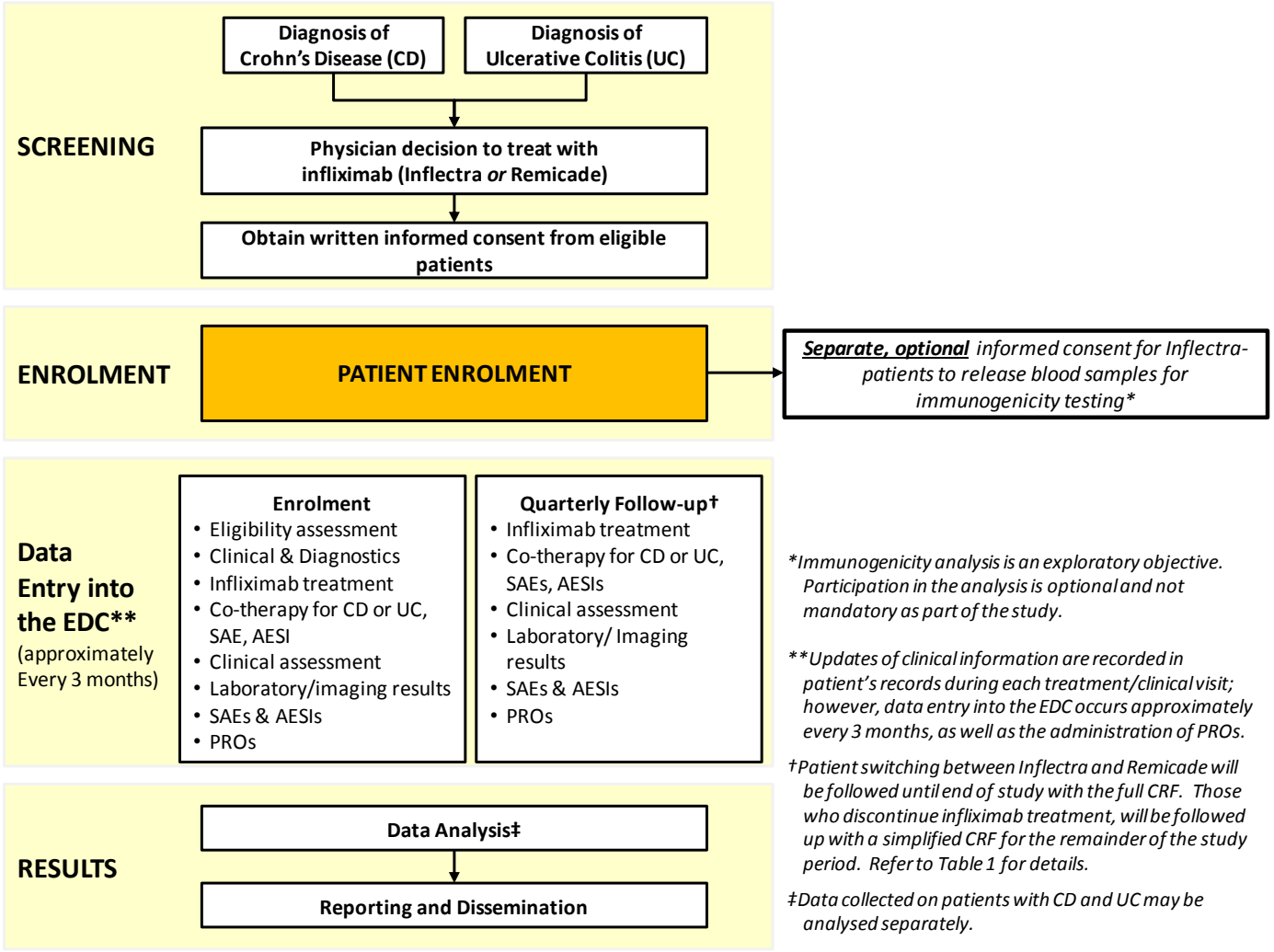
There is no study visit mandated per study protocol. Patients' visit schedules will follow local SOC, typically coinciding with the schedule of infusions of infliximab, with any additional visits at the treating physician's discretion. Medical information will be recorded in patients' medical records during every clinic visit. Data for the study will be extracted from medical charts and entered into the EDC system at enrolment and then approximately every 3 months thereafter up to 2 years. The study design is presented schematically in Figure 1.

7.1.1 Immunogenicity Analysis (optional)

For the exploratory objective of assessing immunogenicity profile of Inflectra, patients receiving Inflectra during the study will be provided with a separate informed consent form (ICF) to obtain authorisation for collecting blood samples taken during their routine pre-

treatment and follow-up work-up for Inflectra therapy for trough level and immunogenicity analyses. Participation in this exploratory analysis is therefore optional. Please refer to Annex 1 for further details regarding the rationale and procedures of the immunogenicity analysis.

Figure 1. Study Design Schematic



**Immunogenicity analysis is an exploratory objective. Participation in the analysis is optional and not mandatory as part of the study.*

***Updates of clinical information are recorded in patient's records during each treatment/clinical visit; however, data entry into the EDC occurs approximately every 3 months, as well as the administration of PROs.*

†Patient switching between Inflectra and Remicade will be followed until end of study with the full CRF. Those who discontinue infliximab treatment, will be followed up with a simplified CRF for the remainder of the study period. Refer to Table 1 for details.

‡Data collected on patients with CD and UC may be analysed separately.

7.2 Setting

7.2.1 Regions/Number of Study Sites

The study will take place in countries in which Inflectra and Remicade are authorised for the treatment of CD and UC. A heterogeneous sample of about 200 sites is planned to be recruited in approximately 15 countries. This will include a mix of academic and community centres to ensure broad physician and patient representation. As this study is designed primarily to characterise the use of Inflectra, sites prescribing only Remicade to treat CD or UC (i.e., not prescribing Inflectra for CD or UC) will not be recruited in the study.

7.2.2 Enrolment

In order to meaningfully describe expected subgroups in this heterogeneous patient population under treatment, approximately 2,500 of the patients enrolled will be included in the Inflectra cohort. In order to assure this number of Inflectra patients is enrolled, enrolment will be closely monitored in real time through the EDC system. It is expected that depending on local formulary regulations or institutional policies, there may be sites that prescribe either Remicade or Inflectra but not both. Sites that only utilise Remicade will not be recruited to participate in the study.

Patients will be recruited for the study during the course of usual care at each investigative site. Patients deemed potentially eligible for the study by their physician will be invited to participate. At the time of study invitation, consenting patients may be enrolled if they are eligible to be included in either the Inflectra or the Remicade cohort and meet study inclusion and exclusion criteria (Sections 7.2.3.1 and 7.2.3.2).

7.2.3 Patient Eligibility

The target study population will include patients with CD or UC, who are being treated, or initiating treatment, with Inflectra or Remicade at the time of study enrolment.

This would include the following treatment subgroups:

- Biologic-naïve patients initiating Inflectra (or Remicade);

- Patients currently being treated with Inflectra (or Remicade);
- Patients who are considered stable by the Investigator under Remicade therapy for CD or UC, who switch to Inflectra;
- Patients switching to Inflectra or Remicade from an alternative biologic therapy (e.g. adalimumab) due to non-responsiveness to or intolerance;
- Patients re-initiating Inflectra or Remicade after having successfully completed and exited a previous course of infliximab therapy in the past.

Patients with fistulating disease or stomas and those receiving combination therapy will be included.

7.2.3.1 Inclusion criteria

1. At least 12 years of age at the time of initial confirmed diagnosis of CD or UC and at least 18 years of age at the time of enrolment to the study.
2. Patients who are prescribed Inflectra or Remicade for the treatment of CD or UC prescribed according to the corresponding summary of product characteristics (SmPC) as determined by the Investigator. Patients with stomas or surgery/pouch will be included.

7.2.3.2 Exclusion criteria

1. Any reported contraindications for Inflectra or Remicade, according to the SmPC.
2. Known hypersensitivity (including severe, acute infusion reactions) to infliximab, its excipients or other murine proteins, at the time of enrolment.
3. Prior history of failure to respond to Remicade or Inflectra.

7.3 Study Variables

7.3.1 Primary Outcomes

- Patients' demographic characteristics
- Clinical and diagnostic characteristics
    - Relevant medical history for CD or UC including prior treatments

- Inflectra treatment
    - Inflectra or Remicade switches and reasons for switch
    - Dose and frequency, augmentation/reduction and reasons for changes
- Co-therapy(ies) for the management of CD or UC
- Serious adverse events (SAEs) or adverse events of special interest (AESI) during the 24-month follow-up period

7.3.2 Secondary Outcomes

- Clinical assessment of disease activity
    - Data relating to Harvey Bradshaw Index (HBI) for patients with CD[5]
    - Data relating to Partial Mayo Scoring System for Assessment of UC Activity, i.e., abbreviated version without the endoscopy sub-score[6]
    - Data relating to the Montreal classification index for CD
    - Data relating to the Montreal classification index for UC:
        - classification by extent
        - classification by severity
    - Data relating to the fistula drainage assessment index for CD
- Laboratory results related to the treatment or assessment of CD or UC
- Imaging results related to the treatment or assessment of CD or UC

7.3.3 Exploratory Outcomes

- Immunogenicity profile of patients receiving Inflectra
- QoL as measured by the short Inflammatory Bowel Disease Questionnaire (SIBDQ)[7]
- Changes in the work productivity and activity impairment as measured by the Work Productivity and Activity Impairment Questionnaire – Specific Health Problem V2.0 [WPAI: SHP V2.0[8]]
- Healthcare resource utilisation (HRU) relating to the management of CD or UC, any SAEs or AESI

7.4 Data Sources

CRFs will be designed to gather the data needed for the study that are collected as part of SOC. Patients will be completing a set of PRO instruments on paper during their SOC visits at enrolment and then approximately every 3 months (based on the visit that is closest in time to 3 months after the last visit) thereafter. Site research staff will enter PRO and patient-reported HRU data into the EDC system. Patients' medical charts, any relevant diagnostic reports, and the paper-based PROs and patient-reported HRU survey are the source documents for study data collection. Clinical information recorded in patients' medical charts and/or diagnostic reports will be abstracted and entered into the EDC system, as well as the completed PROs and patient-reported HRU survey. Table 1 summarises the data collection schedule of the study.

Table 1. Study Data Collection Schedule

	Once at enrolment	*Every 3 months up to 24 months*	
	Enrolment	**Follow-up Period***	**Infliximab treatment discontinuation****
Eligibility assessment and written informed consent *(including separate consent for immunogenicity testing, if applicable)*	X		
Relevant medical history for CD or UC • Diagnosis of CD or UC: extent, severity, duration • Prior treatments	X		
Infliximab therapy – Inflectra or Remicade • Dose, frequency: augmentation/reduction, reasons of changes • Switch(es) or discontinuation, reasons of switch/discontinuation	X	X	
Co-therapy *(frequency, dose, augmentation/reduction, switching, reason of switch)* • Steroid use • Medication(s) relating to the treatment of CD or UC or management of the symptoms of CD or UC • Medication(s) relating to the management of SAE/AESI	X	X	X
Clinical assessment • Data relating to Harvey-Bradshaw Index (HBI) for CD • Data relating to Partial Mayo Scoring System for Assessment of Ulcerative Colitis Activity for UC (abbreviated version excluding endoscopy sub-score) • Montreal classification for CD • Montreal classification for UC: o classification by extent o classification by severity • Fistula drainage assessment • Clinical remission/relapse	X	X	X**
Laboratory results leading to CD or UC treatment decision	X	X	
Imaging results leading to CD or UC treatment decision	X	X	
Patient-reported outcomes (PROs) • Short Inflammatory Bowel Disease Questionnaire (SIBDQ) • Work Productivity and Activity Impairment (WPAI) • Healthcare Resource Utilisation questionnaire (HRU)	X	X	
Safety outcomes • Serious adverse event (SAE) • Adverse event of special interest (AESI)		X	X

* *Recording of medical data into patients' charts occurs during their usual care visit. Data entry into the EDC system occurs approximately every 3 months.*

** *Patients who discontinue infliximab treatment will be followed for the remainder of the study period using a simplified CRF. HBI,Partial Mayo scoring, Montreal classification for CD or UC and fistula drainage assessment may not be applicable to simplified data capture depending on local SOC, but information on clinical remission or relapse will be captured to the extent possible.*

7.5 Sample Size

The study will enrol approximately 3,300 patients with CD or UC, who are either already being treated or initiating treatment with Inflectra or Remicade. The study is designed primarily to characterise the use of Inflectra in patients with CD or UC. Patients being initiated or treated with Remicade will constitute a smaller although substantial SOC cohort and are expected to provide context for the Inflectra cohort. The sample size is based on both practical and statistical considerations. The sample size must be relatively large given there are 2 diseases (CD and UC) under study with 5 population subgroups within each. Additionally, the study will seek to characterise population and drug utilisation patterns across 15 countries. In order to meaningfully describe expected subgroups in this heterogeneous patient population under treatment, approximately 2,500 of the patients enrolled will be included in the Inflectra cohort. There is no calculation of power for this study because the objectives are descriptive rather than inferential.

In achieving one part of the primary objective of the study of documenting the safety of Inflectra in real-world clinical practice, the simulated rates of SAEs and AESI associated with the use of infliximab are being used to estimate the sample size of the study. The table below shows the 2-sided confidence intervals associated with observed AESI rates ranging from 0.1% to 10% in patient populations of 825 and 2,475 patients. The confidence intervals are exact binomial 95% confidence intervals.

Table 2. Observed AESI Rates

Precision of Observed AESI Rates with a Sample Size of 825

(2-sided 95% confidence interval)

Observed Rate	Exact 95% Confidence Interval
0.1%	0.00, 0.45
0.5%	0.13, 1.24
1.0%	0.42, 1.90
2.0%	1.11, 3.13
5.0%	3.59, 6.68
10.0%	7.98, 12.19

Precision of Observed AESI Rates with a Sample Size of 2475

(2-sided 95% Confidence Interval)

Observed Rate	Exact 95% Confidence Interval
0.1%	0.01, 0.29
0.5%	0.25, 0.85
1.0%	0.62, 1.44
2.0%	1.47, 2.61
5.0%	4.15, 5.90
10.0%	8.83, 11.23

7.6 Data Management

7.6.1 Electronic Data Capture (EDC) System

The database will be designed using DataTrak One, a proprietary electronic data capture (EDC) system provided by Datatrak International, Inc., a third party vendor contracted by Hospira in accordance with written security policies.

7.6.2 Data Entry

All reported data from the enrolled Investigator's site will be entered via a secure web-based EDC study database. All sites will be fully trained in using the EDC system, including CRF completion guidelines. Site personnel will be provided with secure usernames and passwords in order to enter study data into the EDC system. All participating sites will only have access to view and enter the data for their own patients. A data manager will perform concurrent review during the course of the data collection period. The data manager will generate *ad-hoc* queries to sites when required, and the site management team will follow-up to request completion of such queries.

7.6.3 Statistical Software

All analyses will be performed using SAS for Microsoft Windows operating system statistical software (SAS Institute, Cary, North Carolina, USA) version 9.2 or higher, using validated implementations of each application or SAS custom programming.

7.7 Data Analysis

Considering the observational design of the study and its objectives, the statistical analysis will be descriptive in nature. Summary tabulations will be presented that will display the number of observations, mean, standard deviation, median, minimum and maximum for continuous variables and the number and percentage per category for categorical data. Duration of steroid-free remission, proportion of patients remaining in clinical remission at different follow-up milestones, and proportion of patients with reduction in steroid use will be computed.

In keeping with one component of the primary objective of evaluating the safety of Inflectra up to 2 years, for each type of SAE and AESI, both incidence rate and exposure-adjusted incidence rate will be calculated with confidence intervals. Generalised linear models will be used to examine the impact of risk factors and predictors on outcomes of interest, as appropriate.

As this is an observational study, not designed to test any *a priori* hypotheses, the sample size selected may not be sufficient to detect any statistical significance. Given the expected heterogeneity of patients commonly seen in observational studies, patients will be stratified (e.g., UC vs. CD, by subgroup, by country) based on final data available for analysis.

7.8 Quality Control and Quality Assurance

The study will be conducted following International Conference on Harmonisation (ICH) guidance for industry Good Clinical Practice (GCP) (E6).[9] Quality Assurance representative(s) of Hospira (or their designee) may conduct audit visits at any time during the study period. All necessary related data and documents will be made available for inspection.

7.8.1 Site Training and Initiation

A meeting will be held to train the Investigators (treating physicians) and their site staff on the study requirements and use of the EDC system. Hospira (or their designee) will contact each site to review site initiation procedures. Ongoing site management will occur throughout the entire duration of the study. Additional outreach and training including on-site visits will occur for sites (Investigators and staff) needing remedial training and to address quality control concerns prior to analysis.

7.8.2 Site Monitoring

In-house site management or remote monitoring will be used to manage sites during the operational/maintenance phase of the programme. Site contact will be more frequent during enrolment and then decrease during the subject follow-up period due to more limited site involvement. All inbound calls from sites will be triaged immediately and all calls (inbound and outbound) will be tracked, including inquiry type, site identification (ID), query resolution and centre feedback.

7.9 Limitations of the Research Methods

7.9.1 Lost to Follow-up

All patients will be followed for up to 2 years. If a patient misses more than 1 usual care visit, the site will attempt to communicate with the patient and document the patient's reason for not returning. Sites will be requested to attempt to contact patients at various times of the day and evening, and on different days of the week. If the patient cannot be contacted after the due diligence process, the treating physician will attempt to contact the patient's designated secondary contacts, including the patient's general practitioner and next of kin or out-of-household contacts to obtain information on the patient's whereabouts and vital status. If the patient's care has been transferred to another healthcare professional (HCP), the treating physician at the enrolling site will be responsible for obtaining the required follow-up information from the new treating physician. Patients who do not return for at least 2 scheduled visits, and for whom no information is available will be considered lost to follow-up.

7.9.2 Study Limitations

Recognising that this is an observational study, there are some limitations or potential biases inherent in this study design: survivor bias, selection bias and the risk of systematic longer follow-up period in the Remicade patient group (given the higher probability of current use). The observational study will include patients who initiated Inflectra or Remicade prior to implementation of the study ("prevalent exposure"). One limitation of this approach is that patients who initiate treatment and discontinue shortly thereafter would not be included and could differ in demographic and clinical characteristics from those who become enrolled ("survivor bias"). A further limitation of this approach is that Remicade patients are more likely to be prevalent patients, while a higher proportion of Inflectra patients will be biologic-naïve at the time of study entry. This may have implications on HRU as biologic-naïve patients may present with less advanced disease.

Given the historic availability of Remicade safety and effectiveness information, the observation groups of the study will include different numbers of patients. Therefore, the

estimation of the true incidence of AEs will be supported by different statistical powers, according to those subgroup sizes. The width of the confidence intervals around the estimated incidence rates will differ between subgroups (wider with Remicade). Consequently, the findings may be difficult to compare or the comparison may not be clinically meaningful. Events may occur in the Inflectra observation group, but the comparison groups may be too small to determine if the differences across the subgroups are significant. Historically available information for Remicade may be utilised to provide additional context. However, the findings from this study will be descriptive and not inferential in nature, due to the study nature and design.

7.10 Other Aspects

7.10.1 National Leaders Committee

A National Leaders Committee has been established which includes clinicians and scientists with expertise in CD or UC, epidemiology and biostatistics, with a National Leader chosen for each country involved in the study. Committee members will provide ongoing subject matter expertise for the programme. In collaboration with Hospira, the Committee will be responsible to review the data from the study over time, to make recommendations to Hospira regarding study conduct, and assist in study execution at the national and international levels. The Committee will be involved in case report form review and development, statistical analysis plan development and review, Clinical study report (CSR) review, as well as publication development, if the findings from the study warrant publications in the future.

7.10.2 Concomitant Medication Use

As this is an observational study, where treatment decisions are left to the discretion of the treating physician, prescription of Inflectra or Remicade or any other concomitant medication will not be influenced by the study protocol in any way. Therefore, the current study protocol does not impose any restriction on the prescription of concomitant medications. It is left to treating physician’s discretion taking into account local standard of care and SmPC

directions. With regard to co-therapy(ies), as indicated in Table 1, data on the following drug usage will be extracted from medical charts and entered into the EDC system:

- Steroids
- Medication(s) related to the treatment of CD or UC or management of the symptoms of CD or UC
- Medication(s) related to the management of SAE or AESI

Information on other types of concomitant medication will be recorded in the patients' medical charts as per routine practice but will not be captured as part of study data.

7.10.3 Regulatory Authorities

The approved protocol will be submitted to Regulatory Authorities in accordance with the regulations of the countries and participating sites' local clinical research regulatory requirements when applicable.

7.10.4 Protocol Modifications

Amendments to the protocol can only be made by Hospira. All protocol amendments must be signed and dated by the Investigator physicians, and if required, submitted and approved by the Regulatory Authorities and Institutional Review Board/Independent Ethics Committees (IRB/IEC), prior to implementation of the amendment. The National Leaders Committee may provide feedback to Hospira on protocol modifications.

7.10.5 Compensation to Investigators

Study Investigators will be compensated for time spent in completing study requirements consistent with local prevailing conditions. This compensation schedule will be determined in accordance with national and local IRB/IEC guidelines and fair market value for the work performed.

8 PROTECTION OF HUMAN SUBJECTS

8.1 Informed Consent

Prior to any data collection under this protocol, the ICF must be signed by the patient, in accordance with local practice and regulations. Information about the study will be explained to the patient by the Investigator or designee. A copy of the ICF, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must also be documented in the patient's medical records prior to any data collection under this protocol. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and Hospira.

In order to ensure patient confidentiality, patients will be assigned a unique study identification number (ID). The key, matching study IDs with patient names will be maintained by the site, and only the study IDs and demographics will be recorded on the data collection forms. Upon enrolment, in localities where this is permissible, patients will be asked to provide their name, phone and electronic mail (e-mail) contact information and similar information on secondary contacts. This information will not be entered into the study clinical database. The Investigator and local site staff will securely store information separately from other study information. This information will only be used to obtain patient vital status and disposition, if the patient becomes lost to follow-up.

In any presentations or in publications of the results of the study, the patients' identities will remain anonymous and confidential. Hospira, its designee(s), and various government health agencies may inspect the records of the study. Every effort will be made to keep the patients' personal medical data confidential.

8.2 Independent Ethics Committee or Institutional Review Board

Prior to the collection of any study related data, IRB/IEC approval of the protocol, informed consent and all patient enrolment materials will be obtained in each country and for each site, as applicable.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

9.1 Definitions

The definitions to follow for classification of adverse events (AEs) (e.g., adverse event, serious adverse event, suspected unexpected serious adverse reaction) are in accordance with those outlined in the "Safety and Medical Management Plan" and in the EMA's Guideline on Good Pharmacovigilance Practices (GVP).[10] Safety reporting procedures for AEs relating to Hospira products will be detailed in the "Safety and Medical Management Plan."

9.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the investigational product.

Such an event can result from use of the drug as stipulated in the protocol or labelling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Clinically significant abnormalities are to be followed to resolution (i.e. become stable, return to normal, return to baseline, or become explainable).

Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol-specific criteria, and/or if the Investigator considers them to be AEs.

9.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to Hospira as a serious adverse event (SAE) within 24 hours of occurrence or notification by the study site:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalisation	An event requiring formal in-patient hospitalisation regardless of the time spent at the hospital. Stays at the emergency room are not considered hospitalisation as long as the patient is not formally admitted to the hospital, regardless of the length of that stay.
Prolongation of Hospitalisation	An event that occurs while the study subject is hospitalised and prolongs the subject's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth or any anomaly that result in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (*e.g.*, sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalisation, but based on medical judgment may jeopardise the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalisation, prolongation of hospitalisation, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Other	• Both spontaneous and elective abortions are to be treated as SAEs. • Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event

9.1.3 Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an AE that is assessed as suspected, serious and unexpected. Unexpected means that the nature or severity of the AE is not consistent with the applicable product information (e.g., Investigator's brochure for a unauthorised investigational product or summary of product characteristics for an authorised product).

9.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE: Severity and seriousness need to be independently assessed by the treating physician for each AE recorded on the CRF.

Mild	The event is transient and easily tolerated by the subject.
Moderate	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

9.3 Relationship

The relationship of Inflectra or Remicade to an AE will be determined by the treating physician. Treating physicians should use their knowledge of the patient, the circumstances surrounding the event, the temporal sequence between the event and the use of infliximab, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to Inflectra or Remicade, indicating “yes” or “no” accordingly.

The following factors should be taken into consideration:

- Temporal relationship between the event onset and the use of Inflectra or Remicade
- Course of the event, considering especially the effects of dose reduction on the event
- Course of the event after the discontinuation and/or reintroduction of Inflectra or Remicade (where applicable)

- Biological plausibility for the occurrence of the event with the use of Inflectra or Remicade or still with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to be associated with the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

The Investigator will use the following definitions to assess the relationship of the AE to the use of the product:

Not Related: There is evidence against a reasonable causal relationship between the use of Inflectra or Remicade and the occurrence of the event, either due to lack of temporal relationship, or lack of biological plausibility, or to the existence of more plausible alternative explanations for the occurrence of the event of concern such as underlying or concurrent illness.

Related: There is evidence in favour of a reasonable causal relationship between the use of Inflectra or Remicade and the occurrence of the event due to plausible temporal relationship (the event occurred within a reasonable time after drug administration) and also biological plausibility, despite the potential existence of alternative explanations for the occurrence of the event of concern such as the event could not be reasonably explained by known characteristics including concomitant therapies and/or the adverse event abated after discontinuing the study drug.

The Investigator should give an opinion as to whether the event is related or not related. In addition, the Investigator should also provide an alternative etiology for the event, especially if he/she considers the event not related.

9.4 Adverse Events of Special Interest (AESI)

Table 3. AESI for this Study

Bowel stenosis, stricture, obstruction (in Crohn's disease)
Colon carcinoma/dysplasia (in ulcerative colitis)
Congestive heart failure
Demyelinating disorders
Haematological reactions
Hepatitis B virus (HBV) reactivation
Hepatobiliary events
Hepatosplenic T cell lymphoma (HSTCL)
Hypersensitivity
Intestinal or perianal abscess (in Crohn's disease)
Lack of efficacy
Leukaemia
Lymphoma (not HSTCL)
Malignancy (excluding lymphoma)
Opportunistic infections
Pregnancy exposure
Sarcoidosis/sarcoid-like reactions
Serious infections including sepsis (excluding opportunistic infections and tuberculosis)
Serious infusion reactions during a re-induction regimen following disease flare
Serum sickness (delayed hypersensitivity reactions)
Skin cancer
Systemic lupus erythematosus/lupus-like syndrome
Tuberculosis
Use of infliximab during lactation

9.5 Always Serious Adverse Event List

Always Serious Adverse Event List for this study include reports of the following:

Table 4. Serious Adverse Event List

A			
Abortion	Acute liver failure	Acute respiratory (pulmonary) failure	Acute renal failure
Acute adrenalcortical insufficiency	Adrenal hemorrhage	Acute Respiratory Distress Syndrome (ARDS)	Agranulocytosis

(continued)

Table 4. Serious Adverse Event List

Alveolitis, allergic or fibrosing	Anemia, aplastic	Anemia, hemolytic	Anaphylaxis, anaphylactic shock
Anaphylactoid reaction	Aplastic bone marrow	Apnea (all ages)	Asphyxia, all ages
Asystole	Attempted suicide	Atrioventricular (AV) Block, third degree (aka, complete heart block)	
B			
Acute blindness	Brain death	Brain stem hemorrhage	
C			
Cardiac arrest/circulatory arrest/cardiorespiratory arrest	Cardiomyopathy	Cavernous sinus thrombosis	Cerebral edema
Cerebral vascular accident (stroke) includes hemorrhagic, thrombotic, embolic strokes to any region of the brain	Cheyne-Stokes Respiration	Colitis, hemorrhagic, pseudomembranous or ulcerative	Coma (all types)
Convulsions (seizures), all types	Creutzfeldt-Jakob Disease.		
D			
Deafness, acute	Death (all causes)	Delirium	Disseminated Intravascular Coagulation (DIC)
E			
Embolism, arterial	Embolism, venous	Embolism, pulmonary	Encephalomyelitis
Encephalomyelitis	Epiglottitis	Erythema Multiforme	
F			
Fibrillation, ventricular	Fibrosis, mediastinal	Fetal distress, demise	
G			
Gangrene	Glomerulonephritis	Goodpasture's Syndrome	Guillain-Barre Syndrome
H			
Hemolytic-uremic syndrome	Hemorrhage, all intracranial	Hemorrhage, neonatal	Hemorrhage, retroperitoneal

(continued)

Table 4. Serious Adverse Event List

Hepatitis, infectious and non-infectious	Hemopericardium	Hemothorax	Hepatic encephalopathy
Hepatic failure, necrosis	Hepatocellular damage, neonatal	Hepato-renal syndrome	Hyperpyrexia, Malignant ("Malignant Hyperthermia")
I			
Intestinal ischemia, necrosis or death	Intestinal perforation or stenosis	Intrauterine death	
L			
Laryngeal edema	Leukemia	Leukoencephalopathy, reversible or posterior multifocal	Lymphoma
M			
Malignancy, primary occurrence. Excludes non-melanotic skin cancer.	Malignant hypertension	Manic reaction	Meningitis
MS aggravation or MS like syndrome	Myelitis	Myeloproliferative disorder	Myocardial infarction
Myocarditis	Myositis		
N			
Neonatal respiratory failure	Nephritis	Nephropathy, toxic	Neuroleptic Malignant Syndrome
O			
Optic nerve atrophy, neuritis			
P			
Pancreatitis	Pancytopenia	Pemphigus	Peritonitis
Phlebitis, deep vein thrombosis –(DVT)	Pleural fibrosis	Polyarteritis nodosa	Pregnancy, ectopic
Pulmonary hypertension, primary	Pulmonary fibrosis	Pulmonary hemorrhage, infarction	Pulmonary embolism
Pulmonary edema (acute)	Pure Red Cell Aplasia (PRCA)	Purpura	Psychosis, acute onset.
Q			
Quadriplegia			

(continued)

Table 4. Serious Adverse Event List

R			
Red cell aplasia	Renal failure, acute	Renal Tubular Necrosis	Respiratory Distress Syndrome (neonatal)
Respiratory arrest	Respiratory depression, neonatal	Respiratory paralysis	Retrobulbar neuritis
Retroperitoneal Fibrosis	Reye's syndrome	Rhabdomyolysis	
S			
Sagittal Sinus Thrombosis	Sclerosing syndromes	Seizure	Serotonin Syndrome
Status asthmaticus	Status epilepticus	Stevens-Johnson Syndrome	Stillbirth
Subarachnoid hemorrhage	Subdural hemorrhage/hematoma	Sudden Infant Death Syndrome (SIDS)	
T			
Thrombocytopenia with platelet count <50,000 (severe)	Thromboembolism	Thrombosis (excluding superficial sites)	Torsades De Pointes
Toxic Epidermal Necrolysis			
U			
Uterine perforation			
V			
Vasculitis			
W			
Wallenburg's Syndrome	Withdrawal syndrome		

9.6 Adverse Event Reporting

Safety reporting procedures for AEs relating to Hospira products will be detailed in the "Safety and Medical Management Plan." To be in line with EMA Pharmacovigilance's current guidance, medication errors such as overdose will be captured as part of adverse event reporting. All the AESI in Table 3 must be reported, regardless of the seriousness assessment made by the Investigator. Refer to Always Serious Adverse Event List which defines the events that would be expected to be reported as serious (Table 4).

In the event of a SAE, whether related to study drug or not, the Principal Investigator or representative must make an accurate and adequate report within 24 hours by telephone, e-mail, or fax to Hospira Global Complaint Management or Global Product Safety.

Hospira Global Complaint Management
Phone: +1-800-441-4100
Email: ProductComplaintsPP@hospira.com

Global Product Safety Fax: +1 222-212-4079

In addition, the Principal Investigator will submit the SAE reports to the IRB/IEC in accordance with applicable requirements within 15 calendar days of discovering the SAE.

Copies of each report will be kept in the site's study files, and adequate documentation will be provided to Hospira, including documentation of IRB/IEC notification, as applicable.

A subject experiencing one or more SAEs will receive treatment and follow-up evaluations by the Principal Investigator or may be referred to another appropriate physician for treatment and follow-up.

SAEs will also be collected for any subject from the time the subject signs the study-specific informed consent. This includes subjects who are screen failures. All SAEs should be followed to resolution of the event or until the SAE is determined by the Investigator to be no longer clinically significant.

9.6.1 Reporting of Pregnancy and Lactation

Pregnancy and lactation are to be reported in compliance with the risk-management plan (RMP) for Inflectra: Inflectra RMP™.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1 Reporting to Regulatory Agencies

All reports will be submitted to the regulatory authorities by Hospira based on country/region reporting requirements and pursuant to required timeframes.

10.2 Use of Information and Publications

All data generated from this study are the property of Hospira. Hospira shall have the right to publish such data and information without approval from the sites. Hospira will establish a uniform procedure for analysing, publishing, and disseminating findings from this study. Co-authors of publications may include participating physicians, Hospira personnel, members of the National Leaders Committee, and/or other relevant thought leaders who contribute substantially to the publication. Data from planned interim analyses will be published by Hospira at time points deemed appropriate based on study progress. Publications will adhere to the International Committee of Medical Journal Editors (ICMJE) guidelines. Study data may not be published by participating sites without review and authorisation by Hospira.

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ANNEX 1. IMMUNOGENICITY ANALYSIS PROTOCOL

Post-Marketing Observational Cohort Study of Patients with Inflammatory Bowel Disease Treated with Inflectra in Usual Clinical Practice: Immunogenicity Analysis

1 BACKGROUND/RATIONALE

Inflectra is an IgG_1 chimeric human-murine monoclonal antibody (mAb) biosimilar to Remicade (infliximab, Janssen Biotech, Inc.) and a potential source of immunogenicity in humans. Since Inflectra was approved by the EMA for the indication of Crohn's Disease (CD) and Ulcerative Colitis (UC) only recently, there is no documentation of the incidence of immunogenicity of Inflectra and its impact on t*h*e effectiveness and safety in patients treated with Inflectra for inflammatory bowel disease (CD or UC).

2 OBJECTIVES

To evaluate immunogenicity profile (including trough level as well as testing for anti-drug antibodies - ADA) of Inflectra in the treatment of patients with CD or UC.

3 STUDY POPULATION

The immunogenicity analysis is an optional testing available during this study to patients receiving Inflectra while enrolled in the "Post-Marketing Observational Cohort Study of Patients with Inflammatory Bowel Disease Treated with Inflectra (infliximab) in Usual Clinical Practice." The overall target patient population is described in detail in the observational study protocol. The final immunogenicity analysis cohort will be a sample of the observational study population that provide a separate written informed consent for study purposes to release the blood samples collected as part of their routine clinical care. There is no pre-determined sample size for the immunogenicity analysis.

4 STUDY DESIGN & PROCEDURE

4.1 Enrolment

Following enrolment into the observational study, patients receiving Inflectra during this study will be offered the opportunity to voluntarily participate in the immunogenicity analysis by signing a separate informed consent form (ICF). The optional immunogenicity analysis may include pre-Inflectra treatment, follow up and trough level immunogenicity

testing upon Investigator request. To maximise enrolment, sites are encouraged to obtain consent for this optional testing when patients provide written ICF for participation in the observational study. Declining participation in the immunogenicity analysis will not prevent patients from participating in the observational cohort study.

4.2 Blood sampling

For the observational cohort study, no specific laboratory testing is mandated or recommended as per study protocol. The blood samples to be retained for the immunogenicity analysis are already drawn during routine pre-treatment and follow-up work-ups for Inflectra therapy.

Upon receiving written ICF for the optional immunogenicity analysis, patients' blood samples collected during routine clinical care will be retained, transported and stored at a central repository managed by the laboratory vendor(s) approved by Hospira. The site personnel will be responsible for identifying patients who are participating in the immunogenicity analysis and preparing the blood samples for collection and transportation by the laboratory vendor. The laboratory vendor, working jointly with Hospira, will be responsible for providing each site with the operational procedures pertaining to the collection and transportation of the biological samples. These procedures will be described in detail in a study laboratory manual prepared by the laboratory vendor and provided to the site. A best effort will be made to collect the following specimens at the specified time points of the study period:

	At Enrolment*	**During follow-up Period****
At least 5mL of peripheral serum	X	X
**The sample obtained at enrolment is defined as the earliest available blood sample prior to initiating Inflectra therapy* ***Any subsequent tests requested by the patient's treating physician will be collected to monitor the trough level as well testing for anti-drug antibodies.*		

4.3 Bioassay analysis (laboratory vendor)

Blood samples will be collected, transported and stored (in the central repository) by the designated laboratory vendor. Analytical methods will be described in detail in the study laboratory manual prepared by the vendor. Tests to determine trough level and antidrug antibody will be performed using the blood samples collected. Hospira will supply the assays used.

4.4 Patient withdrawal & discontinuation or termination

Patients can withdraw consent of participation in the immunogenicity analysis at any time, and this will not affect their participation in the observational cohort study. However, patients who withdraw from the observational cohort study will automatically be discontinued from the immunogenicity analysis. Hospira reserves the right to terminate the immunogenicity analysis or the observational study at any time. Reasons for terminating the immunogenicity analysis or the observational study may include, but are not limited to:

- Unsatisfactory enrolment
- Termination of the post-marketing observation study

4.5 Retention of records (specific to laboratory vendor)

The vendor should maintain source documentations for the period outlined in their standard practice or specified by any local regulations, whichever is longer.

5 STUDY CLOSE-OUT AND RIGHTS

At close-out, before this immunogenicity analysis is considered complete or terminated Hospira requires that data and documentation be returned to Hospira or its designee, including:

- All available protocol-specified laboratory data by means of case report forms (CRFs) (including resolved data queries)
- Properly completed CRFs by study coordinator or other appropriate site staff
- Site termination document verified/signed by Investigators who participate in the immunogenicity analysis

APPENDICES

Appendix 1 Harvey Bradshaw Simple Index

Harvey-Bradshaw Simple Index

Variable	Description	Scoring
1	General well-being	0 _ very well 1 _ slightly below par 2 _ poor 3 _ very poor 4 _ terrible
2	Abdominal pain	0 _ none 1 _ mild 2 _ moderate 3 _ severe
3	Number of liquid stools daily	1 per occurrence
4	Abdominal mass	0 _ none 1 _ dubious 2 _ definite 3 _ definite and tender
5	Complications 1 per item:	• Arthralgia • Uveitis • Erythema nodosum • Aphthous ulcer • Pyoderma gangrenosum • Anal fissure • New fistula • Abscess
Total score		Sum of variable scores

Appendix 2 Partial Mayo Scoring System

Mayo Scoring System for Assessment of Ulcerative Colitis Activity.*

Stool frequency†
0 = Normal no. of stools for this patient
1 = 1 to 2 stools more than normal
2 = 3 to 4 stools more than normal
3 = 5 or more stools more than normal
Subscore, 0 to 3

Rectal bleeding‡
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passes
Subscore, 0 to 3

Physician's global assessment§
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Subscore, 0 to 3

* The Partial Mayo score ranges from 0 to 9, with higher scores indicating more severe disease.
† Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
‡ The daily bleeding score represents the most severe bleeding of the day.
§ The physician's global assessment acknowledges the two other criteria, the patient's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status.

Appendix 3 Summary of revised 'Montreal classification' of Crohn's Disease

Age at diagnosis (A)	
A1	16 years or younger
A2	17-40 years
A3	Over 40 years

Location (L)		**Upper GI modifier (L4)**	
L1	Terminal ileum	L1 + L4	Terminal ileum + Upper GI
L2	Colon	L2 + L4	Colon + Upper GI
L3	Ileocolon	L3 + L4	Ileocolon + Upper GI
L4	Upper GI	-	-

Behaviour (B)		**Perianal disease modifier (p)**	
B1*	Nonstricturing, nonpenetrating	B1p	Nonstricturing, nonpenetrating + perianal
B2	Stricturing	B2p	Stricturing + perianal
B3	Penetrating	B3p	Penetrating + perianal

*B1 category should be considered 'interim' until a prespecified time has elapsed from the time of diagnosis. Such a time period may vary from study to study (eg, 5-10 years is suggested) but should be defined in order for B1 behaviour to be considered 'definitive'. GI Gastrointestinal

Appendix 4 'Montreal classification'of Ulcerative Colitis

Key points

- A classification system for UC is proposed that incorporates:
- Disease extent; and
- Disease severity of individual acute relapses.

Classification by extent

UC can be defined by the extent of colorectal inflammation at a radiographic, endoscopic or histological level. For the purposes of simplification, we propose that the extent of UC be defined by endoscopic appearance and by maximal extent during follow-up. The three subgroups of UC defined by extent are:

1. Ulcerative proctitis (E1): involvement limited to the rectum (ie, proximal extent of inflammation is distal to the rectosigmoid junction).
2. Left-sided UC (E2) (also known as distal UC): involvement limited to the portion of the colorectum distal to the splenic flexure.
3. Extensive UC (E3) (also known as pancolitis): involvement extends proximal to the splenic flexure.

Classification by severity

UC can be classified broadly into four disease activity/severity categories:

1. UC in clinical remission (S0): No symptoms of UC.
2. Mild UC (S1): in the classic description of disease activity by Truelove and Witts[1], this was defined as four or fewer bloody stools daily, lack of fever, pulse of less than 90 beats/min, hemoglobin of 105 g/L or greater and erythrocyte sedimentation rate (ESR) of less than 30 mm/h. A similar definition was given in the practice guidelines for management of UC recently published by the American College of Gastroenterology (ACG)[2]: four or fewer stools daily (with or without blood), no systemic signs of toxicity and a normal ESR.
3. Moderate UC (S2): Truelove and Witts[1] defined this as the state between mild and severe. The ACG guidelines defined moderate disease as more than four stools daily but with minimal signs of systemic toxicity[2].
4. Severe UC (S3): This was defined as the passage of at least six bloody stools daily, pulse of at least 90 beats/min, temperature of at least 37.5°C, hemoglobin of less than 105 g/L and ESR of at least 30 mm/h[1]. The ACG guidelines defined severe colitis as at least six bloody stools daily and evidence of toxicity (fever, tachycardia, anemia or elevated ESR)[2]. The latter guidelines separated 'fulminant colitis' from 'severe'. Fulminant patients were those with at least 10 stools daily, continuous bleeding, toxicity, abdominal tenderness and distension, requirement for blood transfusion and colonic dilation on plain abdominal films[2].

[1]Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. BMJ, 1955;2:1041-1048.
[2]Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2004 Jul;99(7):1371-85.

Appendix 5 Simple fistula assessment

Fistula drainage assessment

Endpoints	**Definition**
Improvement	Improvement defined as a decrease from baseline in the number of open draining fistulae of ‡ 50% for at least two consecutive visits (at least 4 weeks)
Remission	Remission defined as closure of all fistulae that were draining at baseline for at least two consecutive visits (at least 4 weeks)

Closure of individual fistulae defined as no fistula drainage despite gentle finger compression.

Appendix 6 Inflectra: Summary of Product Characteristics

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002778/WC500151489.pdf

Appendix 7 Remicade: Summary of Product Characteristics

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf

Appendix 8 Detailed protocol updates

The following amendment has been made to this protocol since the date of preparation. The rationale behind protocol amendment is to appropriately address several comments received by National Leaders (Principal Investigators) mainly pertaining to study's operational aspects. Detailed explanation for each individual change can be found in the below table.

Amendment No.	**Date of Amendment**
Version 2.0	19-Feb-2015

Change No.	**Section/page (of protocol Version 1.0)**	**Description of protocol amendment**
1	Throughout the protocol	Inflammatory Bowel Disease (IBD) is specified as **Crohn's Disease (CD) or Ulcerative Colitis (UC)** after National Leader's request for clarity reasons
2	List of abbreviations, Page 6	Short Inflammatory Bowel Disease Questionnaire (SIBDQ) was added to reflect the change in the patient-reported instrument used in the study. SIBDQ is shorter but still found valid, reliable, and able to detect meaningful clinical changes in HRQOL7
3	Throughout the protocol pertaining to protocol title	Infliximab was added in brackets next to Inflectra for consistency reason
4	3. Abstract/population; Page 9	The sentence **'Patients with fistulating disease or stomas and those receiving combination therapy will be included'** was added to clarify that this population, not usually included in IBD studies, will additionally be included In population subgroups the wording or Remicade was consistently put into brackets. Additionally, at 4th subgroup the wording 'of the latter' was removed

5	3. Abstract/primary study outcomes; Page 10	**'In the six months prior to enrolment for biologic naïve patients or in the 12 months prior to enrolment for biologic experienced patients'** wording was removed because SAEs and AESI prior to enrolment will not be collected (very difficult for physicians to collect in particular when patient is new)
6	3.Abstract/secondary outcomes; Page 10	**'Data relating to the Montreal classification index for CD** **Data relating to the Montreal classification index for UC:** **classification by extent** **classification by severity** **Data relating to the fistula drainage assessment index for CD'** were added as additional clinical assessments
7	3.Abstract/exploratory outcomes; Page 10	The wording **'short'** was added to sentence 'QoL as measured by Inflammatory Bowel Disease Questionnaire (IBDQ)' to reflect the change of validated instrument used. IBDQ was also changed to "**SIBDQ"** for the aforementioned reason As a result the SIBDQ-pertaining reference paper was added on 11. References section: **"Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol. 1996 Aug;91(8):1571-8"** and the IBDQ-pertaining reference paper "**Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989 Mar; 96: 804-10"** was removed
8	3. Abstract/Study limitations; Page 12	The following sentence was removed **"For all patients with "prevalent exposure," data collection will include information on any AESI and SAE experienced during Inflectra or Remicade treatment prior to study enrolment, so that any AESI that occur shortly after treatment initiation will not be under-represented in the study population. A safety analysis will compare AESIs and SAEs experienced during Inflectra or Remicade treatment prior to enrolment with events after enrolment"** to reflect that SAEs and AESI will not be collected prior to enrolment
9	4. Amendments and updates; Page 13	'**Amendments and updates'** were changed to '**Protocol amendment: summary of changes'**
10	5. Rationale and Background; Page 14	The following sentence was deleted "**2 major types of inflammatory bowel disease (IBD)"** since IBD is clarified as CD or UC

11	6.2 Secondary Study Objectives; Page 18	The following sentence was added **"Effectiveness is a measure of the extent to which a specific intervention, procedure, regimen, or service when deployed in the field in routine circumstances, does what it is intended to do for a specified population. Effectiveness should be distinguished from 'efficacy', which is a measure of the extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions"** to clearly define effectiveness as opposed to efficacy
12	Figure 1; Page 20	The study design schematic was updated to reflect the definition of IBD as CD or UC
13	7.2.2 Enrolment; Page 21	The following wording was removed **"All patients who meet the enrolment criteria are potentially eligible and may be invited to participate in the study. Sites will be asked to record limited, de-identified, information on all potentially eligible patients who present to the practice, whether or not they consent and are enrolled in the study. This information will include age, gender, the reason for not enrolling in the study (if applicable) and the date the patient enrolled (if applicable). This information will be used to evaluate how likely the study sample compares to the total population receiving infliximab that are screened at the participating sites"** and replaced by **"Patients will be recruited for the study during the course of usual care at each investigative site. Patients deemed potentially eligible for the study by their physician will be invited to participate. At the time of study invitation, consenting patients may be enrolled if they are eligible to be included in either the Inflectra or the Remicade cohort and meet study inclusion and exclusion criteria (Sections 7.2.3.1 and 7.2.3.2)"** to correctly describe the study enrolment process
14	7.2.3 Patient Eligibility; Page 22	The following sentence was added **'Patients with fistulating disease or stomas and those in combination therapy will also be included'** to specify additional patients subgroups included in the study
15	7.2.3.1 Inclusion criteria; Page 22	Inclusion criterion 1: **'At least 18 years of age at the time of initial confirmed diagnosis of IBD'** was changed to **'at least 12 years at the time of initial confirmed diagnosis of CD and UC and at least 18 years of age at the time of enrolment to the study'** as the first course of treatment of the adolescence population in the UK is Remicade Inclusion criterion 2: The following sentence was added **'Patients with stomas or surgery/pouch will also be included'** to indicate additional patient subgroups included
16	7.3.1 Primary Outcomes; Page 23	Same as in change 5.

17	7.3.3 Secondary Outcomes; Page 23	Same as in change 6.
17	7.3.3 Exploratory Outcomes; Page 23	Same as in change 7.
18	Table 1. Study Data Collection Points; Page 25	The following clinical assessments were added to Clinical Assessment list: • **Montreal classification for CD** • **Montreal classification for UC:** ○ **classification by extent** ○ **classification by severity** • **Fistula drainage assessment** and also to table footnote ** The **"SIBDQ"** replaced IBDQ in Patient-reported outcomes list The following sentence was removed from the table footnote***: ***"Any occurrences of AESI recorded in medical charts in the 6 months prior to enrolment for biologic -naïve patients or in the 12 months prior to enrolment for biologic-experienced patients, will be extracted and entered into the EDC system"***
19	7.9.2 Study limitations; Page 30	Same as in change 8.
20	9.4 Adverse Events of Special Interest (AESI) Table 3, Page 39	'**Infusion reaction associated with shortened infusion duration [RA [RA)**' was deleted following National Leaders meeting suggestion
21	11 References; Page 44	With reference to change 4: IBDQ-pertaining reference paper "**Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989 Mar; 96: 804-10"** was removed and the SIBDQ-pertaining reference paper was added **"Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol. 1996 Aug;91(8):1571-8"**
22	Appendix 3; Page 51	The detailed summary of the revised **'Montreal Classification' of Crohn's Disease** was added following National Leaders meeting suggestion to include additional clinical assessments

23	Appendix 4; Page 52	**The 'Montreal Classification' of Ulcerative colitis** was added with a detailed account of classification by extend and classification by severity following National Leaders meeting suggestion to include additional clinical assessments
24	Appendix 5; Page 55	The description of the '**fistula drainage assessment'** was added following National Leaders meeting suggestion to include additional clinical assessments As a result, the Inflectra and Remicade Product Characteristics became appendix 6 and 7 respectively
25	Appendix 8; Page 58	Detailed description of protocol updates was added
26	Sponsor Signatures Page	**Jeff White, Senior Clinical Manager**, is replacing **Susan Reid, Director** **MS** title was added next to Mary Jane Esmenda's name

Sponsor Signatures

Study Title:	Post-Marketing Observational Cohort Study of Patients with Inflammatory Bowel Disease (IBD) Treated with Inflectra (infliximab) in Usual Clinical Practice (CONNECT-IBD)
Study Number:	ZOB INF 1402
Version:	V2.0
Final Date:	23 February 2015

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: 24 February 2015
Paul Audhya, MD, MBA
Vice President Medical Affairs EMA
Hospira Inc.

Signed: _____ Date: 25 FEB 15
Amy Potthoff, BS
Vice President, Medical Operations
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Signed: _____ Date: 25 Feb 2015
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Investigator's Signature

Study Title:	Post-Marketing Observational Cohort Study of Patients with Inflammatory Bowel Disease (IBD) Treated with Inflectra (infliximab) in Usual Clinical Practice (CONNECT-IBD)
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I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Name: _____

Title: _____

Site Address: _____

_____