POST-AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL UP0038 AMENDMENT 2

HEALTHCARE PROFESSIONAL AND PATIENT SURVEYS TO EVALUATE THE EFFECTIVENESS OF THE RISK MINIMISATION EDUCATIONAL MATERIALS FOR CERTOLIZUMAB PEGOL (CZP; CIMZIA®)

Final Post-Authorization Safety Study Protocol	19 Jul 2016
Post-Authorization Safety Study Protocol Amendment 1	11 Jul 2018
Post-Authorization Safety Study Protocol Amendment 2	17 Jan 2019

PASS information

Title	Healthcare Professional and Patient Surveys to Evaluate the Effectiveness of the Risk Minimisation Educational Materials for Certolizumab Pegol (CZP; CIMZIA®)
Protocol version identifier	3.0
Date of last version of protocol	17 Jan 2019
EU PAS register number	EUPAS14867
Active substance	Certolizumab pegol (CZP) (Tumour necrosis factor alpha inhibitor; L04AB05)
Medicinal product	Certolizumab pegol (CIMZIA®)
Product reference	N/A
Procedure number	EMEA/H/C/001037
Marketing authorisation holder(s)	UCB Biopharma SPRL.
Joint PASS	No
Research question and objectives	The overall objective of this study is to evaluate the effectiveness of the risk minimisation measures being implemented in the EU: Patient and healthcare provider educational program. Surveys will be used to assess the effectiveness of the risk minimisation methods. The aims of the surveys are to: • Evaluate the effectiveness of the CZP Risk Management Plan (RMP) educational program in achieving its goals by measuring patient knowledge and understanding of the serious risks associated with CZP. • Measure healthcare providers' knowledge of the serious risks associated with the use of CZP, proper prescribing of the product and proper monitoring for the key risks associated with the use of CZP.
Country(-ies) of study	This study will be conducted in 7 countries: Denmark, France, Germany, Greece, Norway, Sweden, and the United Kingdom.

Marketing authorisation holder(s)

Author	N/A
Marketing authorisation holder(s)	UCB Biopharma SPRL Allée de la Recherche 60 B-1070 Brussels BELGIUM
MAH contact person	[redacted] Safety Lead, CIMZIA [redacted]

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
CAWI	Computer-aided web interview
CZP	Certolizumab pegol
EMA	European Medicines Agency
EU	European Union
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
HCPs	Healthcare professionals
MAA	Marketing authorisation application
MAH	Marketing Authorisation Holder
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
REMS	Risk evaluation and mitigation strategy
RMP	Risk Management Plan
SAE	Serious adverse event
SADR	Serious adverse drug reaction
TNF	Tumor necrosis factor
US	United States

3 RESPONSIBLE PARTIES

This study is sponsored by UCB Biopharma SPRL ("UCB"). Surveys will be used for data collection, and will be administered by Kantar Health.

There will be no principal or co-ordinating investigator for this study; the surveys will be distributed by Kantar Health to the various EU countries in which the effectiveness of the educational materials is being assessed.

4 ABSTRACT

Title

Healthcare Professional and Patient Surveys to Evaluate the Effectiveness of the Risk Minimisation Educational Materials for Certolizumab Pegol (CZP; CIMZIA®)

Rationale and background

The Risk Minimisation Educational Materials for CZP are a suite of materials developed for prescribing physicians, other healthcare professionals (HCPs), and patients to enhance the communication of key safety and prescribing information for CZP. The educational materials provide information on the safety concerns of CZP and on the measures used to mitigate them. The study described in this protocol consists of surveys that will assess the effectiveness of the educational materials.

Research question and objectives

The overall objective of this study is to evaluate the effectiveness of the educational material risk minimisation measures being implemented in the EU, in HCPs who are prescribing and/or administering CZP, and in patients who are prescribed CZP.

Study design

This post-authorization safety study (PASS) will be conducted by means of a cross-sectional survey of a sample of HCPs and patients in Denmark, France, Germany, Greece, Norway, Sweden, and the UK. Two surveys will be used for the qualitative collection of data, and these will be administered locally: a healthcare professional survey – for use with prescribing physicians and healthcare professionals who administer CZP, and a patient survey – for use with patients who have received CZP.

Population

The target population for the HCP survey will be HCPs who have prescribed or monitored patients receiving treatment with CZP, and who have not previously completed a survey regarding the risks of CZP.

The target population for the patient survey will be patients who have not previously participated in any surveys about the educational tools for CZP and who have received at least one prescription of CZP within the last 6 months.

Variables

The primary outcome of these surveys is the proportion of respondents who received, were aware of, or accessed each of the CZP educational materials (Patient Alert Card and Prescriber Guide):

- A summary of correct responses to each individual question on the understanding of the potential risks associated with CZP treatment (HCP survey).
- A summary of correct responses to each question regarding CZP risks (patient survey).

Data sources

Responses to the HCP and patient surveys will be analysed in order to calculate the percentage of correct responses to the individual questions on the understanding of the potential risks associated with CZP treatment.

Study size

The recommended sample size for each European country included in this study is 40 HCPs (rheumatologists and rheumatology nurses), and 20 patients. For Denmark, Sweden and Norway a smaller sample size will be used (Nordic combined sample: 40 HCPs and 15 patients). Refer to Section 9.5 for additional information.

Data analysis

To evaluate knowledge of the CZP educational materials, two key assessment measures will be required: a presentation of the percentage of HCPs/patients who received, were aware of or accessed each of the CZP educational materials and to what extent those materials were read; and a summary of correct responses to each individual question on the understanding of CZP.

The percent of correct responses to individual questions will be tabulated and reported in aggregate. The questions are categorical in nature and the frequency of percent answers that are correct will be presented.

Milestones

The distribution of the surveys is planned to begin in August 2016 and will continue until 31 July 2019.

5 AMENDMENTS AND UPDATES

The original final protocol has been amended twice. Protocol Amendment 1 was prepared in support of RMP v14 (procedure EMEA/H/C/001037/II/0072). This amendment was not submitted to any of the participating countries as additional feedback from European Medicines Agency (EMA) was received during the procedure. Protocol Amendment 2 includes additional updates based on Pharmacovigilance Risk Assessment Committee (PRAC) feedback and the corresponding updates introduced in RMP v14.1 (procedure EMEA/H/C/001037/II/0072, positive opinion dated 17 Jan 2019).

Amendment Number	Date	Section of protocol changed	Amendment or update	Reason
2	17 Jan 2019	PASS Information; Section 4	Identifier and date of last version of protocol: 3.0-17 Jan 2019	New identifier and amendment date added.
2	17 Jan 2019	Section 4; Section 9.5	Clarification that dermatologists will not be surveyed.	With approval of RMP v14.1, the distribution of the Prescriber Guide has stopped. Consequently, HCP surveys have ceased, and the addition of dermatologists is no longer relevant.
2	17 Jan 2019	Section 7	Rationale that the experience with the	Change based on PRAC feedback and in line with the

Amendment Number	Date	Section of protocol changed	Amendment or update	Reason
			use of TNF inhibitors provides an adequate level of understanding to HCPs and the issuance of the Prescriber Guide is no longer necessary has been added.	agreed RMP v14.1 (procedure EMEA/H/C/001037/II/0072, positive opinion dated 17 Jan 2019).
2	17 Jan 2019	Section 7; Section 8; Section 9.5; Section 9.7	The distribution of the Prescriber Guide and the HCP survey will cease upon the approval of RMP v14.1.	Change based on PRAC feedback and in line with the agreed RMP v14.1 (procedure EMEA/H/C/001037/II/0072, positive opinion dated 17 Jan 2019).
2	17 Jan 2019	Table 1; Section 9.3	Patient Alert Card will be renamed to Patient Reminder Card at the next update of the card's contents.	Change based on PRAC feedback and in line with the agreed RMP v14.1 (procedure EMEA/H/C/001037/II/0072, positive opinion dated 17 Jan 2019).
2	17 Jan 2019	Section 9.1	Text has been included regarding the amendment history of the protocol.	Clarification of the purpose and use of the different protocol versions.
2	17 Jan 2019	Section 9.5	The sample size of each European country and Nordic combined sample of 40 HCPs will not be met.	With approval of RMP v14.1, the distribution of the Prescriber Guide has stopped. Consequently, HCP surveys have ceased.
2	17 Jan 2019	Section 9.7	All data from the HCP surveys collected up to the point of approval of RMP v14.1 will be analysed.	With approval of RMP v14.1, the distribution of the Prescriber Guide has stopped. Consequently, HCP surveys have ceased.
2	17 Jan 2019	Throughout	Clarifications have been made including minor rewording and correction of typographical errors.	Provides consistency within the document.
1	11 July 2018	PASS Information;	Updated date of last version of protocol:	New amendment date added.

Amendment Number	Date	Section of protocol changed	Amendment or update	Reason
		Section 4	11 July 2018.	
1	11 July 2018	PASS Information	Added EU PAS register number EUPAS14867.	New information added.
1	11 July 2018	PASS Information	Updated Research Objectives to match body text.	Updated to provide consistency within the document.
1	11 July 2018	PASS Information; Section 4; Section 7; Section 9.1; Table 2	Removed Italy and Spain. Updated text to note PASS conducted according to local regulations.	For compliance reasons, PASS was not feasible in Spain and Italy.
1	11 July 2018	PASS Information	Updated MAH Contact Person.	MAH contact information was outdated and was updated.
1	11 July 2018	Section 4; Section 9.5; Table 2	Dermatologists added to HCP study population; indications expanded.	Dermatologists added to include a new audience of prescribers with the newly approved psoriasis indication.
1	11 July 2018	Section 4; Section 6	Updated dates for end of data collection, final report of study results, and Registration in EU PAS register.	Milestones were outdated and were updated.
1	11 July 2018	Section 7	Reference to sections of the RMP removed.	RMP template has been updated and these sections as listed are no longer correct.
1	11 July 2018	Section 9.2	Males and females added.	Clarification of study population.
1	11 July 2018	Section 11	Removed text under “Reconciliation”.	Text removed to clarify reconciliation of reporting is done at the end of the program.
1	11 July 2018	Annex 2	Safety contact information updated.	Contact information was outdated and was updated.
1	11 July 2018	Annex 3	New version of ENCePP checklist added.	A new version of the checklist was completed.
1	11 July 2018		Clarifications made throughout document including minor rewording and correction of typographical errors.	Updated to provide consistency within the document.

6 MILESTONES

Milestone	Planned date
Start of data collection	01 August 2016
End of data collection	31 July 2019
Registration in the EU PAS register	30 August 2016
Final report of study results	30 November 2019

7 RATIONALE AND BACKGROUND

The Risk Minimisation Educational Materials for CZP are a suite of materials developed for prescribing physicians, other healthcare professionals (HCPs), and patients to enhance the communication of key safety and prescribing information for CZP.

The educational materials provide information on the safety concerns of CZP and on the measures used to mitigate them. These educational materials are one component of the overall EU-Risk Management Plan (EU-RMP) for CZP, approved by the EMA, and UCB committed to the development and distribution of the educational materials as part of the Marketing Authorization Application (MAA). The details of the risk minimisation materials for the program and how these have been implemented in the EU are described in the RMP.

The effectiveness evaluation methods consist of a quantitative assessment and a qualitative assessment involving sample surveys of HCPs (ie, prescribing physicians and HCPs who administer CZP) and patients who have received CZP. As per EU regulations, the effectiveness of the risk minimisation measures must be assessed on an ongoing basis.

The Prescriber Guide provided to HCPs for CZP focuses on informing about risks that are overall shared with those of other tumor necrosis factor (TNF) inhibitors, which have been used for several years. The experience with the use of other TNF inhibitors provides an adequate level of understanding of the potential risks and management thereof. The distribution of the Prescriber Guide and the HCP survey was stopped based on PRAC feedback and in line with the agreed RMP v14.1 (procedure EMEA/H/C/001037/II/0072, positive opinion dated 17 Jan 2019).

The approach to collecting qualitative information is provided in Table 1, below, and is the focus of the surveys discussed in this study protocol.

Table 1 Educational materials – qualitative evaluation methods

Tool	Metric	Method	Target Values (agreed with EMA)	Timing
Prescribing physician and HCP tools	Estimated proportion of directly contacted prescribing physicians who have used the educational tools	Sample survey of prescribing physicians who have been contacted.	35% to 60%	18 months post launch then annually after first data collection

Table 1 Educational materials – qualitative evaluation methods

Tool	Metric	Method	Target Values (agreed with EMA)	Timing
Prescribing physician and HCP tools	Prescribing physicians and healthcare professionals who administer CZP – feedback on real-world usage and potential improvements	Qualitative sample survey of prescribing physicians and healthcare professionals. Participants will be asked about their usage of the tools, perceived effectiveness of the tools and suggestions for improvement.	Not applicable	18 months post launch then annually after first data collection
Patient Alert Card[a]	Estimated proportion of patients who have received/used the patient alert card[a]	Sample survey of patients	35% to 50%	18 months post launch then annually after first data collection
Patient Alert Card[a]	Patient feedback on real-world usage and potential improvements	Qualitative sample survey of patients. Participants will be asked about their usage of the tools, perceived effectiveness of the tools and suggestions for improvement.	50% to 80% (patients who have used the alert card)	18 months post launch then annually after first data collection

CZP=certolizumab pegol; EMA=European Medicines Agency; HCP=healthcare professional; MAH=Marketing Authorisation Holder; PRAC=Pharmacovigilance Risk Assessment Committee; RMP=Risk Management Plan

[a] Based on PRAC feedback and the corresponding updates introduced in RMP v14.1 (procedure EMEA/H/C/001037/II/0072, positive opinion dated 17 Jan 2019), the MAH intends to rename Patient Alert Card to Patient Reminder Card at the next update of the card's contents.

Previous Surveys

Version 1

In order to assess the educational tools in line with the requirements detailed in Table **1**, UCB developed HCP and patient surveys. The surveys included questions on whether the HCP or patient had received the educational tools, their understanding of the tools, and their confidence in understanding the risks associated with CZP.

Third-party providers were used to undertake the qualitative assessment of the educational tools in alignment with local regulations in each country. The surveys were administered in Belgium and Luxembourg (data were combined), Czech Republic, Finland, France, Denmark, Germany, Greece, Hungary, Italy, Norway, Slovakia, Slovenia, Spain, Sweden, and the UK.

In the 16 countries where the surveys were conducted, the proportion of physicians who had read the prescriber guide exceeded the EMA target values. For HCPs administering CZP, the patient

medication guide, the healthcare administration and monitoring guide and the patient alert card were all widely read, and the proportion of HCPs reading them exceeded the target values in all countries assessed.

The results from the survey indicated that the HCPs were confident in understanding the identified and potential risks of CZP treatment based on the information provided in the educational tools and that HCPs who were familiar with the patient tools considered them to be useful to their patients. For the patient survey, data were available from patients in Belgium and Luxembourg, Finland, Germany, Greece, Hungary, Netherlands, Slovenia, Sweden and the UK. The proportion of patients reading the patient alert card was over 95% in all countries.

Version 2

In April 2011, UCB sought informal validation from the EMA on the approach to the collection of the qualitative data to ensure this was in line with the requirements. The feedback from the EMA specifically related to the qualitative assessment of the tools can be summarised as follows:

- The surveys collected data on the general understanding of the educational tools but did not include an assessment of the understanding of specific risks – this data would be needed in order to evaluate the impact of the risk minimisation tool.
- A clear plan for the enrolment of participants in the survey before the beginning of this activity was required.

The surveys were updated in accordance with this feedback. Questions specific to the risks of CZP were included and the aims of the updated surveys were:

- HCP survey – Measuring healthcare providers' knowledge of the key risks associated with the use of CZP, proper prescribing of the product, and proper monitoring for the key risks associated with the use of CZP.
- Patient survey – Evaluate the effectiveness of the CZP patient RMP educational tools program in achieving its goals by measuring patient knowledge and understanding of the key risks associated with CZP.

Prior to the update of these surveys, the data collection process had already commenced in France, Finland, Denmark, Germany, Hungary, Norway, and Sweden. These countries utilized the updated surveys in their next data collection. In Belgium and Luxembourg, Czech Republic, Greece, Italy, Slovakia, Slovenia, Spain, and the UK, version 2.0 of the surveys was used and the results showed a high understanding of the knowledge of the key risks associated with the use of CZP, proper prescribing of the product, and proper monitoring for the key risks associated with the use of CZP following review of the tools.

Post-authorisation Safety Study (PASS)

UCB is planning to continue performing assessments of the RMP Educational Materials, on a regular basis, in countries where more than 800 patients have been exposed to CZP representing the different relevant EU regions and where a PASS can be conducted according to local regulations.

In accordance with the PASS definition ("Post-authorisation safety study: Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures") in Directive 2001/83/EC (DIR) Art 1(15), UCB is now conducting a PASS in order to assess the effectiveness of the CZP RMP Educational Materials.

Updated versions of the surveys will be used in this study to assess the current levels of patient and HCP knowledge of the key risks associated with CZP following the distribution of the updated educational materials (Version 4.0, distributed from February 2015). The results of these surveys will provide an assessment of the effectiveness of the educational materials, and this information, may be shared with the EMA. The results from these assessments will be reviewed and any adaptations to the educational tools and their distribution will be made. At each update of the educational tools, the questionnaires will also be updated to ensure their content is in line with the educational tools.

Due to local adaptation of the materials and National Health Authorities approvals, the distribution dates varied from country to country. UCB will conduct this PASS 18 months post-distribution of the Educational Materials in the 7 countries.

8 RESEARCH QUESTION AND OBJECTIVES

The overall objective of this study is to evaluate the effectiveness of the education material risk minimisation measures being implemented in the EU, in patients who are prescribed CZP.

Specifically, the objectives of the surveys are to:

- Measure healthcare providers' knowledge of the serious risks associated with the use of CZP, proper prescribing of the product and proper monitoring for the key risks associated with the use of CZP.
- Evaluate the effectiveness of the CZP RMP educational program in achieving its goals by measuring patient knowledge and understanding of the key risks associated with CZP.

The distribution of the Prescriber Guide and the HCP survey was stopped based on PRAC feedback and in line with the agreed RMP v14.1. Hence, no further data is being collected on this study objective.

9 RESEARCH METHODS

9.1 Study design

This PASS is sponsored by UCB and will be conducted by Kantar Health (a global healthcare consultancy), with the aim to evaluate the effectiveness of the CZP risk minimisation educational materials being implemented in the EU. The study will be conducted by means of a cross-sectional survey of a sample of HCPs and patients in Denmark, France, Germany, Greece, Norway, Sweden, and the UK.

Two surveys will be used for the qualitative collection of data, and these will be administered locally:

- Healthcare professional survey – for use with prescribing physicians and healthcare professionals who administer CZP
- Patient survey – for use with patients who have received CZP.

The survey will take approximately 15 minutes for respondents to complete and will be offered online only (computer-aided web interview; CAWI), except where there are local restrictions (eg, in Greece, where patients will be interviewed by telephone; their answers will be inputted online via a unique web link). Online surveys allow flexibility, so that the HCP or patient can complete the survey at a time most convenient to them. Each survey will be composed of multiple choice, open, and close-ended questions.

9.2 Setting

Recruitment for this survey will be overseen by Kantar Health, but will vary between individual countries. In order to identify HCPs and patients who are suitable for this study, HCPs will be contacted for this survey by using local networks, and the HCPs will then contact patients that may be eligible for this study. The recruitment processes in the various countries where this study will take place are outlined in Table 2 below:

Table 2 Recruitment methods

Country	Recruitment Process
France ***Via specialists*** ***Also potentially via patient associations or social networks***	• The agency will work in partnership with HCPs who have been engaged to participate. • The HCPs will communicate with their eligible patients. • In addition, the agency will also work closely with patient associations and via appropriate social networks to identify potential patient respondents.
Germany ***Via specialists***	• The agency will contact HCPs to discuss research needs (email is not appropriate at this stage). • Once HCPs have agreed to participate, the patient referral letter will be sent along with any other relevant information. • The HCP will discuss with their patients; patients will then contact the local agency. Should this happen, the project and needs will be explained again. • If the patient agrees, screening will take place. • The agency will provide the web link required to complete the survey.
UK ***Via patient associations*** ***Via social media*** ***Via specialists***	• Charities and support groups for approved indications will be contacted. These groups will contact patients that have previously indicated that they are interested in participating in research. • The local agency will also target patient groups online, via social media. • All patients who express an interest will be screened by telephone.
Greece ***Via specialists***	• HCPs known to the agency via their database will be engaged to help recruit patients. HCPs will arrange a time for the agency to contact the patients for screening and interview. • The agency will not receive the contact details for patients for confidentiality reasons.
Nordic Countries ***Via specialists*** ***Via patient associations*** ***Via patient databases***	• HCPs and nurses will recruit patients. The intention is that the HCPs will talk to their patients and provide them with the agency contact details so that patients can contact the agency directly. • Alternatively, the local agency will recruit directly from their database of patients or via patient associations.

The HCPs and patients selected via the methods described above will then be sent the survey. The initial questions will identify whether the respondent meets the inclusion criteria for this study; if the respondent is not suitable they will automatically exit the survey. These criteria are outlined below.

The target population for the HCP survey will be:

- HCPs who have prescribed or monitored patients receiving treatment with CZP
- HCPs who have not previously completed a survey regarding the risks of CZP

The target population for the patient survey will be:

- Patients who are male or female and are 18 years of age or older
- Patients who have not previously participated in any surveys about the educational tools for CZP
- Patients who have received at least 1 prescription of CZP within the last 6 months
- Patients who are not healthcare providers (eg, a doctor, nurse, pharmacist, etc.)

9.3 Variables

The primary outcome of these surveys is the proportion of respondents who received, were aware of, or accessed each of the CZP educational materials (Patient Alert Card and Prescriber Guide). Based on PRAC feedback and the corresponding updates introduced in RMP v14.1 (procedure EMEA/H/C/001037/II/0072, positive opinion dated 17 Jan 2019), the Marketing Authorisation Holder (MAH) intends to rename Patient Alert Card to Patient Reminder Card at the next update of the card's contents.

The outcomes for these surveys are:

- A summary of correct responses to each individual question on the understanding of the potential risks associated with CZP treatment (HCP survey)
- A summary of correct responses to each question regarding CZP risks (patient survey)

The results of the surveys will be reviewed by the internal UCB CZP Benefit-Risk team. In cases where the number of HCPs or patients using the educational materials is below the target values described in Table **1** above, a strategy will be developed to ensure that the use of the materials is increased. Suggestions for improvement of the materials will be considered for potential incorporation into subsequent versions of those materials.

9.4 Data sources

The responses to the HCP and patient surveys will be analysed. The percentages of correct responses to each individual question on the understanding of the potential risks associated with CZP treatment (HCP survey), and the percentage of patients answering each question regarding CZP risks will be calculated.

9.5 Study size

The sample size for the original surveys in Europe was generated based on the sample size utilised in a comparable exercise in the United States (US) conducted as part of the Risk Evaluation and Mitigation Strategy (REMS) for CZP.

In the US a total of 250 HCPs completed the survey to assess the effectiveness of the US educational materials. It is estimated that there is a total of 5000 HCPs prescribing CZP in the US.

Based on a consideration of population size it is therefore considered appropriate to assess a similar number of physicians/HCPs (N=250) and patients (N=250) within Europe.

The recommended sample size for each European country included in this study is therefore 40 HCPs (rheumatologists and rheumatology nurses), and 20 patients. For Denmark, Sweden and

Norway these numbers are not practical so a smaller sample size will be used (Nordic combined sample: 40 HCPs and 15 patients).

The distribution of the Prescriber Guide and the HCP survey was stopped based on PRAC feedback and in line with the agreed RMP v14.1. Due to the premature completion of this part of the study, the sample size of each European country and Nordic combined sample of 40 HCPs will not be met.

9.6 Data management

The raw data from the surveys will be collected and analysed by Kantar Health.

9.7 Data analysis

The raw data will be analysed by Kantar Health.

To evaluate healthcare providers' knowledge of the CZP educational materials, two key assessment measures will be required:

- A presentation of the percentage of HCPs who received, were aware of or accessed each of the CZP educational materials and to what extent those materials were read
- A summary of correct responses to each individual question on the understanding of CZP

The distribution of the Prescriber Guide and the HCP survey was stopped based on PRAC feedback and in line with the agreed RMP v14.1. All data from the HCP surveys collected up to this point will be analysed.

In order to evaluate patients' knowledge of the CZP educational materials program, two key assessment measures are required:

- A presentation of the percentage of patients who received, were aware of, or accessed the CZP educational materials and to what extent those materials were read and understood.
- A summary of correct responses to each question regarding CZP risks.

9.8 Quality control

Kantar Health has received ISO 20252:2012 (International Standard for Market Research) accreditation, which has strict standards on data quality, integrity and protection (Certification Number 1019). Kantar Health's global quality and compliance team will ensure the research in this study meets this standard, and abides by market research codes of conduct (MRS, EphmRA and BHBIA), which covers steps to ensure data quality / integrity and data protection. This also applies Kantar Health's fieldwork partners, who will be recruiting respondents.

All HCPs will undergo checks before they are included in the fieldwork partner's panels (ie, to ensure they are a qualified HCP) and in the case of both patients and HCPs, these will be screened using criteria set by UCB to ensure they are eligible to take part in the survey.

Quality control checks begin at the soft launch stage (ie, after the initial interviews have been completed) ahead of fully starting the survey to confirm if answers are being recorded for all questions as expected and the online survey is working correctly. On study completion, quality checks on the raw data will be completed (eg, looking for respondents who completed the survey too quickly, who patterned answered, who have nonsense answers to open-ended questions) and any unsuitable respondents will be removed from the data (and, if possible replaced).

Data tables will be checked twice. All data (questionnaires, raw data, tabulations) will be stored on a secure server by Kantar Health and UCB.

9.9 Limitations of the research methods

To minimise the potential for non-response, respondents will be paid to take part in this study (patients in France will not be paid, in line with UCB's Incentives Policy). Respondents will have a sufficient period of time to complete the survey (HCPs: 5 weeks; patients: 6 weeks) to give respondents time to complete the survey.

Other potential limitations of the research methods include:

- Patient recruitment process/patient referral process by HCPs can be slow; therefore, 6 weeks have been allowed for this stage.
- HCPs in the area of Rheumatology and Biologics are a highly researched population currently, and this may affect the level of response.

10 PROTECTION OF HUMAN SUBJECTS

Ethics approval will be sought, if required by individual countries.

Any information that HCPs and patients disclose as part of this study will be treated in the strictest confidence and the results of the survey aggregated to provide an overall picture of attitudes to the areas being covered in this survey. No answers will be attributable to individuals.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Assessment of Safety

This study will not investigate adverse events (AEs) associated with the use of CZP. This study is designed to collect data about the understanding of risks by HCPs and patients, not data about the effects of CZP, so there will be no prompt for the solicitation of AE reporting.

While it is not the intention of the surveys to solicit AEs, if an adverse event, or any other safety relevant information related to UCB's own products is mentioned by a HCP or patient during completion of the surveys, Kantar Health will report this to UCB.

Kantar Health shall notify UCB of any adverse event or other safety relevant information as soon as possible and at the latest within one (1) calendar day from the Receipt Date (as defined below). In the event that a calendar day falls on a weekend or a holiday, the information shall be sent on the next business day.

As part of the survey, patients and HCPs will be asked if they will waive the confidentiality given to them in this study if an adverse event or any other safety relevant information is mentioned so that the UCB Pharma Drug Safety Department may contact them directly to obtain further information. If a respondent does not agree to waive confidentiality, Kantar Health will report the adverse event or other safety relevant information without providing any of the patient's personal details. An additional question in the survey will ask respondents to confirm that UCB Pharma may contact the patient/physician again if the Drug Safety Department requires further details. If respondents provide their name during adverse event reporting, this will not be linked in any way to their responses to the survey. These two questions will be excluded from the versions of the surveys to be distributed in Germany, as this would contravene German privacy laws.

Reporting of Adverse Events (AEs), and other safety relevant information

The safety relevant information to be reported by Kantar Health to UCB, if mentioned by a survey respondent, includes (see also the detailed definitions below):

- reports of AEs
- reports of pregnancy/lactation exposure
- reports of medication errors, overdose, abuse, misuse or occupational exposure
- reports of lack of therapeutic efficacy
- reports of drug interactions
- reports of suspected transmission of an infectious agent via a UCB product
- reports of suspected AEs associated with a suspected or confirmed falsified medicinal product or quality defect (combined complaint) of a UCB product
- reports of off-label use of UCB products
- reports of unexpected therapeutic benefit
- product quality complaints.

"Receipt Date" (Date of Awareness)

Receipt date means the date on which Kantar Health receives notification of an AE or other safety relevant information. For reports received electronically, the Receipt Date shall mean the date the AE or other safety relevant information arrives on a server, the date on a facsimile transmission, or the date a voicemail is recorded; and not the date the report is actually retrieved from a server, fax machine, or from voicemail. For avoidance of doubt, the Receipt Date shall be counted as day 0 for reporting purposes. The time clock starts again at day 0 when follow-up information is received by Kantar Health. The Receipt Date of any safety related information shall be clearly mentioned on documents sent to UCB.

All documentation related to the AE or other safety relevant information to be reported by Kantar Health shall be made in English using the applicable UCB reporting form (Annex 1. List of stand-alone documents) and sent by electronic mail to UCB (see Annex 2. Safety Contact Details).

Kantar Health shall indicate that the information provided is in the frame of study UP0038, to enable categorization of the information in UCB database.

Kantar Health is required to report pregnancy of a study participant, pregnancy of a study participant's partner and a study participant giving breastfeeding, using the "Pregnancy Report and Outcome Form" (Annex 1. List of stand-alone documents). The procedure for reporting a pregnancy or breastfeeding is identical to the procedure for reporting safety relevant information.

When feasible upon receiving AE or other safety relevant information, or upon receipt of follow-up information on a previously received AE or other safety relevant information from Kantar Health, UCB shall send an acknowledgment of receipt by electronic mail. If Kantar Health does not receive such acknowledgment within two (2) working days from the date on which the initial or follow-up report was sent, Kantar Health should resend the information and mark it as "re-sent." When the sending of acknowledgments by UCB is not feasible, compliance with the transmitting and receipt of AE or other safety relevant information must be managed via the agreed reconciliation process (see Section Reconciliation).

Follow-up

UCB shall follow up on the AE or other safety relevant information received from Kantar Health. Kantar Health shall provide reasonable assistance to UCB to obtain additional information on AE or other safety relevant information.

Attempts should be made by UCB to obtain missing or incomplete information.

The causal relationship between the UCB Compound and an AE must be asked to the reporter for each AE.

The progression of a pregnancy and the eventual birth (if applicable) must be followed-up. Every reasonable attempt should be made to follow the development and health of the child for at least 30 days after birth for any significant medical issues or development delay.

If the patient is lost to follow up and/or refuses to give information, written documentation of attempts to contact the patient needs to be provided by the treating physician and filed at the site.

Reconciliation

During the conduct of UP0038, Kantar Health shall keep accurate and detailed records of each AE and other safety information it becomes aware of. Each case report must be assigned a unique identifier to support the reconciliation of AEs and other safety relevant information. Kantar Health shall send to UCB (see Annex 2. Safety Contact Details) an inventory of all AE and other safety relevant information reported, at the end of the program. The following information should be provided to enable reconciliation: Kantar Health case number, the Product, the country where the report originated, date report received by Kantar Health, and the date report was submitted to UCB.

In the event a discrepancy is found, Kantar Health shall immediately provide a copy of any missing AE or other safety relevant information to UCB. In addition, Kantar Health shall provide detailed explanations for the discrepancy and indicate the corrective action that was taken or is planned.

Drug Safety Training

UCB will provide initial Pharmacovigilance and Product Quality Complaint recording and reporting training to Kantar Health and will train identified individuals who will be involved in the UCB-specific project within Kantar Health organization.

It is the responsibility of Kantar Health to ensure that all relevant personnel working on a UCB project are trained on Pharmacovigilance reporting requirements prior to conducting the program for UCB.

In addition to providing Pharmacovigilance training, Kantar Health will ensure continuous training of all employees working on the UCB-specific project and are trained on the management of the documentation according to the sop-016162.

Kantar Health shall ensure that training of its personnel is adequately recorded and shall provide the corresponding documentation to UCB.

Safety contact details

Safety contact information for Kantar Health and UCB is provided in Annex 2. Safety Contact Details.

Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product that 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 product, whether or not related to the medicinal product.

Adverse Drug Reaction (ADR)

An ADR is a response to a medicinal product which is noxious and unintended. 'Response' in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

This includes adverse reactions that arise from:

- The use of a medicinal product within the terms of the marketing authorization
- The use of a medicinal product outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse, and medication errors
- Occupational exposure (this refers to the exposure to a prescribed treatment as a result of one's professional or non-professional occupation)

Serious Adverse Event (SAE)/Serious Adverse Drug Reaction (SADR)

An adverse event or adverse drug reaction is Serious if 1 or more of the following criteria are met:

- Death
- Life threatening: an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Inpatient hospitalisation or prolongation of existing hospitalisation: If a hospitalisation is planned, prior to the patient receiving the first dose of medicinal product it is not classified as serious. However, if a hospitalisation is unplanned and is a result of an adverse experience, this is considered an SAE
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- An important medical event or an event requiring significant intervention: Medical and scientific judgment must be exercised in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the above definition. These are usually considered serious.

Other safety relevant information

Other safety relevant information includes the following:

- Off-label use

This relates to situations where the UCB product is intentionally used for a medical purpose not in accordance with the authorised product information.

- Misuse

This refers to situations where the UCB product is intentionally and inappropriately used not in accordance with the authorised product information.

- Abuse

This corresponds to the persistent or sporadic, intentional excessive use of the UCB product, which is accompanied by harmful physical or psychological effects

- Medication error

Medication error refers to any unintentional error in the prescribing, dispensing, or administration of the UCB product while in the control of the healthcare professional, patient, or consumer.

- Occupational exposure

This refers to the exposure to the UCB product, as a result of one's professional or non-professional occupation.

- Lack of therapeutic efficacy
- Overdose

Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgment should always be applied.

- Suspected transmission of an infectious agent via a UCB product
- Suspected adverse reaction associated with a suspected or confirmed falsified medicinal product or quality defect (combined complaint) of the UCB product
- Unexpected therapeutic effect
- Product quality complaint

Any verbal, written or electronic expression of dissatisfaction with the product's identity, quality, stability, reliability, effectiveness, performance or usage. The report could be made by a patient, pharmacist, health care professional, or health authority.

This information is to be reported to UCB regardless if associated or not with an AE.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim results of the study will be incorporated into the CZP EU-RMP and as a PASS in the next periodic safety update report (PSUR). The final study report will be prepared independently by Kantar Health and submitted to UCB for review and approval.

13 REFERENCES

N/A

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Healthcare Professional Questionnaire	23 March 2016	CZP RMP Survey HCPs
2	Patient Questionnaire	9 May 2016	CZP RMP Survey Patients
3	SOP-af-007439	13 July 2016	Adverse Event Report Form for NIS
4	SOP-af-004175	13 July 2016	Pregnancy Report and Outcome Form for Clinical Trial

ANNEX 2. SAFETY CONTACT DETAILS

UCB	Contract Partner
Denmark [redacted]; [redacted] **France** [redacted] **Germany** [redacted] **Greece** [redacted] **Norway** [redacted] **Sweden** [redacted] **UK** [redacted]	**Central Safety Contact, Kantar Health** [redacted] [redacted]

ANNEX 3. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Healthcare Professional and Patient Surveys to Evaluate the Effectiveness of the Risk Minimization Educational Materials for Certolizumab Pegol (CZP, CIMZIA)

Study reference number: UP0038

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7 – 9
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☐	☐	☒	
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	6 – 9
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	6
4.2.2 Age and sex?	☒	☐	☐	9
4.2.3 Country of origin?	☒	☐	☐	9
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☒	
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Are descriptive analyses included?	☐	☐	☒	
10.3 Are stratified analyses included?	☐	☐	☒	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	11
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9
11.2 Are methods of quality assurance described?	☒	☐	☐	9
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted] (MAH contact person, Safety Lead, CIMZIA®)

Date: 19 July 2016

Name of the main author of the protocol amendment: [redacted] (MAH contact person, Safety Lead, CIMZIA)

Date: 17 Jan 2019

Signature: _____

Approval Signatures

Name: UP0038-protocol-amend-2

Version: 1.0

Document Number: CLIN-000130323

Title: UP0038 Protocol Amendment 2

Approved Date: 31 Jan 2019

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 31-Jan-2019 07:41:59 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Patient Safety Date of Signature: 31-Jan-2019 08:34:39 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: EEA QPPV Date of Signature: 31-Jan-2019 09:56:12 GMT+0000