PASS information

Title	Clinical effectiveness and safety of CT-P10 in patients with diffuse large B-cell lymphoma: an observational study in Europe
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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 clinical effectiveness and safety profile of CT-P10 treatment in patients with DLBCL in the real world clinical setting in Europe? **Primary research objective:** To describe the clinical effectiveness of CT-P10 for the treatment of DLBCL. **Secondary objectives:** To describe the following in patients who have received CT-P10 for the treatment of DLBCL: 1. Safety associated with CT-P10 treatment. 2. Demographic, clinical, and DLBCL disease characteristics. 3. Treatment patterns. **Sub-group analyses** • Clinical effectiveness and safety of rapidly infused CT-P10. • Clinical effectiveness and safety in patients switched from reference rituximab to CT-P10.
Country(-ies) of study	France, Germany, Italy, the Netherlands, Spain and the UK.
Authors	HeeJung Kang RPh., MScMed. Celltrion Healthcare Co., Ltd. Carly Rich Ph.D. pH Associates Ltd.

Marketing authorisation holder(s)

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PROTOCOL SIGNATURES

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TITLE:	Regional Medical Director
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NAME:	Ayman Farahat
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On behalf of the Chief Investigator, Professor Pier Luigi Zinzani:

I have carefully read this protocol entitled **"Clinical effectiveness and safety of CT-P10 in patients with diffuse large B-cell lymphoma: an observational 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:	

INVESTIGATOR APPROVAL SIGNATURE PAGE

On behalf of the Principal Investigator at each site:

I have carefully read this protocol entitled **"Clinical effectiveness and safety of CT-P10 in patients with diffuse large B-cell lymphoma: an observational 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.

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1. Table of contents

2. List of abbreviations and key definitions

2.1 Key definitions

Abbreviation	Definition
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse event
ASH	American Society of Haematology
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
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FL	Follicular lymphoma
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
IRR	Infusion-related reaction
IQR	Interquartile range
ISPE	International Society for Pharmacoepidemiology
LDH	Lactate dehydrogenase
NHL	Non-Hodgkin's lymphoma
PASS	Post Authorisation Safety Study
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure
UK	United Kingdom

2.2 Key definitions

- **Index date:** defined as the date of CT-P10 initiation.
- **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 DLBCL until the index date (to capture patient's demographic and clinical characteristics).
- **Post-index observation period:** patients will be observed for a period of 30 months after the index (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 Revised Response Criteria for Malignant Lymphoma (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 the revised response criteria for malignant lymphoma(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
Main protocol author(s)	HeeJung Kang RPh., MScMed. Celltrion Healthcare Co., Ltd. 4th Floor, 19 Academy-ro 51, Yeonsu-gu, Incheon South Korea Carly Rich Ph.D. pH Associates The Weighbridge, Brewery Courtyard, Marlow, Bucks, United Kingdom SL7 2FF
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Coordinating Investigator (Country 2)	To be confirmed once sites are recruited.

4. Abstract

Title
Clinical effectiveness and safety of CT-P10 in patients with diffuse large B-cell lymphoma: an observational study in Europe

Protocol version
2.0

Date of last version of protocol
18 April 2018

Rationale and background
Celltrion manufacture CT-P10, the first monoclonal antibody biosimilar version of rituximab to be approved by the European Medicines Agency (EMA) for the treatment of rheumatic diseases and specific blood cancers including NHL and CLL (4). In France, Germany, Italy, the Netherlands, Spain and the United Kingdom (UK) it is licensed as Truxima™ for intravenous use in adults with rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis, non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL).

Diffuse large B-cell lymphoma (DLBCL) represents 30 to 58% of NHL, with the crude incidence in Europe being 3.8 per 100,000 patient years (5). Patients with DLBCL are often treated with a combination of four chemotherapy drugs, plus rituximab immunotherapy, known by the acronym R-CHOP (6). Clinical similarity between CT-P10 and rituximab has been accepted by the EMA (7). It has been reported that the introduction of CT-P10 in Europe will be associated with significant budget savings, with the reallocation of such enabling more patients to access treatment (8). However, there are currently no studies investigating the effectiveness or safety of CT-P10 treatment in patients with DLBCL in the real world clinical setting. This study will therefore address this evidence gap by collecting real world data on the effectiveness and safety of CT-P10 treatment in patients with DLBCL in European countries.

Research question and objectives
Research question:
What is the clinical effectiveness and safety profile of CT-P10 treatment in patients with DLBCL in the real world clinical setting in Europe?

Primary research objective:
To describe the clinical effectiveness of CT-P10 for the treatment of DLBCL.

Secondary objectives:
To describe the following in patients who have received CT-P10 for the treatment of

DLBCL:

1. Safety associated with CT-P10 treatment.
2. Demographic, clinical, and DLBCL disease characteristics.
3. Treatment patterns.

Sub-group analyses

- Clinical effectiveness and safety of rapidly infused CT-P10.
- Clinical effectiveness and safety in patients switched from reference rituximab to CT-P10.

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 DLBCL who received treatment with CT-P10 in selected centres in six European countries. Patients will have been treated according to routine clinical practice and prescribed in accordance with the approved marketing authorization. Data will be collected retrospectively from the date of diagnosis of DLBCL until the index date (defined as the date of CT-P10 initiation), to capture patient's demographic and clinical characteristics, and for a period of 30 months post index (or until death, if sooner) to collect post initiation data on safety and effectiveness.

Population

Setting

Study sites will be specialist treatment centres or hospitals which routinely use CT-P10 in the treatment of patients with DLBCL, recruited from six European countries (the UK, Spain, France, Germany, the Netherlands and Italy). At least two centres will be included in each country.

Study population

The source population for this study is adult patients with DLBCL who received treatment with CT-P10 as part of their standard clinical care in six European countries.

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

- Patients with a confirmed diagnosis of DLBCL.
- Patients who had received CT-P10 for the treatment of DLBCL.
- Patients at least 18 years of age at the date of diagnosis of DLBCL.
- Patients (or next of kin, if applicable locally) providing written informed consent for study data collection (if this is required according to local country regulations).

- Patients with pre- index medical history data available and at least one clinical response assessment in the 30 months post-index (unless the patient is deceased).

Patients fulfilling any of the following criteria will be excluded from the study:
- Patients whose medical records are unavailable for review.

Variables
The primary endpoints for this study are as follows:
- Overall survival (OS), defined as the time from index until death from any cause.
- 12-, 18-, and 30- month survival rate following DLBCL diagnosis and following the index date.
- Progression free survival (PFS), defined as the time from index until the first documentation of disease progression or death from any cause.
- 12-, 18-, and 30- month PFS rate following DLBCL diagnosis and following the index date.
- Summary of best response to CT-P10.
- Time to complete or partial response, defined as the time from index until first documentation of complete or partial response by the local investigator.

The secondary endpoints for this study are described in detail in section 9.3~~8.3~~; these will include the following parameters for patients with DLBCL treated with CT-P10:
- IRR associated with CT-P10 on day 1 or day 2 post-index.
- Overall safety profile in the 30 months post-index date.
- Treatment patterns during the observation period.
- Patients' baseline demographic, clinical and 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
A target sample of 500 patients will be recruited for this study. This number of patients was determined to ensure a sufficient sample size to allow for key descriptive analyses to be representative of the sample population as a whole, whilst also taking into account recruitment feasibility.

Data analysis
For the primary endpoint analyses, the time-to-event clinical effectiveness endpoint analyses (OS, PFS, time to complete or partial response) will be displayed descriptively using Kaplan Meier plots. Survival rates for 12-, 18-, 30- months post DLBCL diagnosis will also be calculated**.**

For the secondary endpoint safety analyses, the frequency and proportion of patients who experience IRRs on day 1 or day 2 post index will be presented. For all other safety endpoints, rates of events per-patient-per month occuring during the 12-, 18-, and 30- months post index will be reported.

For the demographic, clinical, and DLBCL disease characteristics endpoint analyses, the study population will be described by means of summary statistics. Summary statistics will be displayed for the treatment dose and duration on treatment, and for the reasons for treatment discontinuation.

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
			None	

6. Milestones

Milestone	Planned date
Registration in the EU PAS register	Apr 2018
Start of data collection	May 2018
Interim analysis	Jul 2018
End of data collection	Dec 2020
Interim data presented at ASH 2018	Dec 2018
Interim data presented at ASH 2019	Dec 2019
Interim data presented at ASH 2020	Dec 2020
Final report of study results	Feb 2021

7. Rationale and background

Celltrion is the manufacturer of CT-P10, the first monoclonal antibody biosimilar of rituximab to be approved by the European Medicines Agency (EMA) for the treatment of rheumatic diseases and specific blood cancers including NHL and CLL (4). In France, Germany, Italy, the Netherlands, Spain and the United Kingdom (UK) it is licensed as Truxima™ for intravenous use in adults with rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis, non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL). Rituximab is a genetically engineered chimeric mouse/ human antibody directed at binding to CD20 located on the pre-B and mature B lymphocytes expressed in >95% of all B-cell NHL (9).

Diffuse large B-cell lymphoma (DLBCL) represents 30 to 58% of NHL, with the crude incidence in Europe being 3.8 per 100,000 patient years (5). The incidence increases with age and varies considerably across Europe (5). Although DLBCL is an aggressive cancer, advances in medicine have meant that the treatment options are provided with the intent to cure and in recent years there have been important survival improvements in patients with DLBCL in all European regions (10). Patients are often treated with a combination of four chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine & prednisolone), plus rituximab immunotherapy, known by the acronym R-CHOP (8). 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 (11–13).

Biosimilars such as CT-P10 are typically available at lower cost than the reference drug; therefore, they have the potential to reduce treatment costs and expand market competition forcing originator companies to revise their pricing policies and hence increase patient accessibility. It has been reported that the introduction of CT-P10 in Europe will be associated with significant budget savings, with the reallocation of such enabling more patients to access treatment (8). However, there are currently

no studies investigating the effectiveness or safety of CT-P10 treatment in patients with DLBCL in the real world clinical setting.

This study will therefore address this evidence gap by collecting real world data on the effectiveness and safety of CT-P10 treatment in patients with DLBCL in European countries. In so doing, it will provide physicians and healthcare providers with detailed information on the effectiveness and safety of CT-P10. This will enable them to make evidence-based decisions on the most effective treatment strategies in patients with DLBCL and to advise patients accordingly.

8. Research question and objectives

8.1 Research question:

What is the clinical effectiveness and safety profile of CT-P10 treatment in patients with DLBCL in the real world clinical setting?

8.2 Primary research objective:

To describe the clinical effectiveness of CT-P10 for the treatment of DLBCL.

8.3 Secondary objectives:

To describe the following in patients who have received CT-P10 for the treatment of DLBCL:

1. Safety associated with CT-P10 treatment.
2. Demographic, clinical, and DLBCL disease characteristics.
3. Treatment patterns.

Sub-group analyses

- Clinical effectiveness and safety of rapidly infused CT-P10.
- Clinical effectiveness and safety in patients switched from reference rituximab to CT-P10.

9. Research methods

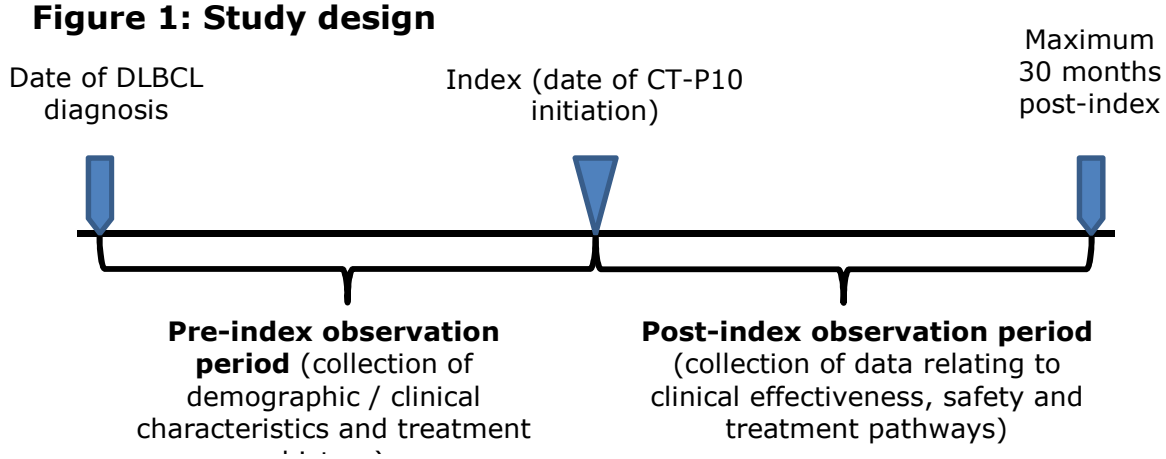
This study has been designed and will be conducted according to the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

(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 for patients with DLBCL who received treatment with CT-P10 in selected centres in six 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 DLBCL until the index date (defined as the date of CT-P10 initiation), to capture patient's demographic and clinical characteristics, and for 30 months post index (or until death, if sooner) to collect post-initiation data on safety and effectiveness (as shown in Figure 1). In cases where the full 30 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 30 months has elapsed.

Figure 1: Study design



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 outcomes (death, progression free survival and complete or partial response). Furthermore, it will enable the results of the study to be available in a timelier manner than would be possible with a prospective design.

9.2 Setting

9.2.1 Study population

The source population for this study is adult patients with DLBCL who received treatment with CT-P10 as part of their standard clinical care in six European countries.

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

- Patients with a confirmed diagnosis of DLBCL.
- Patients who had received CT-P10 for the treatment of DLBCL.
- Patients at least 18 years of age at the date of diagnosis of DLBCL.
- Patients (or next of kin, if applicable locally) providing written informed consent for study data collection (if this is required according to local country regulations).
- Patients with pre-index medical history data available and at least one clinical response assessment in the 30 months post-index (unless the patient is deceased).

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

- 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 six 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. Patients will be selected for inclusion in consecutive chronological order according to the index date, until the required sample size or the centre-specific recruitment target is reached. 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 30 month post-index observation period has elapsed.

Patients (or their next of kin, if appropriate locally) will be asked 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 from the date of diagnosis of DLBCL until the index date (defined as the date of CT-P10 initiation), to capture patient's demographic and clinical characteristics, and for 30 months post index (or until death, if sooner) to collect post initiation data on safety and effectiveness.

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 DLBCL, recruited from six European countries (France, Germany, Italy, the Netherlands, Spain and the UK). 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.

9.3 Variables

The exposure of interest in the present study is treatment with CT-P10. All study patients will be exposed by definition, as this is specified in the inclusion criteria.

The endpoints (outcomes) associated with each of the study objectives are described below, along with the variables that will be required 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 clinical effectiveness of CT-P10 for the treatment of DLBCL	
• OS, defined as the time from index until death from any cause. • 12-, 18-, and 30- month survival rate following DLBCL diagnosis and following the index date. • PFS, defined as the time from index until the first documented evidence of disease progression or death from any cause. • 12-, 18-, and 30- month PFS rate following DLBCL diagnosis and following the index date. • Summary of best response to CT-P10 (complete response / partial response / no response or stable disease / progressive disease). • Time to complete or partial response, defined as the time from index until first documentation of complete or partial response by the local investigator.	• Date of data collection. • Patient alive at 30 months post-index (Yes / No / Not known)? • If no, date of death (DD/MM/YYYY). • All treatment response assessments in the 30 months post-index (date, recorded treatment response [complete response / partial response / no response or stable disease / progressive disease], assessment based on the Revised Response Criteria for Malignant Lymphoma / local criteria / other criteria, types of assessments used to evaluate response. • Date (within 30 months post-index) of last recorded hospital visit.
Endpoint to address the secondary objective	**Variables required to address the secondary objective**
Secondary objective 1: To describe the safety profile of CT-P10 in patients with DLBCL in the 30 months post-index	
• Proportion of patients who experience an IRR* associated with CT-P10 on day 1 or day 2 post-index * IRR defined as any adverse event from a pre-defined list (see Annex 3) occurring on day 1 or day 2 post CT-P10	• Did IRR(s)* occur on day 1 or day 2 post-index (Yes/No)? • If YES, IRR description and date

• Proportion of patients receiving CT-P10 who experience the following safety events in the 30 months post-index, and frequency of each per patient per month:
  ○ Any IRR.
  ○ Any grade 3 or grade 4 IRRs (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
	For all AEs (temporally associated with CT-P10 treatment) during the 30 months post-index:
	• 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

(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	• AE/IRR resulted in treatment discontinuation (Yes/No)
Secondary objective 2: To describe the baseline demographic, clinical and disease characteristics of patients with DLBCL who receive treatment with CT-P10	
Demographic and clinical characteristics (at index date unless specified) • Summary measures of patients' age, sex, ethnicity, employment status, comorbidities (Charlson Comorbidity Index (14)), 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.	• Month and year of birth • Index date • Date of diagnosis of DLBCL • 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 • All relevant ongoing comorbidities at index date (components of Charlson Comorbidity Index will be captured) • All prior chemotherapy regimens and rituximab treatment for DLBCL from diagnosis of DLBCL until 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 index. • ECOG score at closest time point prior to index and date of assessment
DLBCL disease characteristics • Summary of age at diagnosis of DLBCL. • Summary distribution of DLBCL stage as documented (e.g. Lugano or Ann Arbor (I, II, III, IV) at diagnosis and at index date • Summary measures (at index) of: ○ International Prognostic Index (IPI) score for DLBCL (as documented or calculated from component parts) ○ 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 ○ Tumour bulk (largest tumour diameter) and total number of tumour sites	DLBCL disease characteristics: • Month and year of DLBCL diagnosis • DLBCL stage as documented (e.g. Lugano or Ann Arbor [I, II, III, IV]) 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): ○ IPI score ○ LDH ○ Haemoglobin ○ Presence of B symptoms ○ Bone marrow involvement ○ Largest tumour diameter and number of tumour sites ○ Number of extra-nodal sites

○ Extra-nodal status.	
Secondary objective 3: To describe treatment patterns in patients with DLBCL who receive treatment with CT-P10	
• Summary measures of the following CT-P10 treatment parameters: ○ Number of infusions ○ Duration of infusions ○ Starting and subsequent doses ○ Chemotherapy regimen given with CT-P10 (if applicable) and pre-medications received ○ Time on treatment ○ Reason why treatment was discontinued (if applicable) ○ Distribution of subsequent treatment regimens (after discontinuation of CT-P10)	• For CT-P10 treatment (in the 30 month post-index period): ○ Date of each infusion ○ Pre-medications given ○ Treatment doses given (actual and per m^2) ○ Duration of each infusion ○ Name of chemotherapy regimen given with CT-P10 ○ Treatment discontinuation date (the date of discontinuation will be defined as the date of the last dose / infusion) or ongoing. ○ 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). ○

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

A target sample of 500 patients will be recruited for this study. This number of patients was determined to ensure a sufficient sample size to allow for key descriptive analyses to be representative of the sample population as a whole, whilst also taking

into account recruitment feasibility.

500 patients are expected to be recruited into this study. Based upon past literature, it is probable that the proportion of patients surviving and experiencing progression-free survival over a maximum 30 month follow-up period will be in excess of 50%(15). In a European study, survival over 3 years between 2006-8 was 55.4% with this condition. Another study suggested that the % survival at 5 years for DLBCL patients between 2002 and 2012 was 59% with progression free survival at 51%. 95% confidence intervals for survival rates calculated for a sample size of 500 can be seen in the table below.

% Survival	95% Lower Confidence Limit	95% Upper Confidence Limit
5%	3.3%	7.3%
10%	7.5%	13.0%
15%	12.0%	18.4%
20%	16.6%	23.8%
25%	21.3%	29.0%
30%	26.0%	34.2%
35%	30.8%	39.4%
40%	35.7%	44.4%
45%	40.6%	49.5%
50%	45.5%	54.5%
55%	50.5%	59.4%
60%	55.6%	64.3%
65%	60.6%	69.2%
70%	65.8%	74.0%
75%	71.0%	78.7%
80%	76.2%	83.4%
85%	81.6%	88.0%
90%	87.0%	92.5%
95%	92.7%	96.7%

Given a survival rate over 3 years of around 55% and this sample size, confidence intervals between 50.5 and 59.4 would be expected, which should represent adequate precision to characterise this population.

If rates of progression-free survival were similar after 2.5 years the 51% according to a study by Rovira et al. (although this was taken over 5 years rather than 2.5 years), 95% confidence interval widths could range from 8.7 to about 9%. The expected

proportion of patients experiencing a complete response in this paper was about 75%, which could translate to a 95% confidence interval of between 71.0 and 78.7%.

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 standardized 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 and Good Clinical Practice (GCP) and has been globally used for complex interventional clinical trials. 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 analyses, the time-to-event clinical effectiveness endpoint analyses (OS, PFS, time to complete or partial response) will be displayed descriptively using

Kaplan Meier plots from the index event until the date of the event (or censoring, which will occur at the date of the last hospital visit [for OS, where patient is lost to follow-up], the date of data collection [for OS, where patient is known to be alive], the date of the last hospital visit at which the patient was known to be free from disease progression [for PFS], or the date of the last recorded known response [for time to complete or partial response]. Absolute counts and the percentages of these events will be reported. The proportion of patients assessed as having a best response of complete response, partial response, stable disease or progressive disease within the 12-, 18-, and 30- months post-index based the documented assessment of the local investigator will be presented with 95% CI. Survival rates for 12-, 18-, 30- months post DLBCL diagnosis will also be calculated.

9.7.2 Secondary analyses:

For the safety 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. For all other safety endpoints, rates of events per-patient-per month will be reported.

For the demographic, clinical, and DLBCL 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% confidence intervals (CI) will be presented for means and estimates of proportions, as appropriate.

Treatment patterns will be described for the entire study period. Summary statistics will be displayed for the treatment dose and duration on treatment, and for the reason for treatment discontinuation.

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

If numbers are sufficient, subgroup analyses may be conducted to further evaluate the clinical effectiveness and safety of CT-P10 in patients with DLBCL. These may include, but will not be limited to:

- Line of treatment CT-P10 initiated (1st, 2nd or 3rd)
- Infusion time for the second infusion (>90 minutes, 60-90 minutes, <60 minutes)
- Patients switched to CT-P10 from reference rituximab vs those treated with CT-P10 from initiation.

No sensitivity analyses are planned.

9.7.5 Interim analyses

If numbers are sufficient, interim analyses will be conducted on available data to enable submission of an abstract for the 2018 American Society of Haematology (ASH) Annual Meeting. Repeat interim analyses will be conducted for presentation at ASH 2019 and ASH 2020.

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 when data has been collected from at least one of the recruited study centres in each country. 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. No SDV is to be performed and this lack of SDV could impact on the quality of the data collected.
- Pseudonymised data provided for this study will be obtained from physicians and study sites that are willing to participate in the study. Therefore, study findings may not be generalisable to all patients with DLBCL treated with 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.

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 country-specific requirements. Where required, approval to conduct the study 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 in order to preserve patient confidentiality. 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 next of kin) will 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 two 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 report, the results of this non-interventional study will be submitted for publication at the 2018, 2019 and 2020 ASH annual conferences. 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.

A full study report will also be prepared documenting the study methods, results and conclusions, supported by appropriate data tables and figures.

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Annex 1. List of stand-alone documents

None

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