PASS information

Title	The safety and clinical effectiveness of rapid infusion with CT-P10 in patients with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia: a retrospective non-interventional post-authorisation safety study in Europe
Protocol version identifier	2.0
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Product reference	EMEA/H/C/004112
Procedure number	Not applicable
Marketing authorisation holder(s)	Celltrion Healthcare Hungary Kft. Váci út 1-3, WestEnd Office Building B torony 6th floor H-1062 Budapest Hungary
Joint PASS	No

Research question and objectives	**Research question:** What is the safety profile and clinical effectiveness of rapidly infused CT-P10 in patients with non-Hodgkin's lymphoma (NHL) or chronic lymphocytic leukaemia (CLL) in the real world clinical setting? **Hypothesis:** This is a descriptive study and there is no *a priori* hypothesis to be tested. **Primary research objective:** To describe the incidence of infusion-related reactions (IRR) associated with rapid infusion of CT-P10 in patients with NHL or CLL on day 1 or day 2 after the index event (index event defined as the first rapid infusion of CT-P10, which must have been given as part of the second or a subsequent treatment cycle). **Secondary research objectives:** To describe the following in patients who receive rapid infusion of CT-P10 for the treatment of NHL or CLL: 1. Safety profile in the 6 months post-index date (index date defined as the date of the first rapid infusion of CT-P10, which must have been given as part of the second or a subsequent treatment cycle), including incidence (and frequency per patient per month, where appropriate) of the following safety events: IRRs, grade 3 or grade 4 IRRs, any adverse event (AE), any serious adverse event (SAE), any grade 3 or grade 4 AE, AEs as the primary cause for treatment discontinuation. 2. Clinical effectiveness in the 6 months post-index date (to be analysed separately for NHL and CLL), including overall survival (OS), progression free survival (PFS), best response, overall (complete/partial) response rate, time to complete or partial response.

	3. NHL / CLL treatment patterns during the observation period (from diagnosis of NHL or CLL to 6 months post-index date), including types and doses of treatment, number and duration of infusions, time on treatment and reasons for discontinuation. 4. Patients' demographic, clinical, and NHL/ CLL disease characteristics.
Country(-ies) of study	UK, Spain, France, Italy and the Netherlands.
Author	HeeJung Kang RPh., MScMed. Celltrion Healthcare Co., Ltd. Laura Baldock BSc. Luke Saunders Ph.D. pH Associates Ltd.

Marketing authorisation holder(s)

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On behalf of the Chief Investigator, Professor Pier Luigi Zinzani:

I have carefully read this protocol entitled **"The safety and clinical effectiveness of rapid infusion with CT-P10 in patients with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia: a retrospective non-interventional post-authorisation safety study in Europe",** and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.

NAME:	Prof. Pier Luigi Zinzani
TITLE:	
SIGNATURE:	
DATE:	

INVESTIGATOR APPROVAL SIGNATURE PAGE

On behalf of the Principal Investigator at each site:

I have carefully read this protocol entitled **"The safety and clinical effectiveness of rapid infusion with CT-P10 in patients with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia: a retrospective non-interventional post-authorisation safety study in Europe",** and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.

NAME:	
TITLE:	
SIGNATURE:	
DATE:	

1. Table of contents

2. List of abbreviations and key definitions

2.1 List of abbreviations

Abbreviation	Definition
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse event
ASH	American Society of Hematology
CFR	Code of Federal Regulations
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
DLBCL	Diffuse large B-cell lymphoma
DMP	Data management plan
EDC	Electronic data capture
eDCF	Electronic data collection form
EHA	European Hematology Association
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPP	Guidelines for Good Pharmacoepidemiology Practices
IEC	Independent Ethics Committee
IPI	International Prognostic Index
IRB	Institutional Review Board
IQR	Interquartile range
IRR	Infusion-related reaction
ISPE	International Society for Pharmacoepidemiology
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
LDH	Lactate dehydrogenase
NHL	Non-Hodgkin’s lymphoma
PASS	Post-authorisation safety study
R&D	Research and Development
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure
UK	United Kingdom

2.2 Key definitions

- **Index event:** first rapid infusion of CT-P10 (note: first rapid infusion must have been given as part of the second or a subsequent treatment cycle).
- **Index date:** date of first rapid infusion of CT-P10 (note: first rapid infusion must have been given as part of the second or a subsequent treatment cycle) (day 1).
- **Rapid infusion:** defined as a total infusion time for CT-P10 of 90 minutes or less.
- **Infusion-related reaction (IRR):** any adverse event (AE) from a pre-defined list (see Annex 3) occurring on day 1 or day 2 after an infusion of CT-P10.
- **Pre-index observation period:** the pre-index observation period for this study will be from the date of diagnosis of NHL or CLL until the index date, and will be used to capture patients' demographic and clinical characteristics.
- **Post-index observation period:** patients will be observed for a period of 6 months after the index date (or until death, if sooner), to capture safety and clinical outcomes.
- **Adverse event (AE):** An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an AE includes worsening of a pre-existing medical condition.
- **Serious adverse event (SAE):** a SAE is an AE that:
    - is fatal
    - is life threatening (places the subject at immediate risk of death)
    - requires in-patient hospitalisation or prolongation of existing hospitalisation
    - results in persistent or significant disability/incapacity
    - is a congenital anomaly/birth defect
    - other significant medical hazard.

- **Adverse event grade:** AEs will be defined as grade 1, 2, 3, 4 or 5 according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE)[1].
- **Overall survival (OS):** defined as the time from the index date to death from any cause.
- **Progression free survival (PFS):** defined as the time from the index date to the first documented evidence of disease progression or death from any cause. The assessment of disease progression will be based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria for CLL[2] or the Revised Response Criteria for Malignant Lymphoma for NHL[3], if these criteria are used and documented locally. If different criteria are used in routine practice, disease progression will be defined as documented in the medical records.
- **Complete response (CR) or partial response (PR):** will be based on IWCLL criteria for CLL[2] or the Revised Response Criteria for Malignant Lymphoma for NHL[3], if these criteria are used and documented locally. If different criteria are used in routine practice, response will be defined as documented in the medical records.

3. Responsible parties

Role	Person
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Coordinating Investigator (Country 2)	To be confirmed once sites are recruited.

4. Abstract

Title

The safety and clinical effectiveness of rapid infusion with CT-P10 in patients with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia: a retrospective non-interventional post-authorisation safety study in Europe

Protocol version

2.0

Date of last version of protocol

18 April 2018

Rationale and background

In February 2017, CT-P10 became the first biosimilar version of rituximab to be approved by the European Medicines Agency (EMA) for the treatment of rheumatic diseases and specific blood cancers including non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL)[4].

The safety profile of rituximab has been documented in numerous clinical trials, with infusion-related reactions (IRRs), thought to be related to the release of cytokines, being the most commonly reported adverse reaction[8,9]. To minimise the risk of IRRs, the standard administration protocol for rituximab, specified in the summary of product characteristics, takes approximately three to four hours for the first infusion and two to three hours for subsequent infusions for oncology treatment. This standard infusion protocol places a significant burden on the healthcare system and patients and, consequently, many healthcare professionals now administer rituximab as a rapid infusion (over a period of 90 minutes or less)[10] for second or subsequent infusions in patients who did not experience serious complications with their initial infusion(s).

A number of studies have been conducted to evaluate the safety of rapid infusion of rituximab in patients with haematological malignancies and have generally shown rapid administration to be safe and well-tolerated, with low incidences of IRRs[9,11–14]. However, there are very limited data available on the safety of rapid infusion of CT-P10[15]. These data are important to inform future decisions by physicians and healthcare providers regarding the most appropriate and cost-effective treatment strategy.

This study will address this evidence gap by collecting real world data on the safety and effectiveness of rapidly infused CT-P10 in patients with NHL and CLL in Europe.

Research question and objectives

Research question:

What is the safety profile and clinical effectiveness of rapidly infused CT-P10 in patients with NHL or CLL in the real world clinical setting?

Hypothesis:
This is a descriptive study and there is no *a priori* hypothesis to be tested.

Primary research objective:
To describe the incidence of infusion-related reactions (IRR) associated with rapid infusion of CT-P10 in patients with NHL or CLL on day 1 or day 2 after the index event (index event defined as the first rapid infusion of CT-P10, which must have been given as part of the second or a subsequent treatment cycle).

Secondary research objectives:
To describe the following in patients who receive rapid infusion of CT-P10 for the treatment of NHL or CLL:

1. Safety profile in the 6 months post-index date (index date defined as the date of the first rapid infusion of CT-P10, which must have been given as part of the second or a subsequent treatment cycle), including incidence (and frequency per patient per month, where appropriate) of the following safety events: IRRs, grade 3 or grade 4 IRRs, any adverse event (AE), any serious adverse event (SAE), any grade 3 or grade 4 AE, AEs as the primary cause for treatment discontinuation.
2. Clinical effectiveness in the 6 months post-index date (to be analysed separately for NHL and CLL), including overall survival (OS), progression free survival (PFS), best response, overall (complete/partial) response rate, time to complete or partial response.
3. NHL / CLL treatment patterns during the observation period (from diagnosis of NHL or CLL to 6 months post-index date), including types and doses of treatment, number and duration of infusions, time on treatment and reasons for discontinuation.
4. Patients' demographic, clinical, and NHL/ CLL disease characteristics.

Study design

A European, multi-centre, retrospective non-interventional post-authorisation safety study (PASS) based on secondary use of hospital medical records. The study will involve the collection of patient-level data from hospital medical records for patients with NHL or CLL who received treatment with CT-P10 in selected centres in five European countries. Patients will be selected based on the treatment they received as part of their standard clinical care in the real world. Data will be collected retrospectively from the date of diagnosis of NHL or CLL until the index date (defined as the date of the first rapid infusion of CT-P10 [as part of the second or a subsequent treatment cycle]), to capture patients' demographic and clinical characteristics, and for a period of 6 months post-index (or until death, if sooner), to capture safety and clinical outcomes.

Population
Setting
Study sites will be specialist treatment centres or hospitals that routinely use CT-P10

for the treatment of patients with NHL or CLL, recruited from five European countries (the UK, Spain, France, Italy and the Netherlands). At least two centres will be included from each country.

Study population

The source population for this study is adult patients with NHL or CLL who received treatment with rapidly infused CT-P10 as part of their standard clinical care in five European countries.

Patients fulfilling the following criteria will be potentially eligible for inclusion in the study:

- Patients with a confirmed diagnosis of NHL (follicular lymphoma [FL] or diffuse large B-cell lymphoma [DLBCL]) or CLL.
- Patients who had received rapidly infused CT-P10 for their second or a subsequent treatment cycle; 'rapidly' defined as 90-minutes or less.
- Patients at least 18 years of age at the date of diagnosis of NHL or CLL.
- Patients (or next of kin, if appropriate locally) providing written informed consent for study data collection (if this is required according to local country regulations).

Patients fulfilling any of the following criteria will be excluded from the study:

- Patients who had received reference rituximab for any previous treatment cycles (i.e. prior to the index event) within the same line of treatment.
- Patients whose medical records are unavailable for review.

Variables

The exposure of interest in the present study is treatment with CT-P10, administered by rapid infusion. All study patients will be exposed by virtue of the inclusion criteria.
The primary outcome is the proportion of patients who experience IRRs associated with rapidly infused CT-P10 on day 1 or day 2 after the index event.
The secondary outcomes for this study are described in detail in section 9.3; these will include the following parameters for patients with NHL or CLL treated with rapidly infused CT-P10:

- Overall safety profile in the 6 months post-index date
- Clinical effectiveness in the 6 months post-index date
- NHL/CLL treatment patterns during the observation period.
- Patients' demographic, clinical and NHL/CLL disease characteristics

Data sources

All data for the study will be sourced from patients' hospital medical records (paper and/or electronic, as applicable locally), infusion records and other local databases or electronic systems.

Study size

The proposed sample size for this study is 300. Given that the study is primarily descriptive, aiming to characterise the IRR rate in patients receiving rapid infusion of CT-P10, assessments of the utility of this sample size is primarily based on the precision with which rates can be estimated. The mean frequency/incidence of IRRs for rapidly infused rituximab across a range of studies was reported to be 8.84% (95% confidence interval [CI]: 7.12 to 10.81) in a meta-analysis by Polwart[16].

Assuming the rate of IRRs in patients receiving rapid infusion of CT-P10 are similar to those found in previous rituximab studies (rounding to 10%), we can expect the 95% CIs to be between 6.8 and 14.0% with a sample size of 300; a 95% CI width of 7.2%. If the sample size for the study was increased by 100 patients, the gain in precision would be a 95% confidence interval width of 6.2%, while for 200 patients the width would increase to 8.8%. The highest IRR rates among the studies investigated by Polwart gave an IRR rate of approximately 30%. For this IRR rate the 95% confidence interval would span between 24.9 and 35.5% for a sample of 300. Given the diminishing returns of the effect of increasing study sample size on the precision of estimates derived, a sample size of 300 patients is considered to be acceptable.

The expected sample size split for patients with NHL and CLL is based on the epidemiology of both diseases, with approximately 76,800[17] and 20,200[18] patients with NHL and CLL, respectively, being alive at the end of 2010 in the UK. Based on these prevalence estimates, and assuming a similar prevalence across Europe, it is expected that the sample will comprise approximately 240 patients with NHL and 60 with CLL who received rapid infusion CT-P10.

Data analysis

For the primary endpoint analysis, the frequency and proportion of patients receiving CT-P10 who experience IRRs on day 1 or day 2 after the index event will be presented with 95% confidence intervals (CI). The proportional Z-test will be used to compare the IRR rate observed in this study with rates previously reported for reference rituximab in the literature.

For the secondary endpoint safety analyses, rates of events per-patient-per month will be reported. The time-to-event clinical effectiveness endpoint analyses (OS, PFS, time to complete or partial response) will be displayed descriptively using Kaplan Meier plots.

For the demographic, clinical, and NHL/CLL disease characteristics endpoint analyses, the study population will be described by means of summary statistics. Appropriate tests for differences between disease groups will be employed according to the data distribution.

Summary statistics will be displayed for the treatment dose and duration on

treatment, and for the reasons for treatment discontinuation.

Milestones
Start of data collection: Jun 2018.
End of data collection: Dec 2018.
Final report of study results: Feb 2019.

5. Amendments and updates

All amendments to this protocol will be documented in the table below.

Protocol deviations will be documented in a Protocol Deviation Log (maintained in a separate document).

Number	Date	Section of study protocol	Amendment or update	Reason

6. Milestones

Milestone	Planned date
Registration in the EU PAS register	Apr 2018
Start of data collection	May 2018
Interim analysis (for submission to ASH 2018)	July 2018
End of data collection	Dec 2018
Publication at ASH 2018	Dec 2018
Publication at EHA 2019	Jun 2019
Final report of study results	Feb 2019

7. Rationale and background

In February 2017, CT-P10 became the first monoclonal antibody biosimilar version of rituximab to be approved by the European Medicines Agency (EMA)[4]. It is licensed as Truxima™ for intravenous use in adults with rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis, and specific blood cancers including non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukaemia (CLL). Clinical similarity between CT-P10 and rituximab

has been accepted by the EMA based on evidence in a population of patients with moderate to severe rheumatoid arthritis using the American College of Rheumatology-20 response and in a population of patients with follicular lymphoma (FL) using overall response rate as markers of clinical effectiveness[5–7].

The safety profile of rituximab has been documented in numerous clinical trials, with infusion-related reactions (IRRs), thought to be related to the release of cytokines, being the most commonly reported adverse reaction[8,9]. The majority of these occur at the first infusion and decrease with subsequent infusions, with the peak time to onset ranging from 30 to 120 minutes[19]. IRRs are usually mild to moderate in nature with symptoms such as fever, rash, and cardiovascular or respiratory insufficiency; more severe anaphylactic type reactions occur rarely[20].

To minimise the risk of IRRs, the standard administration protocol for rituximab, specified in the summary of product characteristics, takes approximately three to four hours for the first infusion and two to three hours for subsequent infusions for oncology treatment. The recommended initial rate for first infusions is 50 mg/hour; after the first 30 minutes, this is gradually increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Patient observations are undertaken every 15 minutes. Second infusion rates start at an initial rate of 100 mg/hour, increasing at 100 mg/hour increments at 30 minute intervals, to a maximum of 400 mg/hour[19]. This standard infusion protocol places a significant burden on the healthcare system in terms of the lengthy observation times required and impact on nursing and administration staff workloads, and may also be inconvenient for patients; consequently, many healthcare professionals now administer rituximab as a rapid infusion (over 90 minutes or less) for second or subsequent infusions in patients who did not experience serious complications with their initial infusion(s). For example, a survey conducted in 2009 of 20 major UK cancer centres[10] found that over 70% were using rapid rituximab infusion protocols.

A number of studies have been conducted to evaluate the safety of rapid infusion of rituximab in patients with haematological malignancies and have generally shown rapid administration to be safe, with low incidences of IRRs[9,11–14]. In addition, the safety of rapid infusion rituximab has been investigated in patients with rheumatoid arthritis, with one systematic review reporting that both the 90 minute, and a shorter 60 minute schedule, appear to be well-

tolerated[8]. However, with the exception of a recently-published abstract reporting data from a single UK centre[15], there are no data available on the safety of rapid infusion of CT-P10.

This study will address this evidence gap by collecting real world data on the safety and effectiveness of rapid infusion of CT-P10 in patients with NHL and CLL in Europe. In so doing, it will provide physicians and healthcare providers with more detailed information on the safety profile of rapidly infused CT-P10, to enable them to make evidence based decisions on the most appropriate and cost-effective treatment strategy.

8. Research question and objectives

8.1 Research question

What is the safety profile and clinical effectiveness of rapidly infused CT-P10 in patients with NHL or CLL in the real world clinical setting?

8.2 Hypothesis

This is a descriptive study and there is no *a priori* hypothesis to be tested.

8.3 Primary research objective

To describe the incidence of IRR associated with rapid infusion of CT-P10 in patients with NHL or CLL on day 1 or day 2 after the index event (index event defined as the first rapid infusion of CT-P10, which must have been given as part of the second or a subsequent treatment cycle).

8.4 Secondary research objectives

To describe the following in patients who receive rapid infusion of CT-P10 for the treatment of NHL or CLL:

1. Safety profile in the 6 months post-index date (index date defined as the date of the first rapid infusion of CT-P10, which must have been given as part

of the second or a subsequent treatment cycle), including incidence (and frequency per patient per month, where appropriate) of the following safety events: IRRs, grade 3 or grade 4 IRRs, any adverse event (AE), any serious adverse event (SAE), any grade 3 or grade 4 AE, AEs as the primary cause for treatment discontinuation.

2. Clinical effectiveness in the 6 months post-index date (to be analysed separately for NHL and CLL), including overall survival (OS), progression free survival (PFS), best response, overall (complete/partial) response rate, time to complete or partial response.
3. NHL / CLL treatment patterns during the observation period (from diagnosis of NHL or CLL to 6 months post-index date), including types and doses of treatment, number and duration of infusions, time on treatment and reasons for discontinuation.
4. Patients' demographic, clinical, and NHL/CLL disease characteristics.

9. Research methods

This study has been designed and will be conducted according to the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; http://www.encepp.eu/index.shtml) and International Society for Pharmacoepidemiology (ISPE; https://www.pharmacoepi.org/resources/guidelines_08027.cfm) guidance, as appropriate.

9.1 Study design

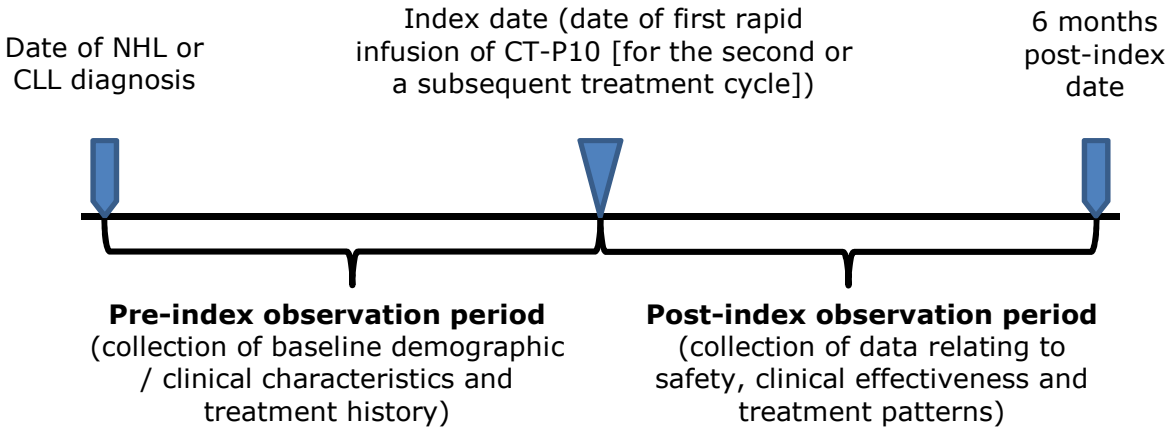
This is a European, multi-centre, retrospective non-interventional post-authorisation safety study (PASS) based on secondary use of hospital medical records.

The study will involve the collection of patient-level data from hospital medical records (including infusion records) for patients with NHL or CLL who received treatment with CT-P10 in selected centres in five European countries. Patients will be selected based on the treatment they received as part of their standard clinical care in the real world.

Data will be collected retrospectively from the date of diagnosis of NHL or CLL until the index date (to capture patient's demographic and clinical characteristics), and for 6 months post-index (or until death, if sooner), to capture safety and clinical outcomes, as shown in **오류! 참조 원본을 찾을 수 없습니다.**. In cases where the full 6 month post-index observation period is not available at the time of initial patient identification/recruitment, the retrospective data collection will be undertaken in batches at agreed intervals throughout the observation period and completed once the full 6 months has elapsed.

A retrospective design was selected as most appropriate for collecting data since it is expected (based on scoping interviews with clinicians in the participating countries) that the outcomes of interest will be well-documented in patients' medical records, including the primary outcome (incidence of IRR), which will be recorded in infusion records. Furthermore, it will enable the results of the study to be available in a timelier manner than would be possible with a prospective design.

Figure 1: Study design



9.2 Setting

9.2.1 Study population

The source population for this study is adult patients with NHL or CLL who received treatment with rapidly infused CT-P10 as part of their standard clinical care in five European countries.

Patients fulfilling the following criteria will be potentially eligible for inclusion in the study:

- Patients with a confirmed diagnosis of NHL (follicular lymphoma [FL] or diffuse large B-cell lymphoma [DLBCL]) or CLL.
- Patients who had received rapidly infused CT-P10 for their second or a subsequent treatment cycle; 'rapidly' defined as 90-minutes or less.
- Patients at least 18 years of age at the date of diagnosis of NHL or CLL.
- Patients (or next of kin, if appropriate locally) providing written informed consent for study data collection (if this is required according to local country regulations).

Patients fulfilling any of the following criteria will be excluded from the study:

- Patients who had received reference rituximab for any previous treatment cycles (i.e. prior to the index event) within the same line of treatment.
- Patients whose medical records are unavailable for review.

As only limited exclusion criteria will be applied, and patients will be included from a range of centres in five European countries, it is expected that the study population will be representative of the overall source population.

9.2.2 Patient identification and recruitment

Potentially eligible patients will be identified by members of the direct care team at each centre from hospital pharmacy records or other local department databases and assessed against the remaining eligibility criteria. Patients who meet all of the inclusion criteria and none of the exclusion criteria will be included in the study. All eligible patients at the participating centres will be included. If an insufficient

number of patients are identified at initial recruitment, a second round of (retrospective) recruitment may be undertaken at a later date, when more patients meet the eligibility criteria. Patients may be recruited to the study before the full 6 month post-index observation period has elapsed.

Patients (or their next of kin, if appropriate locally) will be approached by the local care team and invited to provide consent for study data collection, if this is required according to local country regulations.

9.2.3 Observation period

Data will be collected retrospectively for each patient from the date of diagnosis of NHL or CLL until the index date and for a period of 6 months post-index (or until death, if sooner).

9.2.4 Study sites

Study sites will be specialist treatment centres or hospitals which routinely use CT-P10 in the treatment of patients with NHL or CLL, recruited from five European countries (the UK, Spain, France, Italy and the Netherlands). Based on the target sample size, each country will recruit approximately 60 patients. To reduce any bias potentially arising from using a single site in one country, at least two centres in each country will be included to meet the country targets. Centres will be selected based on their current practice of rapidly infusing CT-P10.

9.3 Variables

The exposure of interest in the present study is treatment with CT-P10, administered by rapid infusion as part of the second or a subsequent treatment cycle. All study patients will be exposed by definition, as this is specified in the inclusion criteria.

The endpoints associated with each of the study objectives are described below, along with the variables that will be collected in order to address the objectives. Response options for each variable will be further detailed in the electronic data collection form (eDCF).

The endpoints below will be reported using descriptive statistics of distribution, central tendency and dispersion, as appropriate for the data collected.

Endpoint to address the primary objective	Variables required to address the primary objective
Primary objective: To describe the incidence of IRR associated with rapid infusion of CT-P10 in patients with NHL or CLL on day 1 or day 2 after the index event (index event defined as the first rapid infusion of CT-P10, which must have been given as part of the second or a subsequent treatment cycle).	
Proportion of patients who experience an IRR* on day 1 or day 2 after the index event. * An IRR is defined as any AE from a pre-defined list (see Annex 3) occurring on day 1 or day 2 after an infusion of CT-P10.	• Did IRR(s) occur on day 1 or day 2 after the index event (Yes/No)? • If yes, IRR description and date
Endpoint to address the secondary objective	**Variables required to address the secondary objective**
Secondary objective 1: To describe the safety profile of rapidly infused CT-P10 in patients with NHL or CLL in the 6 months post-index date	

• Proportion of patients who experience the following safety events in the 6 months post-index date, and frequency of each per patient per month:
  ○ Any IRR.
  ○ Any grade 3 or grade 4 IRR (according to the Common Terminology Criteria for Adverse Events [CTCAE] version 4).
  ○ Any other AE (excluding IRR).
  ○ Any other grade 3 or grade 4 AE (excluding IRR).
  ○ Any serious adverse event (SAE).
• Proportion of patients with AEs as the primary cause for treatment discontinuation.
• Summary distributions of event type by grade.
• Proportion of all rapid CT-P10 infusions during which IRRs were experienced.
	For all AEs (temporally associated with CT-P10 treatment) during the 6 months post-index (including the index date):
	• Description of AE
	• IRR (Yes/No)
	• Event start date
	• Event end date
	• Seriousness
	• CTCAE v4.0 grade
	• Clinician's assessment of relationship to CT-P10
	• AE resulted in treatment discontinuation (Yes/No).

Secondary objective 2: To describe the clinical effectiveness of rapidly infused CT-P10 in patients with NHL or CLL in the 6 months post-index	
• OS, defined as the time from the index date until death from any cause. • Proportion of patients surviving at six months following NHL or CLL diagnosis and following the index date. • PFS, defined as the time from the index date until the first documented evidence of disease progression or death from any cause. • Proportion of patients surviving and free from disease progression at six months following the index date. • Summary of best response to CT-P10	• Date of data collection. • Patient alive at 6 months post-index (Yes / No / Not known)? • If no, date of death (DD/MM/YYYY). • All treatment response assessments in the post-index period (date, recorded treatment response [complete response / partial response / no response or stable disease / progressive disease], assessment based on IWCLL / Revised Response Criteria for Malignant Lymphoma / local criteria / other criteria, type(s) of

(complete response / partial response / no response or stable disease / progressive disease). • Proportion of patients achieving a complete or partial response. • Time to complete or partial response, defined as the number of days from the index date until first documentation of complete or partial response by the local investigator.	assessments used to evaluate response). • Date (within 6 months post-index) of last recorded hospital visit.
Secondary objective 3: To describe treatment patterns in patients with NHL or CLL who receive treatment with rapidly infused CT-P10.	
• Summary measures of the following CT-P10 treatment parameters: o Number of infusions o Duration of infusions o Starting and subsequent doses o Chemotherapy regimen given with CT-P10 (if applicable) and pre-medications received o Time on treatment o Reason why treatment was discontinued (if applicable) • Distribution of subsequent treatment regimens (after discontinuation of CT-P10).	• For CT-P10 treatment (in the post-index period): o Date of each infusion. o Pre-medications given. o Treatment doses given (actual and per m^2). o Duration of each infusion. o Name of chemotherapy regimen given with CT-P10. o Treatment discontinuation date (the date of discontinuation will be defined as the date of the last dose / infusion) or ongoing. o Treatment ongoing at 6 months post-index (Yes / No / not known). o Reason for permanent discontinuation (adverse event, death, disease progression, completed course of treatment, budget constraints, other). • Name, type and start date of subsequent treatment regimens (after discontinuation of CT-P10).
Secondary objective 4: To describe the baseline demographic, clinical and disease characteristics of patients with NHL or CLL who receive treatment with rapidly infused CT-P10.	
Demographic and clinical characteristics (at index date unless specified) • Summary measures of patients' age, sex, ethnicity, employment status, comorbidities (Charlson Comorbidity Index [22]), disease duration and prior chemotherapy and rituximab exposure. • Number of other diagnosed malignancies. • Summary of Eastern Cooperative Oncology Group (ECOG) performance status at closest time point prior to the index date. • Summary measures of duration of CT-P10 infusion(s) given prior to the index event. • Proportion of patients who experienced IRRs with CT-P10 infusion(s) given prior to the index event (by IRR grade).	• Month and year of birth • Index date • Date of diagnosis of NHL or CLL • Sex (male/female) • Ethnicity • Employment status (full time / part time / unemployed / student / retired / home-maker) at closest time point prior to index date and date documented. • Relevant comorbidities ongoing at index date (components of Charlson Comorbidity Index will be captured) • Prior treatment regimens for NHL or CLL from diagnosis of NHL or CLL to the index date (name and type of treatment, start date, stop date [for

	most recent regimen and most recent rituximab only]). • Other malignancies diagnosed prior to the index date. • ECOG score at closest time point prior to the index date and date of assessment. • Date and duration of any CT-P10 infusion(s) given prior to the index event and description / CTCAE v4 grade of any IRRs experienced.
NHL / CLL disease characteristics • Summary of diagnosis (including type of NHL [FL / diffuse large B-cell lymphoma, DLBCL]) • Summary of NHL or CLL stage as documented in the medical records (e.g. Lugano or Ann Arbor [I, II, III, IV] for NHL, Binet [A, B, C] for CLL) at initial diagnosis and at index date. • Summary measures (at the index date) of: o International Prognostic Index (IPI) score for DLBCL (as documented or calculated from component parts) o Follicular lymphoma (FL)IPI for FL (as documented or calculated from component parts) o Lactate dehydrogenase (LDH), presence of B-symptoms (unexplained fever [temperatures above 100.4°F or 38°c; unexplained weight loss of more than 10% of original body weight during the last 6 months; drenching night sweats) and bone marrow involvement for NHL o Tumour bulk (largest tumour diameter) and total number of tumour sites o Extra-nodal status	NHL / CLL disease characteristics: • Diagnosis (FL/DLBCL/CLL) • NHL stage as documented in the medical records (e.g. Lugano or Ann Arbor [I, II, III, IV]) and date of assessment (at initial diagnosis and closest prior to index date) • CLL stage (Binet A, B, C) and date of assessment (at initial diagnosis and closest prior to index date). • Result and date of assessment for the following (closest prior to index date): o IPI score (for DLBCL) o FLIPI (for FL) o LDH o Haemoglobin (part of FLIPI) o Presence of B symptoms (for NHL) o Bone marrow involvement (for NHL) o Largest tumour diameter and number of tumour sites o Number of extra-nodal sites

9.4 Data sources

All data for the study will be sourced from patients' hospital medical records (paper and/or electronic, as applicable locally), infusion records and other local databases or electronic systems. Data will be collected either by an external researcher or a member of the patients' direct care team (to be agreed in each country before data collection commences).

All data will be collected in pseudonymised form; patients will be identified in study records by a unique study code to preserve patient confidentiality, while allowing data management queries to be raised.

9.5 Study size

The proposed sample size for this study is 300. Given that the study is primarily descriptive, aiming to characterise the IRR rate in patients receiving rapid infusion of CT-P10, assessments of the utility of this sample size is primarily based on the precision with which rates can be estimated. The mean frequency/incidence of IRRs for rapidly infused rituximab across a range of studies was reported to be 8.84% (95% confidence interval [CI]: 7.12 to 10.81) in a meta-analysis by Polwart[16]. Given this, 95% CIs around estimates of possible IRRs for rapidly infused CT-P10 at different sample sizes are given below:

IRR %	200 patients		250 patients		300 patients		350 patients		400 patients	
	95% LCI	95% UCI	95% LCI	95% UCI	95% LCI	95% UCI	95% LCI	95% UCI	95% LCI	95% UCI
8%	4.6%	12.7%	5.0%	12.1%	5.2%	11.7%	5.4%	11.4%	5.5%	11.1%
9%	5.4%	13.9%	5.8%	13.3%	6.0%	12.8%	6.2%	12.5%	6.4%	12.2%
10%	6.2%	15.0%	6.6%	14.4%	6.8%	14.0%	7.1%	13.6%	7.2%	13.4%
12.5%	8.3%	17.9%	8.7%	17.2%	9.0%	16.8%	9.2%	16.4%	9.4%	16.1%
15%	10.4%	20.1%	10.8%	20.0%	11.2%	19.6%	11.4%	19.2%	11.6%	18.9%
20%	14.7%	26.2%	15.2%	25.5%	15.6%	25.0%	15.9%	24.6%	16.2%	24.3%
30%	23.7%	36.9%	24.4%	36.1%	24.9%	35.5%	25.2%	35.1%	25.5%	34.8%

Assuming the rate of IRRs in patients receiving rapid infusion of CT-P10 are similar to those found in previous rituximab studies (rounding to 10%), we can expect the 95% CIs to be between 6.8 and 14.0% with a sample size of 300; a 95% CI width of 7.2%. If the sample size for the study was increased by 100 patients, the gain in precision would be a 95% confidence interval width of 6.2%, while for 200 patients the width would increase to 8.8%. The highest IRR rates among the studies investigated by Polwart gave an IRR rate of approximately 30%. For this IRR rate the 95% confidence interval would span between 24.9 and 35.5% for a sample of 300. Given the diminishing returns of the effect of increasing study sample size on the precision of estimates derived, a sample of 300 patients is considered acceptable.

The expected sample size split for patients with NHL and CLL is based on the epidemiology of both diseases, with approximately 76,800[17] and 20,200[18] patients

with NHL and CLL, respectively, being alive at the end of 2010 in the UK. Based on these prevalence estimates, and assuming a similar prevalence across Europe, it is expected that the sample will comprise approximately 240 patients with NHL and 60 with CLL.

9.6 Data management

Data management and handling of data will be conducted according to the study specific data management plan (DMP) and pH Associates standard operating procedures (SOPs). Data will be collected via an electronic data capture (EDC) system using a standardised electronic data collection form (eDCF) designed specifically for the study. Before the start of data collection, site staff collecting data from patients' hospital medical records will be trained in data entry into the eDCFs by study management staff and consistency checks will be built into the eDCF to ensure data quality.

Data management for eDCFs will be carried out using MACRO™, a data management system which has a secure web-based data entry interface and is fully validated and compliant with Food and Drug Administration (FDA) Information Governance standard 21 Code of Federal Regulations (CFR) part 11. The MACRO™ system has restricted access permissions for data entry management and analysis and maintains an audit trail of all changes to data and activity in the system in line with 21 CFR part 11. If corrections are needed to an eDCF, queries will be raised in the EDC system by the study data manager and these will be resolved by the responsible investigator (or designee) by reference to the source records.

9.7 Data analysis

A detailed description of statistical methods will be documented in a separate statistical analysis plan (SAP) to be finalised before data collection is completed.
Analyses will be performed by pH Associates using Stata (StataCorp LLC) and Microsoft Excel. Data from all participating centres will be pooled for analysis.

9.7.1 Primary analyses

For the primary endpoint analyses, the frequency and proportion of patients receiving CT-P10 who experience IRRs on day 1 or day 2 after the index event will be presented with 95% CI. The proportional Z-test will be used to compare the IRR rate observed in this study with rates previously reported for reference rituximab in the literature.

9.7.2 Secondary analyses

For the secondary endpoint safety analyses, rates of events per-patient-per month will be reported. Secondary clinical effectiveness endpoints will be reported separately for patients with NHL or CLL. The time-to-event clinical effectiveness endpoint analyses (OS, PFS, time to complete or partial response) and CT-P10 treatment duration will be displayed descriptively using Kaplan Meier plots from the index event until the date of the event or censoring. Patients who are known to be alive at 6 months post-index will be censored on that date for OS whereas patients who are lost to follow-up will be censored at the date they were last known to be alive (i.e. the last recorded hospital visit within the 6 months post-index). For PFS, patients will be censored on the date they were last known not to have disease progression (i.e. the date of last documented response assessment) and for time to complete or partial response, patients will be censored at the date of the last recorded known response. For treatment duration, censoring will occur at the 6 months post-index date (if CT-P10 treatment is known to be ongoing at 6 months) or the date of the last infusion (if the patient is lost to follow-up). Absolute counts and the percentages of these events occuring in each disease indication group will be reported. Survival rates for 6 months post NHL or CLL diagnosis will also be calculated. Summary data will be tabulated and also displayed graphically where appropriate.

The proportion of patients assessed as having a best response of complete response, partial response, stable disease or progressive disease within the 6 months post-index based the documented assessment of the local investigator and the proportion of patients with a complete or partial response, will be presented with 95% CI.

For the demographic, clinical, and NHL/CLL disease characteristics endpoint analyses, the study population will be described by means of summary statistics. Distributions and descriptive statistics of both central tendency (medians and means) and dispersion (standard deviation, interquartile range [IQR]) will be presented for

quantitative variables. Categorical variables will be described with frequencies and percentages; distributions, modes, medians, IQR and range will be reported as appropriate. 95% CI will be presented for means and estimates of proportions, as appropriate. Where appropriate differences between disease groups will be evaluated using two-sample t-tests or Mann-Whitney U-tests for continuous normally and non-normally distributed variables, respectively, while the chi-squared test will be employed for nominal variables. Normality of variables will be evaluated through inspecting histograms of their distributions.

Treatment patterns for NHL or CLL in patients who receive rapid infusion of CT-P10 will be described for the entire study period. Summary statistics will be displayed for the treatment dose and duration on treatment, and for the treatment discontinuation reason.

All percentages will be reported to the nearest whole number; therefore, in reporting study results in tables, figures and associated text, percentages may not add up to 100% due to rounding.

9.7.3 Missing data

Where data are missing from the original medical record, the affected analyses will be conducted using only the results of those patients with data available and the number included in each analysis will be stated.

9.7.4 Subgroup and sensitivity analyses

Subgroup analyses may be conducted to further evaluate the safety and clinical effectiveness of CT-P10 in patients with NHL or CLL. This may include, but will not be limited to:

- Diagnosis (NHL [further stratified by FL / DLBCL] / CLL).
- Infusion time for the index event (90 minutes, 60<90 minutes, <60 minutes).
- Patients with / without prior exposure to a rituximab-containing regimen.

No sensitivity analyses are planned.

9.7.5 Interim analyses

Interim analyses are planned in order to submit data to the American Society of Hematology (ASH) 2018 and European Hematology Association (EHA) 2019 Annual Meetings.

9.8 Quality control

Data collectors will be provided with data collection guidelines to facilitate consistent completion of the eDCF and will receive training in the requirements of the study protocol and correct completion of the eDCF prior to commencement of data collection.

All clinical data submitted will be checked for eligibility, completeness and accuracy and queries will be raised by the pH Associates data management team using agreed manual and programmed validation checks, which will be specified in the study DMP. Study centres will be required to cooperate with the data management team in the resolution of these queries.

A feasibility test for data collection will be carried out in at least one of the recruited study centres. The purpose of this pilot will be to check the availability and quality of data that will be collected in the study, and to confirm the length of time required to collect the data.

As requested by Celltrion, source data verification (SDV) will be not be performed as part of data quality control.

9.9 Limitations of the research methods

- Patient or next of kin consent may be a requirement for this study in some of the participating countries; this may introduce selection bias, resulting in a study sample that may not be representative of the wider patient population of interest.
- The interpretation of data collected retrospectively will be dependent on the completeness and quality of the medical records and the reliability of the abstraction of data from the medical records.
- The primary endpoint of this study is the incidence of IRR on day 1 or day 2 after the index event. It is expected (based on scoping interviews) that IRRs occurring during or shortly after the CT-P10 infusion should be reliably documented in

patients' infusion records, however, it is possible that IRRs occurring the day after the infusion may be less well-documented. This may result in an underestimate of the overall incidence of IRR during the observation period, particularly of milder events. The IRR rate may also be underestimated as a result of the definition of a rapid infusion as 90 minutes or less, since this may result in the exclusion of cases where the initial intention was to infuse CT-P10 over 90 minutes, but the infusion was delayed or stopped due to IRRs.

- The patient records included in this study will be from physicians and study sites that are willing to participate. Therefore, study findings may not be generalisable to all patients with NHL or CLL treated with rapid infusion of CT-P10 or to all physicians who treat these patients in the participating countries.
- As this is a non-interventional study conducted in a routine clinical practice setting, the assessment of treatment response may not be uniform, particularly with regard to the timing of evaluations. In particular, it is likely that disease progression for the identified patients will have been monitored at less frequent intervals than would be required in a clinical trial and therefore progression events will be identified later. This may result in upwardly biased estimates of PFS. For this reason, any findings regarding the endpoints of clinical response should be considered to be 'real world estimates' which may not be directly comparable to those observed in clinical trials.
- This is a descriptive study and no adjustments to control for confounding will be carried out.
- No SDV will be performed as part of this study and this lack of SDV could impact on the quality and consistency of the data collected.

9.10 Other aspects

Amendments must be made only by prior agreement between Celltrion Healthcare, pH Associates and the study Chief Investigator. The Independent Ethics Committee (IEC) or Institutional Review Board (IRB) must be informed of all amendments and give approval for substantial amendments. The Chief Investigator must send a copy of the approval letter from the IEC/IRB to the sponsor.

pH Associates, Celltrion Healthcare and the investigator reserve the right to terminate participation in the study according to the study contract. pH Associates will notify

the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to the sponsor and the Chief Investigator.

10. Protection of human subjects

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy, and will be conducted in accordance with the ethical principles of the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/).

The study will comply with each participating country's requirements for ensuring the wellbeing and rights of patients in non-interventional PASS.

This is an observational study of routine practice to be conducted by retrospective chart review; there will be no changes to patient management and no additional visits are required for the study. There is no additional risk to participants as all data will be collected from medical records and patients will have no direct involvement in the study.

Approval from an IEC or IRB will sought in each participating country, according to local requirements. Where required, approval to conduct the study and for release of pseudonymised data for analysis and reporting will also be sought in each participating centre.

No personally identifiable information on any study participant will be collected or removed from the centres participating in the study. Patients will be assigned a study-specific unique patient identification number which will be referenced in a study log. This patient log will not leave the participating centre location and will be the responsibility of the principal investigator at that study centre.

To comply with the General Data Protection Regulation (GDPR):

- The study is designed to minimise the data collected to that which is required for the planned analyses, and study data will include no direct identifiers.
- No directly identifiable information on any study participant will be collected or removed from the centres participating in the study. Patients will be assigned a study-specific unique patient identification number which will be referenced in a

study log. The patient log will not leave the participating centre location and will be the responsibility of the principal investigator at that study centre.

- Patients (or their next of kin) will give consent to access to their personal data for this research, if this is required according to country-specific regulations.
- Data will be transferred to and held securely by pH Associates at their offices within the UK during the conduct of the study.
- The duration of archiving of study data will be minimised to that required to ensure that queries arising from peer review of any publication arising from the study can be answered by reference to the source data if necessary.
- Study data will be archived after the end of the study (defined as the date of the approved clinical study report) for 2 years (in England, by pH Associates on behalf of Celltrion Healthcare).
- No use will be made of the data except for the study described in this protocol.
- At the end of the archive period the study data will be securely destroyed and the destruction documented.

11. Management and reporting of adverse events/adverse reactions

11.1 Definitions

11.1.1 Adverse events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an AE includes worsening of a pre-existing medical condition.

An adverse drug reaction (ADR) is an AE that is considered related to the medicinal product.

11.1.2 Serious adverse events

A SAE is any AE as defined above that:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

A hospitalisation meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

A serious adverse drug reaction (SADR) is a SAE that is considered related to the medicinal product.

11.1.3 Product complaints

A product complaint is any oral, electronic or written communication that alleges deficiencies with any Study Sponsor marketed product or medical device component(s). This may include, but is not limited to, damaged/broken product or packaging, product appearance whose colour/markings do not match the labelling, labelling discrepancies/inadequacies in the labelling/instructions (example: printing illegible), missing components/product, any fault of quality and/or effectiveness, or any falsification of the medicinal product.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalisation while using the device and use errors.

11.1.4 Special situations

This includes any incidence of drug exposure during pregnancy or breastfeeding,

overdose, off-label use, medication errors, occupational exposure, abuse, misuse or lack of therapeutic efficacy whilst using CT-P10 or any other Study Sponsor product.

Exposure during pregnancy or breastfeeding: All pregnancies occurring in female patients while taking CT-P10 or other Study Sponsor products, all pregnancies occurring in female partners of male patients taking CT-P10 or other Study Sponsor products, and any exposure of infants to CT-P10 or any other Study Sponsor product via breast milk.

Overdose: This refers to the 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 judgement should always be applied. Overdose can be intentional or accidental.

Off-label use: This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

Medication error: This is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the patient.

Occupational exposure: This refers to the exposure to a medicinal product as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Abuse: This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Misuse: This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.

Lack of therapeutic efficacy: This refers to a lack of the anticipated clinical effect of a medicinal product.

11.2 Reporting procedures

Safety data collection and reporting will be conducted in accordance with EU Good Pharmacovigilance Practice (GVP).

11.2.1 Reporting procedures for adverse events

This retrospective study is based on secondary use of data previously collected from healthcare professionals for other purposes. Any SAEs or IRRs temporally related to CT-P10 or other Study Sponsor products identified during the course of the retrospective review shall be reported to PAREXEL (CLTPharm@parexel.com) by the Principal Investigator at each centre within three calendar days of discovery. Initial AE/ADR information and all follow-up information must be recorded on the AE form and reported to PAREXEL (CLTPharm@parexel.com). Investigators may be requested to provide follow-up information concerning adverse events, including an evaluation of causality and seriousness. Reports of all AEs will be summarised in the study report. AEs analysed in this study will be specified using the appropriate level of the MedDRA classification.

ADRs for non-Study Sponsor products should be reported in accordance with local laws and regulations to the relevant Regulatory Authority and/or drug Marketing Authorisation Holder.

11.2.2 Reporting procedures for product complaints

Any product complaints related to CT-P10 or other Study Sponsor products identified during the course of the retrospective review shall be reported to PAREXEL (CLTPharm@parexel.com) by the Principal Investigator at each centre within three calendar days of discovery. Product complaints should be reported whether or not they are associated with an AE.

11.2.3 Reporting procedures for special situations

All special situations associated with CT-P10 or other Study Sponsor products should be reported to PAREXEL (CLTPharm@parexel.com) by the Principal Investigator at each centre within three calendar days of discovery. Special situations should be reported whether or not they are associated with an AE.

Reporting of non-compliance event data, concerning any use of CT-P10 or other Study Sponsor products that does not comply with the terms of the marketing authorisation, will be undertaken in line with local regulations in each country.

12. Plans for disseminating and communicating study results

Upon completion of the study, a full study report will be prepared documenting the

study methods, results and conclusions, supported by appropriate data tables and figures.

Upon completion of the report, it is intended that the results of this study may be presented at a relevant conference and/or submitted for publication in an appropriate peer reviewed medical journal. The study will be reported according to the requirements of STROBE (Strengthening the reporting of observational studies in epidemiology) as specified in the appropriate checklist for the study design (http://www.strobe-statement.org/index.php?id=available-checklists).

Authorship of publications arising from the study will follow the guidelines proposed by the International Committee of Medical Journal Editors (2015) (http://www.icmje.org/icmje-recommendations.pdf). All authors will meet the criteria for authorship, and all people who meet the criteria will be authors and all authors will agree to be accountable for the study. Potential conflicts of interest will be disclosed. All authors will have:

(1) made substantial contributions to conception or design or acquisition of data, or analysis and interpretation of data; AND

(2) participated in drafting the article or revising it critically for important intellectual content; AND

(3) approved the final version to be published.

Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author will have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title

Annex 2. ENCePP checklist for study protocols

A copy of the ENCePP Checklist for Study protocols available at http://www.encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.

Annex 3. Additional information: Infusion related reactions to be captured

The following adverse events are included in the definition of an infusion related reaction and will be captured in this study:

- Abdominal pain
- Anaphylactoid reaction
- Anaphylaxis
- Angina pectoris
- Angioneurotic oedema
- Asthenia
- Bronchospasm
- Cardiac arrhythmia
- Cardiac failure
- Chills/rigors
- Cyanosis
- Diarrhoea
- Dizziness
- Dyspnoea
- Erythema

- Fatigue
- Generalised oedema
- Headache
- Hot flush
- Hypersensitivity
- Hypertension
- Hypotension
- Laryngeal oedema
- Myocardial infarction
- Nausea
- Oropharyngeal pain
- Peripheral oedema
- Pruritus
- Pyrexia
- Rash
- Rhinitis
- Tachycardia
- Throat irritation
- Urticaria
- Vomiting
- Wheezing