Title: An international, multi-centre, non-interventional retrospective study to describe treatment pathways, outcomes, and resource use in patients with classical Hodgkin lymphoma (B-HOLISTIC)

NCT Number: NCT03327571

Protocol Approve Date: 04 May 2017

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

Non-interventional study protocol

Short title: Classical Hodgkin lymphoma real world evidence study

Title: An international, multi-centre, non-interventional retrospective study to describe treatment pathways, outcomes, and resource use in patients with classical Hodgkin lymphoma (B-HOLISTIC)

Study ID: CHL-5001

Sponsor: Takeda Pharmaceuticals International AG
Thurgauerstrasse 130
8152 Glattpark-Opfikon (Zurich)
Switzerland

Study phase: Medical Affairs, Non-registration Company Sponsored (Observational)

Date of final version of protocol: 04 May 2017

1 Administrative information

1.1 Contacts

A separate contact information list will be provided to each site.

1.2 Approval

Representatives of Takeda

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- Guidelines for good pharmacoepidemiology practices (GPP).
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

PPD

2 Summary

Short title of study

B-CD30 + **HO**dgkin **L**ymphoma **I**nternational Multi-centre Retrospective **S**tudy of **T**reatment Pract**I**ces and Out**C**omes (B-HOLISTIC)

Study sites

The study will be conducted across 13 countries within the emerging markets region. The number of sites needed to achieve the required sample size will be determined based on local feasibility within each country.

Objectives

Primary objective:

To describe progression-free survival (PFS) in patients with relapsed or refractory classical Hodgkin lymphoma (RRHL), defined as the time from initiation of first treatment for RRHL to first documentation of relapse or disease progression, or death.

Secondary objectives:

To describe the following in two populations of patients with Hodgkin lymphoma (HL): in those receiving frontline treatment for high-risk stage IIb–IV classical Hodgkin lymphoma (cHL) (Group 1) and in those with RRHL (Group 2):

1. Patient demographic and clinical characteristics.
2. HL treatment pathways.
3. Clinical outcomes:
    a) Overall survival (OS).
    b) 1- and 5-year survival rates.

For each line of therapy:

    c) Best clinical response after completion of treatment, as defined by the International Working Group 2007 Revised Response Criteria for Malignant Lymphoma (1).
    d) Response duration.
    e) PFS (group 1).
4. The adverse events associated with each line of therapy.
5. The HL-related healthcare resource use associated with each line of therapy.
6. The HL-related healthcare costs associated with each line of therapy.

Methodology

An international, multi-centre, retrospective, observational research study to be conducted across 13 countries in the emerging markets region.

This will be a retrospective review of medical records of patients with a diagnosis of high-risk stage IIb–IV cHL who have received frontline treatment with chemotherapy +/- radiotherapy (Group 1), and of patients with a diagnosis of RRHL (Group 2).

Pseudonymised (anonymised-coded) data will be collected according to the agreed minimum dataset (see Appendix 1 and Table 4) using a standardised study case report form (CRF). A web-based electronic CRF will be employed.

Pseudonymised data from all participating centres and countries will be provided to the appointed contract research organisation (CRO) for pooled analysis and reporting.

Number of subjects

To take account of different population sizes, approximately 50–200 patients with cHL (Group 1) and 50–200 patients with RRHL (Group 2) will be included in the study in each participating country.

A sample of 50 patients will provide reasonably reliable country-level estimates of the mean and median PFS (for the primary endpoint), based on predicted confidence limits. Whilst it is hoped that each country will be able to include 100 patients in each group (approximately 1300 per group in total across all 13 countries) to allow description of PFS in different subgroups and for different treatments, it is recognised that this may not be possible in every country, and therefore oversampling may be performed in countries with larger populations of eligible patients to enable the overall sample to be achieved.

Diagnosis/disease/condition and main criteria for inclusion

Patients with cHL or RRHL who are managed in the participating centres and who meet the following eligibility criteria will be included in the study.

Inclusion criteria:

1. Patients newly diagnosed with high-risk stage IIb–IV cHL (for Group 1) or RRHL (for Group 2) between 01 January 2010 and 31 December 2013.
2. Age ≥18 years at diagnosis of cHL (Group 1) or RRHL (Group 2).
3. Alive or deceased.
4. Written informed consent is obtained for study data collection, where necessary, according to local regulations.

Exclusion criteria:

1. Patients for whom the minimum study dataset (see Appendix 1 and Table 4) is not available from their hospital medical records.
2. Patients who have participated in an interventional clinical trial at any stage of their cHL (Group 1) or RRHL (Group 2) management.

In each country, a geographically dispersed sample of sites from different settings (hospitals, cancer institutes, and academic medical centres) will be employed.

Duration of data collection per subject

For each patient included in the newly diagnosed cHL group (Group 1), data on treatments received for cHL and the associated adverse events and resource use will be collected from the date of cHL diagnosis until the date of first documented relapse or disease progression after frontline therapy. All relevant outcomes, including mortality, will be collected during the observation period until the date of death (or data collection, whichever occurs first).

For patients in the RRHL group (Group 2), a summary of treatments received prior to diagnosis of RRHL will be collected; detailed data on treatment pathways, clinical outcomes, adverse events, and resource use will be collected from the date of RRHL diagnosis until the death of the patient or the date of data collection (whichever occurs first).

In both groups, resource use data will be collected for periods when the patient is receiving active treatment for cHL or RRHL to enable the resource use [*and costs*] associated with each line of treatment to be determined.

Criteria for evaluation

Population descriptors:

Data will be collected in relation to practice location, subject gender, age, ethnicity, diagnosis and staging/subtype of disease, relevant clinical laboratory results/procedures, and comorbidities. See Section 9 (Table 4) for full list of variables.

Main outcome variables:

Data will be collected in relation to treatment pathways, clinical outcomes, and adverse events. See section 9 (Table 4) for full list of variables.

Health economics

Data will be collected in relation to HL-related resource use. The granularity and source of reference costs will be agreed at country level and will be detailed in the statistical analysis plan (SAP).

Statistical methods

Descriptive analyses will be conducted to summarize patient demographics and clinical characteristics, treatment patterns, clinical outcomes, and healthcare resource utilisation.

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3 List of abbreviations and definition of terms

Abbreviation	Definition
ABVD	Doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
Allo-SCT	Allogeneic haematopoietic stem cell transplantation
ASCT	Autologous stem cell transplantation
ASHAP	Doxorubicin (Adriamycin), methylprednisolone (Solu-Medrol), high-dose cytarabine (Ara-C), and cisplatin (platinum)
ASR	Age-standardized rate
BEACOPP	Bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone
BMT	Bone marrow transplant
BV	Brentuximab vedotin
CA	Competent authority
cHL	Classical Hodgkin lymphoma
ChlVPP	Chlorambucil, vinblastine, procarbazine, and prednisolone
CHOP	Cyclophosphamide, doxorubicin (hydroxydaunomycin), and vincristine (Oncovin), prednisolone
CI	Confidence interval
CL	Confidence limits
COPP	Cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone
CR	Complete remission
CRF	Case report form
CRO	Contract research organisation
CT	Computerised tomography
CVM	Carboplatin, vinblastine, and methotrexate
CVP	Cyclophosphamide, vincristine, and prednisolone
DHAC	Dexamethasone, doxorubicin (doxorubicin hydrochloride), cytarabine (Ara-C), and carboplatin
DHAP	Dexamethasone, high-dose cytarabine (Ara-C), and cisplatin (platinum)

DMP	Data management plan
EBV	Epstein–Barr virus
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ESHAP	Etoposide, methylprednisolone (Solu-Medrol), high-dose cytarabine (Ara-C), and cisplatin (platinum)
FDG	Fluorodeoxyglucose
GCO	Global Cancer Observatory
G-CSF	Granulocyte-colony stimulating factor
GDP	Gemcitabine, dexamethasone, cisplatin (platinum)
GEM-P	Gemcitabine, cisplatin, and methylprednisolone
GHSG	German Hodgkin Study Group
GPP	Good pharmacoepidemiology practices
HDI	Human development index
High-risk stage IIb–IV cHL	HL is staged using the Ann Arbor staging classification (2). Patients with stage IIb HL are classified as 'high risk' if they have a large mediastinal mass (measuring at least one-third of the transverse diameter of the thorax) or extranodal disease (any tumour spread involving other tissues than those of the lymph nodes, spleen, thymus, Waldeyer's tonsillar ring, appendix, and Peyer's patches)
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HRU	Healthcare resource utilization
ICE	Ifosfamide, carboplatin, and etoposide
ICE±R	Ifosfamide, carboplatin, and etoposide ± rituximab
ICU	Intensive care unit
ID	Identification
IEC	Independent Ethics Committee
IFRT	Involved-field radiotherapy
IGEV	Ifosfamide, gemcitabine, vinorelbine (and prednisolone)
INRT	Involved-node radiotherapy
IPS	International Prognostic Score
IRB	Institutional Review Board

ISRT	Involved-site radiotherapy
LCL	Lower confidence limit
LMIC	Low- and middle-income countries
LOC	Local operating country
MINE	Mesna, ifosfamide, mitoxantrone (Novantrone), and etoposide
MOPP	Mustine, vincristine (Oncovin), procarbazine, prednisolone
OPEC	Vincristine (Oncovin), prednisolone, etoposide, and chlorambucil
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PN	Peripheral neuropathy
PR	Partial remission
PSUR	Periodic safety update report
QA	Quality assurance
Risk factors for relapse	Risk factors for relapse are defined using the International Prognostic Score for newly diagnosed advanced stage cHL (3) and the Josting score for RRHL (4)
RR	Relative risk
RRHL	Relapsed or refractory classical Hodgkin lymphoma. RRHL includes patients with primary refractory HL (those who have failed to achieve a complete remission [CR] with frontline therapy or relapse within 3 months after end of frontline therapy) and patients with relapsed HL (those who have a recurrence >3 months after end of frontline treatment [early relapsers: recurrence within 3–12 months; late relapsers: recurrence >12 months])
RT	Radiotherapy
RWE	Real world evidence
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SCT	Stem cell transplantation

SD	Stable disease
SSR	Special situation report
Stanford V	Cyclophosphamide or ifosfamide, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisolone
StDev	Standard deviation
TB	Tuberculosis
TLFs	Tables, Listings, and Figures
UCL	Upper confidence limit

4 Introduction

Classical Hodgkin lymphoma (cHL) is the more common form of Hodgkin lymphoma (HL), characterised by the presence of Reed–Sternberg cells. The prevalence of all HL and hence cHL (which accounts for the majority of all HL cases) varies both between and within geographical regions, but the condition is typically more prevalent within economically developed countries. Global Cancer Observatory (GCO) data indicate that, in 2012, HL prevalence was four times higher in very high human development index (HDI) countries compared to those whose HDI was low (5). Despite the lower current prevalence of HL within developing countries, it is estimated by the GCO that, by 2030, there will be 12,392 incident cases and 5951 deaths within 10 emerging market countries alone (see Table 1 for list of countries). This amounts to a 16% increase in incident cases and a 39% increase in deaths since 2012 (5).

The incidence of HL by age also varies markedly according to countries' development status, such that, in developing countries, the incidence is higher in childhood and decreases with age, while in developed countries the opposite applies (6). This has led many observers to postulate that regional differences may reflect differences in aetiology, potentially owing to variation in exposure to common infectious agents. Indeed, researchers have found causal associations between serological markers of Epstein–Barr virus (EBV) infection and EBV-positive HL in young adults (relative risk [RR] 4.0; 95% confidence interval [CI] 3.4–4.5) (7). Others have noted that, as HL incidence varies between countries, so does exposure to EBV. In a dataset of 1566 HL patients, Glaser *et al.* found that patients who lived in developing countries were almost twice as likely to have EBV-positive HL compared to those who did not (63.4% versus 36%) (8). A higher incidence of HL has similarly been noted amongst those with AIDS-related immunosuppression: in a study linking AIDS and cancer registry data from 612 HL patients in the United States (US), the RR for HL among those with AIDS versus those without was 11.5 (95% CI 10.6–12.5) (9). In a study conducted amongst HL patients in South Africa, 46% were found to be HIV-positive (10). The authors argue that poor diagnostic capabilities and the absence of robust cancer registries in South Africa highlight the need to strengthen cancer registries in the region.

Table 1: Epidemiological data for HL in 13 emerging market countries

Country	Incidence per 100,000 ASR	Deaths per 100,000 ASR	Prevalence per 100,000 ASR	Male	Female
Argentina*	1.4	0.3	1.3	1.8	0.9
Australia*	1.7	0.2	2.3	2.5	2.1
China*	0.1	0.1	0.1	0.2	0.1
Colombia*	0.9	0.3	0.9	1.1	0.6
Hong Kong[Δ]	0.91	0.1	ND	ND	ND
Mexico*	1.3	0.5	1.2	1.4	1
Republic of Korea*	0.4	0.1	0.4	0.7	0.2
Russia*	1.8	0.6	1.8	2	1.7
Saudi Arabia*	1.6	0.8	1.3	1.4	1.1
Singapore*	0.9	0.1	0.8	1	0.6
South Africa*	0.9	0.3	0.8	1	0.6
Taiwan	ND	ND	ND	ND	ND
Turkey*	2.1	1.1	1.9	2.6	1.2
Average	1.27	0.43	1.24	1.5	0.99

* Data from Global Cancer Observatory (5)

Δ 2012 Data from Hong Kong Cancer Registry Cancer Statistics Query System (11)

ND, no data available; ASR, age-standardised rate.

Although once considered incurable, the prognosis for patients with cHL has improved markedly over recent decades. Today over 80% of newly diagnosed patients can be cured following treatment with chemotherapy either with, or without, involved-field radiotherapy (IFRT) (12). However, this improvement in patient outcomes is largely attributable to the outputs of several American and European cooperative study groups (13,14), as well as to notable improvements in salvage treatments for relapsed or refractory classical HL (RRHL). These include high-dose chemotherapy, autologous stem cell transplantation (ASCT) (15–17), and targeted biological therapies (18). Despite these notable improvements in the standard of care, approximately 5–10% of cHL patients treated in economically developed countries are refractory to initial treatment, and a further 10–30% relapse following an initial positive response (12,15,19). High-quality, population-based, data concerning the underlying patterns of incidence and survival of HL are limited (20) or primarily derived from within

North America (21), western European study populations (20,22), or from developed emerging market countries such as Japan (23) and Australia (24). Population-based data from within emerging markets are scarce or are largely historical. Although global incidence, prevalence, and mortality data are available for most emerging market countries and types of cancer (GLOBOCAN & Global Cancer Observatory), these data are of variable quality and are limited to descriptive epidemiological parameters without linkage of interventional data to patient outcomes (5,25).

Although various real world evidence (RWE) studies have been conducted within emerging market countries, these are typically small hospital-based studies that yield little, if any, generalisable results (16,26–28). As such, RWE on treatment patterns, clinical outcomes, and healthcare resource utilization (HRU) within the emerging market countries is limited. There have been very few RWE studies concerning RRHL and, of those that have been reported, most were conducted in Australia (29,30) or Turkey (18,31,32). With the exception of one multi-centre study (18), the remainder of these studies were one- or two-centre studies with limited sample sizes. While studies of this type generate detailed patient information, there remains a need for RWE, generated at the national level in emerging market countries, that would allow payers and policy-makers to more effectively plan for and deliver national services and to evaluate the impact of treatment interventions for cHL in real world clinical context. These limitations appear all the more relevant given that most randomised trials in oncology are conducted in socioeconomically advantaged subgroups of younger Caucasian patients with fewer comorbidities (33). Owing to potential environmental and patient-related differences between regions, extrapolation of these data from developed countries to emerging markets may be problematic (34). There are several national cancer registries that provide basic epidemiological data relating to HL in various emerging market regions, including Central and Southern America (35), South Africa (36), Taiwan (37), Singapore (38), and Turkey (39). However, as is commonplace with registry studies, individual level data concerning stage of disease, HRU, access to treatments, and outcomes are lacking.

GCO data reveal no significant difference in HL-related mortality rates between developed and developing countries (5). This is unexpected given that patients residing within low- and middle-income countries (LMICs) may have limited access to cancer care services. While first-line chemotherapy regimens for HL are widely available, with reimbursement approval in most emerging market countries (see Table 2), the same may not be true for treatments for RRHL. Anecdotal evidence suggests that in certain LMICs (e.g. Mexico (40) and Argentina (41)), access to autologous and allogeneic stem cell transplants may be extremely limited.

Table 2: **Access to HL treatment within 13 emerging market countries** (42)[1]

Country	HL therapies with regulatory approval	HL therapies with funding/reimbursement approval
Argentina	ABVD, BEACOPP, DHAP, ICE, MINE, RT	ABVD, BEACOPP, DHAP, ICE, MINE, RT
Australia	ABVD, BEACOPP, BV, ChIVPP, COPP, cyclophosphamide, DHAP, ICE±R, MINE, MOPP, RT, Stanford V, SCT	ABVD, BEACOPP, BV, ChIVPP, COPP, cyclophosphamide, DHAP, ICE±R, MINE, Stanford V
China	ABVD, BEACOPP, DHAP, ICE, MINE, RT	ABVD, BEACOPP, DHAP
Colombia	ABVD, BEACOPP, BV, DHAP, ESHAP, ICE, MINE, RT	ABVD, DHAP, ESHAP
Hong Kong	ND	ND
Mexico	ABVD, BEACOPP, DHAP, ICE, MINE, RT	ABVD, BEACOPP, DHAP, ICE
Republic of Korea	ND	ND
Russia	ABVD, BEACOPP, DHAP, ICE, MINE, RT	ABVD, BEACOPP, DHAP, ICE
Saudi Arabia	ND	ND
Singapore	ABVD, ASHAP, BEACOPP, BV, DHAP, ICE, MINE, RT	ABVD, BEACOPP, DHAP
South Africa	ABVD, ASHAP, BEACOPP, CHOP, CVP, cyclophosphamide, DHAP, ESHAP, GDP, GEM-P, ICE, IGEV, MINE, RT, SCT	**Private health insurance for:** ABVD, ASHAP, BEACOPP, ChIVPP, CVM, cyclophosphamide, DHAC, DHAP, ESHAP, GDP, GEM-P, ICE, IGEV, MINE, OPEC, RT, SCT **Government partially funds/reimburses:** ABVD, BEACOPP
Taiwan	ND	ND
Turkey	ABVD, BEACOPP, DHAP, ICE, MINE, RT	ABVD, BEACOPP

ND, no data available.

[1] Real time data are accessible at http://www.lymphomacoalition.org/lcinfo/globalTherapy.php

In view of the current lack of RWE from countries outside Europe and North America, the data collected in this study will be used to describe how patients with high-risk stage IIb–IV cHL and RRHL are treated across different countries in the emerging markets region and the associated clinical outcomes. This will contribute to a greater understanding of current treatment patterns, which will help to inform future clinical decision-making in these countries.

There is a particular need for RWE on clinical outcomes for patients treated after ASCT relapse and in patients with RRHL who are not eligible for ASCT. Currently, the treatment of these patient groups is thought to be unstandardised and likely to vary not only between countries but from one centre to another within a country. This study will describe how patients are treated across regional and geographical boundaries in emerging market countries, and the clinical outcomes associated with treatment.

The study will also provide evidence of the resource use associated with different treatment options, which will be of interest to funding and reimbursement bodies.

5 Study objective(s)

Primary objective:

To describe progression-free survival (PFS) in patients with RRHL, defined as the time from initiation of first treatment for RRHL to first documentation of relapse or disease progression or death.

Secondary objectives:

To describe the following in two populations of patients with HL: in those receiving frontline treatment for high-risk stage IIb–IV cHL (Group 1) and in those with RRHL (Group 2):

1. Patient demographic and clinical characteristics (including known risk factors for relapse, prior therapies, and clinical staging).
2. HL treatment pathways (treatments and treatment sequences received for cHL or RRHL and imaging tests used to evaluate response).
3. Clinical outcomes:
   a) Overall survival (OS).
   b) 1- and 5-year survival rates.

   For each line of therapy:
   c) Best clinical response after completion of treatment, as defined by the International Working Group 2007 Revised Response Criteria for Malignant Lymphoma (1).
   d) Response duration.
   e) PFS (group 1).
4. The adverse events associated with each line of therapy.

5. The HL-related healthcare resource use associated with each line of therapy.
6. The HL-related healthcare costs associated with each line of therapy[†].

[†]It is expected that all participating countries will collect data on patient characteristics, treatment pathways, clinical outcomes, adverse events, and resource use (for the primary objective and secondary objectives 1–5). Allocation of costs (for secondary objective 6) is optional. Sections of the protocol that relate specifically to secondary objective 6 are shown in italics and may be deleted if the country is not participating in this part of the study.

6 Study administrative structure

Takeda Pharmaceuticals International is the sponsor of this non-interventional study, and will engage the services of a contract research organisation (CRO) to operationalise the study globally. Takeda Pharmaceuticals International will retain overall responsibility for the study, but will delegate tasks as necessary to the CRO. A core protocol will be provided to the CRO, and they will be expected to identify/recruit study sites and manage subject recruitment. The data collection will be carried out by the local hospital staff. The appointed CRO will train the data collectors and provide support with data query management. Pseudonymised data from all participating centres and countries will be provided to the CRO for pooled analysis and reporting.

6.1 Study sites

The plan is that the study will be conducted in approximately 100 sites across 13 countries within the emerging markets region (Argentina, Australia, China, Colombia, Hong Kong, Mexico, Republic of Korea, Russia, Saudi Arabia, Singapore, South Africa, Taiwan, and Turkey). Sites in each country will be identified by the CRO in consultation with Takeda, ideally using a national database (where this is available) and will be pre-screened for eligibility using a customised feasibility questionnaire. Sites will be selected on the basis that:

- They are specialist lymphoma treatment centres.
- They have access to data throughout the whole patient pathway (either direct or through collaboration with previous treatment centres, including transplant centres).
- There are appropriate and sufficient personnel available for abstracting medical records and data collection internally (after receiving appropriate training).
- They have a means to identify eligible patients robustly and systematically for the study (database, department records or equivalent).
- Adequate numbers of eligible patients are available for inclusion in the study (minimum 5–10 patients in the RRHL group).

In each participating country, a geographically dispersed sample of sites from different settings (hospitals, cancer institutes, and academic medical centres) will be included. The number of sites needed to achieve the required sample size and obtain good geographic coverage will vary between the participating countries; this will be determined by the CRO (in

consultation with Takeda), depending on the number, size, and geographic spread of potentially eligible study sites in each country.

Global Research will keep a record of the individuals responsible for each participating Study Site, the Site Responsibles.

6.2 Sponsor personnel

Takeda local operating country (LOC) will keep a record of all relevant sponsor personnel.

6.3 Contract research organisation

The CRO will keep a record of all involved CRO personnel involved in any aspect of the study, e.g. site selection, study startup, data collection, query management, safety reporting, analysis, and study reporting.

6.4 Essential documents

The following essential documents must be received by Global Research before the study is initiated at a site:

- Written agreement between Takeda and/or the CRO and the Study Site as locally applicable.
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible.
- Subject information sheet and informed consent form in local language (notified to/approved by Independent Ethics Committees [IECs]/Institutional Review Boards [IRBs] as locally required).
- Written IEC/IRB approval/vote according to local regulations.
- Authority approval according to local regulations.
- Local insurance certificate as applicable.

7 Ethics

This study is an observational study where the existence of the study has no impact on the subject except for collection of informed consent (where required as per country regulations) to use of the subject's data.

7.1 Ethical conduct of the study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki (43), good pharmacoepidemiology practices (GPP) (44), ISPE GPP guideline, and any local regulations. Special attention will be paid to data protection. The CRO will ensure adherence to any country-specific requirements for data protection.

Takeda/the appointed CRO will ensure that the protocol, any amendments, and the subject information sheet/informed consent form are submitted to the relevant IECs/IRBs according to local requirements.

As the sponsor, Takeda is responsible for meeting the ICH requirement for yearly updates to the IECs/IRBs, if applicable.

7.2 Independent Ethics Committee/Institutional Review Board and Authorities

Independent Ethics Committee/Institutional Review Board

According to applicable regulations, the appointed CRO or the Site Study Responsible will:

- Notify or obtain approval from the relevant IEC/IRB of the protocol, any amendments, and the subject information sheet/informed consent form.

The appointed CRO or the Site Study Responsible will submit required documents to the IEC/IRB, such as:

- Periodic updates on the progress of the study.
- Notification of the end of the study.
- A summary of the study results.

Global Research will keep an updated list of all submission and approval dates of all documents submitted to the IEC/IRB and will provide the Site Responsible with a copy of this list. Copies of the documents will be distributed upon request.

Authorities

Global Research or the appointed CRO will send required documents to the competent authority (CA) and/or other national or regional authorities. Global Research will keep an updated list of submission and approval dates and a copy of all documents submitted.

7.3 Subject information and written informed consent

Eligible patients will be approached to provide written informed consent for their medical records to be reviewed for study data collection (if this is required by local laws and regulations).

The Site Study Responsible must give the subject (and, if applicable, parent or legal guardian) oral and written information about the study in a form that the subject (parent or legal guardian) can understand, and obtain the subject's (and, if applicable, the subject's assent and the parent's or legal guardian's) written consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the subject (and, if applicable, parent or legal guardian) must be left with ample time to consider and to pose questions. Since the study is observational the consent only concerns the data collection per se and is not consent to any interventional procedure or treatment.

The subject must agree that sponsor personnel, their representatives, or IEC/IRB or CA personnel (national or other) may require direct access to the subject's data/personal records that were collected, processed, and stored in an anonymous form.

The subject must agree that his/her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g. other companies or authorities, that may be located in other countries with potentially different regulations for data.

The subject or legal guardian, if applicable, has the right to withdraw his/her consent at any time without prejudice. In the informed consent form it is stated that, if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original, signed informed consent forms must be kept on the Site.

For details, see the subject information sheet and informed consent form.

8 Study design and plan

This study is a 'non-interventional study' as defined in: G-STND-PV-006, Directive 2001/20/EC (45), and will follow the guidelines for GPP (44).

This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the subjects.
- Epidemiological methods shall be used for the analysis of collected data.

The study is an international, multi-centre, retrospective observational research study involving retrospective review of medical records (paper and/or electronic, as applicable locally) of patients with a diagnosis of high-risk stage IIb–IV cHL who have received frontline treatment with chemotherapy with or without radiotherapy (Group 1) and/or patients with a diagnosis of RRHL (Group 2). Patients who are diagnosed with high-risk stage IIb–IV classical HL and/or RRHL between 2010 and 2013 will be included.

Pseudonymised data will be collected according to the agreed minimum dataset (see Appendix 1 and Table 4) using a standardised study case report form (CRF). Key variables will include those related to patient characteristics, diagnosis, treatment information, resource use, clinical outcomes, and adverse events.

A web-based electronic CRF will be employed.

For each patient included in the newly diagnosed cHL group (Group 1), data on treatments received for cHL and the associated adverse events and resource use will be collected from the date of cHL diagnosis until the date of first documented relapse or disease progression after frontline therapy. Patients will continue to be observed until the date of death (or data collection, whichever occurs first) for collection of overall survival data.

For patients in the RRHL group (Group 2), a summary of treatments received prior to diagnosis of RRHL will be collected; detailed data on treatment pathways, clinical outcomes, adverse events, and resource use will be collected from the date of RRHL diagnosis until the death of the patient or the date of data collection (whichever occurs first).

In both groups, resource use data will be collected for periods when the patient is receiving active treatment for cHL or RRHL, to enable the resource use [*and costs*] associated with each line of treatment to be determined.

The data collection will be carried out by local hospital staff. The appointed CRO will provide support with data query management. Pseudonymised data from all participating centres and countries will be provided to the CRO for pooled analysis and reporting.

It is expected that data collection for the study will last approximately 12 months.

8.1 Study schedule

The study report should be signed within 12 months after the collection of the last datapoint.

Global Research will ensure that end-of-study notification is submitted to the concerned authorities and IEC/IRB for each site, for each country, and for the complete study, as locally required.

Global Research will ensure that results are posted on 'clinicaltrials.gov' and as required by local authorities.

Based on upcoming knowledge, Takeda might choose to terminate the study prematurely. In such case the Committee(s), study sites, IECs/IRBs, and authorities will be informed promptly.

8.2 Discussion of study design

A retrospective chart review is an appropriate and scientifically robust method of collecting data that currently exists in patients' medical records. By including both living and deceased patients, bias of excluding patients with more severe disease is avoided.

Including 13 countries in the study with multiple sites in each country ensures a geographically dispersed sample of sites from different settings (hospitals, cancer institutes, and academic medical centres) is included, which ensures the data is representative of the emerging markets region.

A prospective study design would not be practical with this patient population owing to the relatively low incidence of HL in some emerging markets countries and the length of follow-up that would be required to determine the study endpoints. The sampling period chosen for this study provides a relatively recent review of clinical practice while also providing sufficient follow-up for the PFS and OS endpoints.

Study limitations:

- Patients may have received some or part of their treatment in outlying hospitals separate from the participating centres, and the available summary of treatment

received there may not be as detailed as that from the participating hospital itself. This may limit the completeness of the details of treatment reported in the study results.

- Retrospective studies rely on the quality of the data routinely recorded in patients' medical records; it is acknowledged that not all of the data fields will be available for every patient.
- The data collected will represent the practices of individual physicians/centres and may vary with non-participating physicians (e.g. those who refused study participation, failed to complete the study requirements on time and were excluded from the study, or were unresponsive to the screening invitation). Patients of non-participating physicians may have profiles, treatments, and outcomes that differ from those of study patients; thus, the generalisability of study results may be limited.
- Adverse events are likely to be underreported or underdocumented in a routine clinical setting compared to what would be expected from a controlled trial or prospective study.
- Assessment of treatment response may be different in a routine clinical setting as compared to the monitoring that would be expected in a controlled trial setting or prospective study.
- Within each country's sample of 50–200 patients with RRHL, the number of patients who relapse after ASCT, and who receive each treatment option after ASCT relapse, may be small, limiting the possibility of subgroup analyses related to ASCT.
- The definition of completion of therapy will differ based on country, therapy, and local guidelines.
- The sampling period for the study (2010–2013) and consecutive selection of patients according to the date of cHL or RRHL diagnosis was chosen to provide sufficient follow-up for the PFS and OS endpoints. However, it is acknowledged that this may bias the data collection towards older practices, especially in centres where there are many eligible patients.

8.3 Selection of study population

To take account of different population sizes, approximately 50–200 patients with cHL (Group 1) and 50–200 patients with RRHL (Group 2) will be included in the study in each participating country.

Patients will be identified at each centre using hospital central management information systems, local department databases, pharmacy databases, or multidisciplinary team records (as applicable locally), and screened for eligibility by a member of the direct care team at each site. Physicians will be asked to select patients for inclusion in the study, according to study-specific inclusion/exclusion criteria (see below) consecutively, according to the date of cHL or RRHL diagnosis, until the target sample size has been met. Written informed consent will be obtained from each patient prior to participation (where required by local regulations).

Inclusion criteria:

1. Patients newly diagnosed with high-risk stage IIb–IV cHL (for Group 1) or RRHL (for Group 2) between 01 January 2010 and 31st December 2013.
2. Age ≥18 years at diagnosis of cHL (Group 1) or RRHL (Group 2).
3. Alive or deceased.
4. Written informed consent is obtained for study data collection, where necessary according to local regulations.

Exclusion criteria:

1. Patients for whom the minimum study dataset (see Appendix 1 and) is not available from their hospital medical records.
2. Patients who have participated in an interventional clinical trial at any stage of their cHL (Group 1) or RRHL (Group 2) management.

A minimum of 50 patients in each group is required to give reasonably reliable country-level estimates of the mean and median PFS (see Section 12.3). Whilst it is hoped that each country will be able to include 100 patients in each group (approximately 1300 per group in total across all 13 countries) to allow description of PFS in different subgroups and for different treatments, it is recognized that this may not be possible in every country, and therefore oversampling may be performed in countries with larger populations of eligible patients to enable the overall sample to be achieved.

The maximum number of patients to be collected in any one country will be determined by the CRO in consultation with Takeda, which will monitor recruitment on an ongoing basis and notify sites when patient recruitment should cease.

The number of patients to be collected at each site (including site-specific recruitment targets and maximum number of patients per site) will also be decided by the CRO, in consultation with Takeda depending on the size of the local patient population and expected number of eligible patients. Patients diagnosed with high-risk stage IIb–IV cHL between 2010 and 2013, who are subsequently diagnosed with RRHL, can be included in both groups, provided that the RRHL diagnosis was also between 2010 and 2013. Examples of study eligibility are shown in Table 3.

Table 3: Patient eligibility for study Group 1 (cHL) and Group 2 (RRHL) – examples

Example	Date of HL diagnosis	Date of RRHL diagnosis	Study eligibility
1	01 March 2013	01 March 2014	Include in cHL group (Group 1) only
2	01 May 2008	01 May 2010	Include in RRHL group (Group 2) only
3	01 February 2011	01 February 2013	Include in both cHL and RRHL groups
4	01 November 2009	01 November 2014	Exclude – patient not eligible

8.4 Treatments

Non-interventional/observational – no treatments/pharmacotherapy are required as part of this study.

9 Conduct

Written informed consent will be obtained prior to any patient-specific data collection, where this is required according to country regulations. The patient level data to be collected from the medical records is shown in Table 4 below.

Table 4: Variables and data

Minimum dataset indicated by * and ***bold, underlined text*** and is also provided in Appendix 1.

Variables	Patients diagnosed with high-risk stage IIb–IV cHL between 01 January 2010 and 31 December 2013, who received frontline treatment with chemotherapy ± radiotherapy (Group 1)	Patients diagnosed with RRHL between 01 January 2010 and 31 December 2013 (Group 2)
Patient and disease characteristics	• ***Practice location (country)**** • ***Gender**** • ***Month and year of birth**** • ***Date of cHL diagnosis**** • Ethnicity • ***Clinical stage at diagnosis**** • Body weight at diagnosis • Histological subtype of cHL • Albumin at diagnosis (g/L) • White blood cell count at diagnosis ($\times 10^9$/L) • Haemoglobin at diagnosis (g/L) • Lymphocyte count ($\times 10^9$/L and percentage of differential) at diagnosis • Presence of B symptoms (Yes/No) at diagnosis • Relevant comorbid conditions (lung disease [including tuberculosis, TB], cardiovascular disease, human immunodeficiency virus [HIV], hepatitis B and C) • Positron emission tomography (PET)/computerised tomography (CT) scan results • ***Date of most recent follow-up/contact****	• ***Practice location (country)**** • ***Gender**** • ***Month and year of birth**** • ***Date of HL and RRHL diagnosis**** • Histological subtype of cHL • ***Date of start and end of frontline treatment**** • ***Date of first relapse after start of frontline treatment (date of scan confirming relapse)**** • Ethnicity • Body weight at first diagnosis and at relapse • Prior therapies for HL (***including frontline**** and pre-relapse) • Clinical stage at first diagnosis and at relapse • Presence of B symptoms (Yes/No) at diagnosis • Haemoglobin at relapse (g/L) • Relevant comorbid conditions (lung disease [including TB], cardiovascular disease, HIV, hepatitis B and C) • ***Date of most recent follow-up/contact****

Treatment pathways	Details of treatments received for cHL from the date of diagnosis until the date of first documented relapse or disease progression after frontline therapy
	
	For frontline treatment and each subsequent line of treatment:
	• ***Treatment modality (chemotherapy, RT, chemotherapy + RT, other treatment [specify])****
	• Clinical stage at initiation
	• ***Start and end dates****
	• ***Therapy regimen****
	• Total doses/cycles administered
	• For RT:
	  ○ ***Type (whole body, IFRT, ISRT, INRT, other)****
	  ○ ***Anatomical site****
	  ○ Number of fractions
	  ○ Total dose
	  ○ Whether given as pre-planned frontline treatment or for residual FDG-avid disease
	
	PET/CT scan details (from date of cHL diagnosis until date of first documented relapse or disease progression after frontline therapy):
	• ***Dates****
	• Deauville rating (1–5)
	• ***Response category recorded (complete remission [CR], partial remission [PR], stable disease [SD], progressive disease [PD])****
		ASCT eligibility details:
		• Considered eligible for ASCT (Yes/No)
		• If no, reasons for ASCT ineligibility (advanced age, comorbid conditions, chemoresistant disease, cumulative toxicities, other)
		• If patient initially considered ineligible for ASCT (due to chemoresistant disease), did they subsequently become eligible? (Yes/No)
		• ***Was ASCT undertaken (Yes/No)****
		• Reasons ASCT not undertaken, if patient eligible (patient refusal, inability to mobilise stem cells, loss of response to chemotherapy, toxicity, other)
		
		Details of treatments received for RRHL from the date of RRHL diagnosis until the date of the patient's death or the date of data collection (whichever occurs first)
		
		For each line of treatment:
		
		• ***Treatment modality (chemotherapy, RT, chemotherapy + RT, ASCT, allo-SCT, other treatment [specify])****
		• Clinical stage at initiation
		• ***Start and end dates****
		• ***Therapy regimen****
		• Total doses/cycles administered
		• Palliative treatment (Yes/No)
		• For RT:
		  ○ ***Type (whole body, IFRT, ISRT, INRT,***

		other)* ○ ***Anatomical site**** ○ Number of fractions ○ Total dose ○ Intent of treatment (obliterate single site of bulky disease as part of original treatment plan/control of disease when other treatments have failed) • For ASCT: ○ Salvage regimen ○ Chemotherapy conditioning regimens used ○ Source of ASCT (bone marrow/peripheral) ○ CD34+ count administered ○ Presence of known risk factor for ASCT relapse (time to first relapse ≤3 months/<12 months, stage IV disease at relapse, bulky disease ≥5 cm at relapse, extranodal disease, inadequate response to salvage chemotherapy (<PR or PET positivity at end of salvage therapy), performance status (ECOG) ≥1) • For allo-SCT: ○ Type of allo-SCT (matched, related, unrelated) PET/CT scan details (from date of RRHL diagnosis until date of the patient's death or the date of data collection (whichever occurs first): • ***Dates**** • Deauville rating (1–5)

		• ***Response category recorded (CR, PR, SD, PD)******
Clinical outcomes	***Occurrence of relapse/disease progression after start of frontline treatment (Yes/No)**** ***Date of first documented relapse or disease progression after start of frontline therapy**** ***Date*** and cause ***of death****, if patient died (HL-related/adverse event/treatment-related/other) Assessments of response to frontline therapy: • ***Date of assessment**** • ***Response (CR, PR, SD, PD)****	All ***date(s) of documented relapse or disease progression during the study observation period** ***Date*** and cause ***of death****, if patient died (HL-related/adverse event/treatment-related/other) Assessments of response to each line of therapy (including ASCT, each treatment received by non-ASCT patients, and each post-ASCT treatment regimen): • ***Date of assessment**** • ***Response (CR, PR, SD, PD)****
Adverse events	Adverse events during frontline HL treatment: • Date • Description • Clinician assessment of treatment-related/unrelated • Type (serious/non-serious)	Adverse events during each therapy (including ASCT, each treatment received by non-ASCT patients, and each post-ASCT treatment regimen): • Date • Description • Clinician assessment of treatment-related/unrelated • Type (serious [as previously defined]/non-serious)
HL-related resource use	From start of frontline treatment until date of first documented relapse or disease progression after frontline treatment. Only for periods when the patient is receiving active treatment for HL. For each type of resource, indicate (Yes/No) whether visit was for adverse event management	From the date of RRHL diagnosis until the date of the patient's death or the date of data collection (whichever occurs first) Only for periods when the patient is receiving active treatment for RRHL. For each type of resource, indicate (Yes/No) whether visit was for adverse event management

	Inpatient hospital admissions with overnight stay: • Admission and discharge dates • Elective or emergency • Reason for admission • Length of stay (overall and by unit/ward – general, high dependency/intermediate, intensive care unit [ICU], bone marrow transplant [BMT] unit) Emergency room visits: • Visit dates Outpatient visits: • Visit dates • New appointment or follow-up • Healthcare professional seen • Face-to-face or telephone Scans and procedures: • Date of scan or procedure • Scan or procedure type RT episodes: • Episode dates Treatment with granulocyte-colony stimulating factor (G-CSF) or other high cost medicines (to be defined): • Start and stop dates • Name of treatment • Dose	Inpatient hospital admissions with overnight stay: • Admission and discharge dates • Elective or emergency • Reason for admission • Length of stay (overall and by unit/ward – general, high dependency/intermediate, ICU, BMT unit) Emergency room visits: • Visit dates Outpatient visits: • Visit dates • New appointment or follow-up • Healthcare professional seen • Face-to-face or telephone Scans and procedures: • Date of scan or procedure • Scan or procedure type RT episodes: • Episode dates Treatment with G-CSF or other high cost medicines (to be defined): • Start and stop dates • Name of treatment • Dose

	• For G-CSF, specify whether pegylated (Yes/No)	• For G-CSF, specify whether pegylated (Yes/No)
HL-related costs	*The granularity and source of costs will be agreed at country level and will be detailed in the SAP*	*The granularity and source of costs will be agreed at country level and will be detailed in the SAP*

10 Safety reporting

10.1 Definitions

Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, a new disease, or worsening in severity or frequency of a concomitant disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse drug reaction

An ADR is any response to a medicinal product that is noxious and unintended and that occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of diseases or for the restoration, correction, or modification of physiological function.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses, or abuse).

As this study is a secondary analysis of medical records, an AE will only be considered as an ADR if there is an explicit statement in the medical record that the adverse event was caused by the medicinal product.

Special situation reports and product quality issues

A special situation report (SSR) includes any of the following events:

- Pregnancy: any case in which a pregnancy patient is exposed to a Takeda product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: infant exposure from breast milk.
- Overdose: all information of any accidental or intentional overdose.
- Drug abuse, misuse, or medication error: all information on medicinal product abuse, misuse, or medication error (potential or actual).
- Suspected transmission of an infectious agent: all information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda product.

- Occupational exposure.
- Use outside the terms of the marketing authorisation, also known as 'off-label'.
- Use of falsified medicinal product.

A Product Quality Issue refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labelling, or design of the product.

10.2 Classifications

Seriousness

A serious ADR or AE (SADR/SAE) is any ADR or AE which results in death, is life-threatening, requires inpatient hospitalisation, or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Life-threatening in this context refers to a reaction/event in which the subject was at risk of death at the time of the reaction/event. It does not refer to a reaction/event that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation, but which might jeopardise the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation, or development of dependency or abuse.

Any suspected transmission of an infectious agent via a medicinal product is considered a serious adverse reaction.

Causality

- Related: A reasonable temporal relationship between the medicinal product administration and the event where there is no other obvious explanation for the occurrence of the event.
- Not related: There is evidence for (an) alternative explanation(s) for the event, e.g. the event is explained by one or more of the following: a) the subject's medical condition (medical history, disease progress, indication); b) a concomitant medication for which the event is labelled; or c) AE occurrence prior to the introduction of the medicinal product.

Outcome

- Fatal: The subject died due to the event. If the subject died due to other circumstances than the event the outcome should be stated as 'not recovered' or 'recovering'.

- Recovered/resolved: The subject has fully recovered from the event or the condition has returned to the level observed at baseline.
- Recovering/resolving: The event is improving but the subject is still not fully recovered.
- Not recovered/not resolved: The event is ongoing at the time of reporting and the subject has still not recovered.
- Recovered with sequelae/resolved with sequelae: As a result of the event, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, or paralysed).
- Unknown: If outcome is not known or not reported.

10.3 Collection of Adverse Events, Special Situation Reports and Product Quality Issues

10.3.1 Spontaneously reported events

If, during the conduct of the study, a member of the research team is spontaneously informed of other AEs or SSRs that are not study endpoints, and the event pertains to a Takeda product (or unbranded generic), such information should be reported to the Sponsor or regulatory agency in the country in which the event occurred (spontaneous reporting contacts are provided in Appendix 2). As such reports are spontaneously notified, causality of any AEs should be assumed unless there is evidence to the contrary.

10.3.2 Events identified from chart review

AEs that are study endpoints (all AEs during treatment) and SSRs, as defined in Table 4, should be systematically identified, abstracted, and summarized as part of any interim analysis and in the final study report.

10.4 Reporting of Adverse Drug Reactions and Special Situation Reports to Regulatory Agencies

The Sponsor shall notify regulatory agencies in accordance with local regulatory requirements or Sponsor's post-marketing commitments.

11 Data quality control and assurance

11.1 Quality control

All CRFs will be field-tested for reliability and validity with a minimum of two or three physicians, and their recruited HL patients.

As this study will involve recruitment and participation of multiple investigators (with their site staff) in multiple countries across the emerging markets region, ensuring that understanding of questions, terms, and guidelines is uniform across physicians is essential to the quality of the data collected and the minimisation of biases in interpretation. A research brief and detailed data collection instructions, including clear, concise definitions of questions, terms, and guidelines, will be provided by the CRO.

Data cleaning and validation will be conducted prior to the conduct of statistical analyses. Database lock will occur at the end of the study (i.e. completion of the data collection described in this protocol), unless otherwise specified (refer to Section 11.4 on Data management for more details). Data validation for key datapoints will be conducted on 10% of the completed CRFs via telephone or queries in the electronic CRF (eCRF). This will include the translation of data from local language into the CRF (where relevant). Physicians will be asked to be re-abstract or provide key datapoints based on the original source document, i.e. the medical record. Physicians should not share patients' confidential information when providing key datapoints.

In the case where certain datapoints are missing from patients' medical records, the method for the handling of this missing data (e.g. imputation of missing values or complete case analysis) will be detailed in the SAP.

Data-related quality controls

The data management processes employed will ensure strict oversight of data entry to ensure the appropriate quality control measures, e.g. CRF review for data logic, data inconsistency, data query and discrepancy resolution, and documentation are conducted.

All work will be subject to quality control and documentation procedures to ensure that the study reporting is accurate and thorough, and the analyses can be reproduced. If the data do not permit an analysis as planned (e.g. through insufficient sample size in a stratified analysis), or if clarifying analyses are required (e.g. an unexpected result that could be explained by a subgroup analysis), the CROs will inform the client and include the additional information and results in reporting.

11.2 Audit from Quality Assurance Unit

The Quality Assurance (QA) Unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

11.3 Inspection by Institutional Review Board/Independent Ethics Committee or competent authority

Representatives from IRB/IEC or competent authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately contact Global Research and must make the records available as requested.

11.4 Data management

Data management will be the responsibility of the appointed CRO. Data management will be carried out according to a data management plan (DMP), which will identify the location of the CRO's data management facility. The DMP must be written and approved before the design of the study database is finalised. The data management provider should approve all data formats before the data collection tools are made available to the sites.

If the written informed consent of a subject is known not to be available in spite of it being required, data for this subject is not entered into or is deleted from the database.

Data management processes

To include detailed processes for the following activities:

- Pilot study.
- Study instruction handouts/materials.
- Internal staff training.
- Study monitoring and physician follow-up.
- CRF editing and online review.
- Data validations.
- Documentation of missing and anomalous data and resolution directly with investigators.

Data tabulations and statistical analyses will be conducted using SAS version 9.4 (this applies to tabulations i.e. data analysis, and statistical analyses, i.e. Tables, Listings, and Figures [TLFs]).

At the conclusion of the study, final, locked datasets will be delivered in a format acceptable to the sponsor, e.g. statistical analysis system (SAS). A detailed format and label program containing a description of each study variable and associated format will accompany their delivery.

Data handling

Data collection, processing, storage, and usage will follow data protection/privacy guidelines in each country. All results will be reported in a de-identified, aggregate manner. Physicians will be identified only by assigned identifiers and patients will be distinguished by assigned identifiers. At the end of data collection, physicians will be instructed to maintain the master

links between patient IDs for the study and the patient ID on site for a time period that is consistent with the study Sponsor's standard operating procedures.

If a subject is erroneously included in the study more than once, only the data relating to the first inclusion will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e. if collected within the timeframe of the first follow-up period.

The current Standard Coding Instructions for coding of medical history, concomitant illness (MedDRA), concomitant medication (WHO-Drug), and adverse events/reactions (MedDRA) must be followed.

The subjects will be identified in the database only by study ID, site ID, subject number, gender, and month and year of birth.

11.4.1 Data collection tools and flow

The study site will receive data collection tools (CRFs, access to electronic data capture, etc.) from Takeda. Whenever possible, complete datasets should be entered.

The Study Site Responsible must sign off the complete dataset for each subject, confirming the collected data. ADR data reported according to Section 10 should be signed off separately by a physician who may or may not be involved in the study.

A web-based electronic CRF will be employed. The data entry site will be password-protected and physicians/site staff completing the study online will receive a password to access the study portal and perform data entry. Further details can be found in the DMP.

12 Statistical methods and determination of sample size

Statistical analyses will be performed by the appointed CRO.

12.1 Statistical analysis plan

For full details of the statistical analyses please refer to the SAP.

This study is observational and epidemiological methods will be employed for data analyses.

Descriptive analysis will be performed of all collected data except data collected only for the purpose of data cleaning, i.e. all data listed in Section 9. Below is the overall approach to the analyses for this study.

All analyses will be conducted separately for Group 1 (cHL) and Group 2 (RRHL). Within each group (for the descriptive and outcomes analyses), endpoints will be presented for the overall sample (aggregated across all countries), at regional level (e.g. South America, Asia–Pacific), and separately for each participating country.

Descriptive analyses will be used to summarize patient demographics and clinical characteristics, treatment patterns, clinical outcomes, and healthcare resource utilisation.

Continuous endpoints

Key continuous endpoints (e.g. duration of treatment, healthcare resource utilisation) will be summarised using the summary statistics of mean and standard deviation, median and range.

Categorical endpoints

Key categorical endpoints will be summarised using both the number and percentage in each category. Only patients with data available for a particular variable will be included in the calculation of a percentage.

Time to event endpoints

Key time to event endpoints (e.g. OS, PFS) will be summarised in terms of the total number of events observed and the proportion of patients who have died/progressed at a given milestone after accounting for censoring using Kaplan–Meier curves.

In addition to the descriptive analyses, multivariate analyses will be included, adjusting for differences in patient demographic, clinical, and treatment characteristics, as well as risk factors that will be conducted for key time to event analyses, when treatment cohorts will be compared within the RRHL or frontline setting.

Objectives-based analysis plan

The endpoints relating to each study objective are listed in Appendix 3. Specific statistical analyses will be discussed in more detail in the SAP, which will also include table shells.

Safety endpoints

ADRs reported in the study as well as ADRs reported directly to authorities and to Takeda International Drug Safety according to Section 10.3 and not captured in the study database will be extracted from the overall safety database and the study database, and listed or tabulated in the final report in the standard way of presenting such data in a periodic safety update report (PSUR).

12.2 Interim and final analyses

An interim analysis is planned, based on all patients' data collected up to a specified timepoint.The interim analysis will include results for key variables and will be discussed further in the SAP along with proposed timeline.

The final analysis will include the full study population and all analyses outlined above, to be delivered in the form of populated data tables and a final clinical study report. Any known deviations from the planned analyses, the reason for such deviations, and all alternative/additional statistical analyses that may be performed, as well as the final statistical analysis, must be described in a revised SAP before completion of data collection. All later deviations and/or alterations will be summarised in the clinical study report.

12.3 Determination of sample size

The aim of this study is to describe the treatments and associated clinical outcomes for patients with high-risk stage IIb–IV cHL and RRHL in different countries in the emerging markets region. This will contribute to a greater understanding of current treatment patterns, which will help to inform future clinical decision-making.

The primary endpoint is to describe PFS in patients with RRHL, defined as the time from initiation of first treatment for RRHL to first documentation of relapse or disease progression or death. Although the results from different countries will be combined, it is important that, for the primary endpoint, the sample is sufficient to provide reasonably reliable results for each participating country separately. It is also intended that subgroup analyses will be performed to describe the outcomes in different patient groups (e.g. those with HIV or hepatitis and early versus late relapsers) and for different treatment regimens (including ASCT versus non-ASCT and brentuximab vedotin versus other treatments).

There are no comparable studies from the emerging markets region that can be used to inform calculation of the required sample size. A recent phase III clinical trial of patients with HL with risk factors for relapse or progression after ASCT observed a median PFS of 42.9 months (for brentuximab vedotin) and 24.1 months (for placebo) (46). However, the study was conducted in the US and Europe and did not include patients who were unsuitable for ASCT (for whom PFS is expected to be lower). It is acknowledged therefore that the results may not be directly applicable to this study. The reliability of a range of mean and median PFS estimates for various sample/subgroup sizes are shown in Table 5 and Table 6.

Table 5: Reliability of the mean progression-free survival at various sample sizes

	95% Confidence limits (CLs)							
	***n* = 25**		***n* = 50**		***n* = 100**		***n* = 200**	
Observed mean PFS (months)	**LCL**	**UCL**	**LCL**	**UCL**	**LCL**	**UCL**	**LCL**	**UCL**
18	15.6	20.4	16.3	19.7	16.8	19.2	17.2	18.8
21	18.2	23.8	19.0	23.0	19.6	22.4	20.0	22.0
24	20.8	27.2	21.7	26.3	22.4	25.6	22.9	25.1
27	23.4	30.6	24.5	29.5	25.2	28.8	25.7	28.3
30	26.0	34.0	27.2	32.8	28.0	32.0	28.6	31.4
33	28.6	37.4	29.9	36.1	30.8	35.2	31.4	34.6
36	31.2	40.8	32.6	39.4	33.6	38.4	34.3	37.7

LCL, Lower confidence limit; UCL, upper confidence limit.

Table 6: Reliability of the median progression-free survival at various sample sizes

	95% CLs							
	***n* = 25**		***n* = 50**		***n* = 100**		***n* = 200**	
Observed median PFS (months)	**LCL**	**UCL**	**LCL**	**UCL**	**LCL**	**UCL**	**LCL**	**UCL**
18	14.3	21.7	15.0	21.0	15.4	20.6	15.7	20.3
20	15.9	24.1	16.6	23.4	17.1	22.9	17.4	22.6
24	19.1	28.9	20.0	28.0	20.5	27.5	20.9	27.1
27	21.5	32.5	22.5	31.5	23.1	30.9	23.5	30.5
30	23.8	36.2	25.0	35.0	25.6	34.4	26.1	33.9
33	26.2	39.8	27.5	38.5	28.2	37.8	28.7	37.3
36	28.6	43.4	30.0	42.0	30.8	41.2	31.3	40.7

LCL, Lower confidence limit; UCL, upper confidence limit.

For both the mean and median PFS time outcomes, samples of 50 or more give reliable outcomes as they generate reasonably reliable estimates of the standard deviation of the PFS distribution. Therefore, a sample of at least 50 (50–200) patients with cHL and at least 50 (50–200) patients with RRHL per country will be used in this study. Whilst it is hoped that each country will be able to include 100 patients in each group (approximately 1300 per group in total across all 13 countries) to allow description of PFS in different subgroups and for different treatments, it is recognised that this may not be possible in every country and therefore oversampling may be performed in countries with larger populations of eligible patients to enable the overall sample to be achieved.

For PFS rates, a previous study of patients receiving salvage therapy for RRHL who were followed up for a median of 45 months showed a variation in the freedom from second treatment failure rate from approximately 30% to 80%, depending on the stage of disease, time to recurrence, and frontline treatment received (4). The reliability of different PFS rate outcomes for various sample/subgroup sizes is shown in Table 7.

Table 7: Reliability of progression-free survival rates for various sample sizes

	95% CLs							
	n = 50		*n* = 100		*n* = 200		*n* = 300	
Observed PFS rate	**LCL**	**UCL**	**LCL**	**UCL**	**LCL**	**UCL**	**LCL**	**UCL**
20%	11%	33%	13%	29%	15%	26%	16%	25%
30%	19%	44%	22%	40%	24%	37%	25%	36%
40%	27%	54%	31%	50%	33%	47%	35%	46%
50%	36%	64%	40%	60%	43%	57%	44%	56%
60%	46%	73%	50%	69%	53%	67%	54%	65%
70%	56%	81%	60%	78%	63%	76%	64%	75%
80%	67%	89%	71%	87%	74%	85%	75%	84%

LCL, Lower confidence limit; UCL, upper confidence limit.

While the reliability of the PFS rates is limited with samples of 200 or less, they are reasonable for 300 or more. It would thus be possible to give estimates at a regional level for this outcome, combining the results of two or more countries.

Secondary endpoints include patient demographic and clinical characteristics, HL treatment pathways, adverse events, and resource use for both the cHL and RRHL groups. Outcomes that are simply counted (e.g. presence or absence of risk factors, use of specific treatments) will have reliability similar to the PFS rates, while those that are measured (e.g. age and measurable risk factors) and healthcare resource use of both hospital visits, inpatient admission, and their respective costs, will be more reliable, similar to the mean PFS. It is acknowledged that, for some analyses (e.g. patients receiving each treatment after ASCT), the number of patients in each country with data available is likely to be small. It will be possible to give reliable estimates at a regional level for these outcomes by combining the results of two or more countries.

13 Reports

A non-interventional study report based on the results obtained will be prepared and submitted to Global Research for distribution. The final study report should be available within 1 year of collection of the last datapoint, and the participating sites should be informed about the results when the report is finalised.

14 Publications

It is planned that results of this study may be presented at an upcoming conference (venue to be determined based on timing of results availability) or submitted for publication in appropriate peer-reviewed medical journal(s).

Takeda has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

Publication requests from individual sites will need to be considered and approved by Takeda and the study Steering Committee.

15 Archiving of study documentation

During the course of the study the Site Responsible must, as a minimum, file the essential documents (Section 6.4), the protocol, any amendments, the list of participating subjects, the written informed consents, the CRFs, and the progress reports in the study site file. After final database lock, the Site Responsible must, as a minimum, store the list of participating subjects and the signed informed consent forms on site for 5 years. The Site Responsible should store additional study documentation for a longer period of time, as required by any local regulations and/or hospital requirement.

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17 Appendices

Appendix 1: Minimum dataset

Variables	cHL (Group 1)	RRHL (Group 2)
Patient and disease characteristics	• Practice location (country) • Gender • Month and year of birth • Date of cHL diagnosis • Clinical stage at diagnosis • Date of most recent follow-up/contact	• Practice location (country) • Gender • Month and year of birth • Date of HL and RRHL diagnosis • Date of start and end of frontline treatment • Date of first relapse after start of frontline treatment (date of scan confirming relapse) • Frontline therapy for HL • Date of most recent follow-up/contact

Treatment pathways	Details of treatments received for cHL from the date of diagnosis until the date of first documented relapse or disease progression after frontline therapy
	
	For frontline treatment and each subsequent line of treatment:
	• Treatment modality (chemotherapy, RT, chemotherapy + RT, other treatment [specify])
	• Start and end dates
	• Therapy regimen
	• For RT:
	  ○ Type (whole body, IFRT, ISRT, INRT, other)
	  ○ Anatomical site
	PET/CT scan details (from date of cHL diagnosis until date of first documented relapse or disease progression after frontline therapy):
	• Dates
	• Response category recorded (CR, PR, SD, PD)
		• Was ASCT undertaken (yes/no)
		
		Details of treatments received for RRHL from the date of RRHL diagnosis until the date of the patient's death or the date of data collection (whichever occurs first)
		
		For each line of treatment:
		• Treatment modality (chemotherapy, RT, chemotherapy + RT, ASCT, allo-SCT, other treatment [specify])
		• Start and end dates
		• Therapy regimen
		• For RT:
		  ○ Type (whole body, IFRT, ISRT, INRT, other)
		  ○ Anatomical site
		PET/CT scan details (from date of RRHL diagnosis until date of the patient's death or the date of data collection (whichever occurs first):
		• Dates

		• Response category recorded (CR, PR, SD, PD)
Clinical outcomes	Occurrence of relapse/disease progression after start of frontline treatment (yes/no) Date of first documented relapse or disease progression after start of frontline therapy Date of death, if patient died Assessments of response to frontline therapy: • Date of assessment • Response (CR, PR, SD, PD)	All date(s) of documented relapse or disease progression during the study observation period Date of death, if patient died Assessments of response to each line of therapy (including ASCT, each treatment received by non-ASCT patients and each post-ASCT treatment regimen): • Date of assessment • Response (CR, PR, SD, PD)

Appendix 2: Spontaneous reporting to sponsor

COUNTRY	DRUG SAFETY EMAIL
Argentina	PPD
Australia	
China	
Colombia	
Hong Kong	
Mexico	
Russia	
Saudi Arabia	
Singapore	
South Africa	
South Korea	
Taiwan	
Turkey	

Appendix 3: Study endpoints

Endpoints will be presented for the overall sample, at regional level (e.g. South America, Asia–Pacific), and separately for each participating country.

Clinical outcomes may also be presented separately for the following subgroups:

- Patients with HIV/hepatitis B or C.
- Patients who receive PET CT versus CT only for evaluation of treatment response.
- In the RRHL group (Group 2):
    - Patients with primary refractory HL (those who have failed to achieve a CR with frontline therapy or relapse within 3 months after end of frontline therapy) versus patients with relapsed HL (relapse >3 months after end of frontline therapy).
    - Early versus late relapsers (early: relapse within 3–12 months after end of frontline therapy; late: relapse >12 months after end of frontline therapy).
    - ASCT versus no ASCT.
    - Patients who receive brentuximab vedotin versus other treatments in the non-ASCT setting.
    - Patients who receive brentuximab vedotin versus other treatments in the post-ASCT setting.

Patient characteristics will be presented overall and by:

- ASCT status (yes/no).
- Non-ASCT patients receiving brentuximab vedotin (yes/no).
- Post-ASCT patients receiving brentuximab vedotin post-relapse (yes/no).

Primary endpoint

PFS in patients with RRHL, defined as the time from initiation of first treatment for RRHL to first documentation of relapse or disease progression or death, censored at date of most recent follow-up/contact.

Secondary endpoints

Secondary study endpoints include patient characteristics (Table 8), treatment pathways (Table 9), clinical outcomes (Table 10), adverse events (Table 11), resource use (Table 12), *and costs (Table 13)*. Endpoints will be reported separately for cHL (Group 1) and RRHL (Group 2) patients. Patients diagnosed with high-risk stage IIb–IV cHL between 2010 and 2013, who are subsequently

diagnosed with RRHL (between 2010 and 2013 inclusive), will be included in the analysis for both groups, as described in Section 8.3 (see examples in Table 3).

Table 8: Endpoints relating to secondary objective 1 (patient characteristics)

Secondary objective 1	Patients diagnosed with high-risk stage IIb–IV cHL between 01 January 2010 and 31 December 2013, who received frontline treatment with chemotherapy ± radiotherapy (Group 1)	Patients diagnosed with RRHL between 01 January 2010 and 31 December 2013 (Group 2)

Patient characteristics	• Gender distribution
	• Distribution and mean (StDev) age at cHL diagnosis
	• Distribution of ethnicity
	• Distribution of clinical staging at diagnosis
	• Distribution and mean (StDev) body weight at diagnosis
	• Distribution of histological subtype of cHL
	• Distribution of known risk factors for relapse (IPS factors) at diagnosis:
	  ○ Age ≥45 years
	  ○ Male sex
	  ○ Stage IV disease
	  ○ Albumin <4 g/L
	  ○ WBC ≥15 × 10^9/L
	  ○ Haemoglobin <10.5 g/L
	  ○ Lymphocyte count <0.6 × 10^9/L or <8% of differential
	• Distribution of IPS score
	• Proportion of patients with B symptoms at diagnosis
	• Distribution of comorbid conditions (lung disease [including TB], cardiovascular disease, HIV, hepatitis B and C)
		• Gender distribution
		• Distribution and mean (StDev) age at diagnosis
		• Distribution of ethnicity
		• Distribution of histological subtype of cHL
		• Distribution and mean (StDev) body weight at first diagnosis and at relapse
		• Distribution of clinical staging at first diagnosis, at relapse, at ASCT (if performed), and at start of treatment with brentuximab vedotin (if used)
		• Distribution of known risk factors for relapse (Josting factors (4):
		  ○ Time to recurrence within 3–12 months after end of frontline treatment
		  ○ Stage III or IV relapse
		  ○ Haemoglobin at relapse <10.5 g/dL for females and <12 g/dL for males
		• Distribution of Josting score (0, 1, 2, 3)
		• Proportion of patients with B symptoms at RRHL diagnosis
		• Distribution of comorbid conditions (lung disease [including TB], cardiovascular disease, HIV, hepatitis B and C)
		• Distribution of prior therapies for HL at each line of treatment

	• Distribution of PET/CT scan status if available	• Median (range) number of previous treatment regimens • Mean (StDev) and median (range) time from end of frontline treatment to first relapse

Table 9: Endpoints relating to secondary objective 2 (treatment pathways)

Secondary objective 2	Patients diagnosed with high-risk stage IIb–IV cHL between 01 January 2010 and 31 December 2013, who received frontline treatment with chemotherapy ± radiotherapy (Group 1)	Patients diagnosed with RRHL between 01 January 2010 and 31 December 2013 (Group 2)

Treatment pathways	• Distribution of frontline treatment regimens
	• Median (range) number of doses or treatment cycles associated with each regimen
	• Frequency of PET/CT assessment and when used (e.g. baseline/after first treatment)
	• Distribution of treatments received for HL after completion of frontline therapy (but before relapse, if this occurred)
	• Distribution of type, site, and dosing of RT (if used), when used (before/during/after chemotherapy) and whether used for pre-planned frontline treatment or for residual FDG-avid disease
		All patients with RRHL
		• Proportion of patients who were considered eligible/ineligible for ASCT
		• Proportion of patients initially considered ineligible for ASCT (e.g. owing to chemoresistant disease) who subsequently became eligible and received ASCT:
		  ○ Treatment received, including median (range) number of doses or treatment cycles associated with each regimen
		  ○ Frequency of PET/CT assessment and when used (e.g. interim and/or end of treatment
		• Proportion of eligible patients who received/did not receive ASCT
		
		Non-ASCT patients:
		• Distribution of reasons for not undergoing ASCT in patients who were ASCT-eligible (patient refusal, inability to mobilise stem cells, loss of response to chemotherapy, toxicity, other)
		• Distribution of reasons for ASCT ineligibility (advanced age, comorbid conditions, chemoresistant disease, cumulative toxicities, other)
		• Distribution of treatment regimens received at each line of treatment and proportion of patients for whom treatment is

		palliative • Median (range) number of doses or treatment cycles received at each line of treatment, for each treatment regimen • Mean (StDev) and median (range) duration of each line of treatment • Proportion of patients with dose delays at each line of treatment for each treatment regimen • Mean (StDev) and median (range) time from relapse (after frontline treatment) to first treatment post-relapse • Mean (StDev) and median (range) time to initiation of each subsequent treatment, both from relapse and from completion of previous treatment • Mean (StDev) and median (range) duration of each line of treatment • Proportion of patients receiving PET/CT at each line of the treatment pathway and frequency of assessment • Proportion of patients receiving radiotherapy at each stage of the treatment pathway • Distribution of type, site, and dosing of radiotherapy, if used **Patients undergoing ASCT:** • Distribution of chemotherapeutic salvage regimens used pre- and post-ASCT • Median (range) number of doses or cycles associated with each salvage regimen • Distribution of chemotherapy conditioning regimens used • Proportion of patients receiving consolidation therapy post-ASCT • Distribution of consolidation therapies used and mean (StDev)

		and median (range) duration of treatment • Time from relapse (after end of frontline treatment) to ASCT • Source of ASCT (bone marrow, peripheral) • Mean (StDev) and median (interquartile range) CD34+ count administered • Distribution of known risk factors for relapse after ASCT (time to first relapse ≤3 months, stage IV disease at relapse, bulky disease ≥5 cm at relapse, extranodal disease, inadequate response to salvage chemotherapy (<PR or PET positivity), performance status (ECOG) ≥1) **Patients who relapse after ASCT:** • Mean (StDev) and median (range) time from ASCT to first relapse post-ASCT • Distribution of post-ASCT regimens received at each line of treatment and proportion of patients for whom treatment is palliative • Median (range) number of doses or cycles received at each line of treatment, for each treatment regimen • Mean (StDev) and median (range) duration of each line of treatment • Mean (StDev) and median (range) time from ASCT to first treatment after relapse • Mean (StDev) and median (range) time to initiation of each subsequent treatment, both from ASCT and from completion of previous treatment • Proportion of patients receiving PET/CT at each stage of the treatment pathway, frequency of assessment, and when assessed

		• Proportion of patients receiving radiotherapy at each stage of the treatment pathway • Distribution of type, site, intent, dosing, and frequency of radiotherapy, if used • Proportion of patients undergoing subsequent ASCTs and median (range) number of ASCTs per patient • Proportion of patients undergoing allogeneic stem cell transplantation (allo-SCT)

Table 10: Endpoints relating to secondary objective 3 (clinical outcomes)

Secondary objective 3	Patients diagnosed with high-risk stage IIb–IV cHL between 01 January 2010 and 31 December 2013, who received frontline treatment with chemotherapy ± radiotherapy (Group 1)	Patients diagnosed with RRHL between 01 January 2010 and 31 December 2013 (Group 2)
Clinical outcomes	• Median PFS, defined as time from initiation of frontline regimen to first documentation of relapse or disease progression or death, censored at date of most recent follow-up/contact • Distribution of best clinical response after completion of frontline treatment (CR, PR, SD, PD), as defined by the International Working Group 2007 Revised Response Criteria for Malignant Lymphoma (1) • Mean (StDev) and median (range) time to best response • Proportion of patients with documented relapse or disease progression at any point after completion of frontline treatment • Median (range) duration of best response, defined as the time from when the criteria for response (CR or PR) are met to first documentation of relapse or disease progression • 1-, 3-, and 5-year* PFS rates • Median OS, defined as the time from diagnosis of cHL to death, censored at date of most recent follow-up/contact • Proportion of patients alive at 1 and 5 years* after diagnosis • For deceased patients:	***Clinical outcomes to be presented for ASCT, each salvage regimen used pre- and post-ASCT, each treatment regimen received by non-ASCT patients, and each post-ASCT regimen in patients who relapse:*** • Median PFS, defined as time from initiation of treatment to first documentation of relapse or disease progression or death, censored at date of most recent follow-up/contact • Distribution of best clinical response after completion of each line of treatment (CR, PR, SD, PD) • Mean (StDev) and median (range) time to best response • For ASCT patients: proportion of patients in response who are assessed as high risk of relapse pre-ASCT (risk factors defined in Table 4 (above). • Proportion of patients with documented relapse or disease progression at any time after completion of treatment • Median (range) duration of best response (as previously defined) • 1-, 3-, and 5-year* PFS rates • Median OS, defined as the time from first relapse

	○ Mean (StDev) and median (range) time to death (from diagnosis and from completion of frontline therapy) ○ Distribution of cause of death (HL-related/adverse event/treatment-related/other)	after frontline therapy to death, censored at date of most recent follow-up/contact • Proportion of patients alive at 1 and 5 years* after first relapse • For deceased patients: ○ Mean (StDev) and median (range) time to death (from initial diagnosis, from first relapse, from ASCT, and from relapse after ASCT) ○ Distribution of cause of death (HL-related/adverse event/treatment-related/other)

* 5 year PFS and OS rates will be reported only for patients with >5-year observation periods.

Table 11: Endpoints relating to secondary objective 4 (adverse events)

Secondary objective 4	Patients diagnosed with high-risk stage IIb–IV cHL between 01 January 2010 and 31 December 2013, who received frontline treatment with chemotherapy ± radiotherapy (Group 1)	Patients diagnosed with RRHL between 01 January 2010 and 31 December 2013 (Group 2)
Adverse events	To be presented overall and separately for adverse events considered by the treating clinician as treatment-related: • Distribution of adverse events associated with frontline treatment, including haematological malignancies, and peripheral neuropathy (PN) • Distribution of adverse event seriousness (serious [as previously defined]/non-serious)	To be presented overall and separately for adverse events considered by the treating clinician as treatment-related: • Distribution of adverse events (including haematological malignancies and PN) associated with: o ASCT o Each treatment regimen received by non-ASCT patients o Each post-ASCT treatment regimen • Distribution of adverse event seriousness (serious [as previously defined]/non-serious)

Table 12: Endpoints relating to secondary objective 5 (resource use)

Secondary objective 5	Patients diagnosed with high-risk stage IIb–IV cHL between 01 January 2010 and 31 December 2013, who received frontline treatment with chemotherapy ± radiotherapy (Group 1)	Patients diagnosed with RRHL between 01 January 2010 and 31 December 2013 (Group 2)
Resource use	Resource use will be reported for: • Frontline chemotherapy ± RT treatment (per patient per cycle) Overall HL-related resource use will be reported, as well as the resource use associated with adverse event management The following resource use parameters will be reported: • Distribution and mean (StDev) number of inpatient hospital admissions and reasons (if available) • For inpatient hospital admissions; mean (StDev) length of stay, overall and by unit/ward (general, high dependency/intermediate, ICU, BMT unit) • Distribution and mean (StDev) number of emergency room visits • Distribution and mean (StDev) number of outpatient visits by healthcare professional seen • Distribution and mean (StDev) number of episodes of radiotherapy received • Distribution and mean (StDev) number of each type of scan/procedure • Distribution and mean (StDev) number of days of treatment with G-CSF/pegylated G-CSF or other high-	Resource use will be reported for: • Salvage therapy (per patient per cycle) • ASCT (per patient per procedure [from start of stem cell mobilization to reinfusion of cells]) • Allo-SCT (per patient per procedure) • Brentuximab vedotin in the non-ASCT setting (per patient per cycle) • Brentuximab vedotin in the post-ASCT setting (per patient per cycle) • Each post-ASCT chemotherapy regimen (per patient per cycle) For each treatment, overall HL-related resource use will be reported, as well as the resource use associated with adverse event management The following resource use parameters will be reported: • Distribution and mean (StDev) number of inpatient hospital admissions and reasons (if available) • For inpatient hospital admissions; mean (StDev) length of stay, overall and by unit/ward (general, high dependency/intermediate, ICU, BMT unit) • Distribution and mean (StDev) number of emergency room visits

	cost medicines • Distribution and mean (StDev) number of courses of treatment with G-CSF/pegylated G-CSF or other high-cost medicines	• Distribution and mean (StDev) number of outpatient visits by healthcare professional seen • Distribution and mean (StDev) number of episodes of radiotherapy received • Distribution and mean (StDev) number of each type of scan/procedure • Distribution and mean (StDev) number of days of treatment with G-CSF/pegylated G-CSF or other high-cost medicines • Distribution and mean (StDev) number of courses of treatment with G-CSF/pegylated G-CSF or other high-cost medicines

Table 13: Endpoints relating to secondary objective 6 (costs)

Secondary objective 6	***Patients diagnosed with high-risk stage IIb–IV cHL between 01 January 2010 and 31 December 2013, who received frontline treatment with chemotherapy ± radiotherapy (Group 1)***	***Patients diagnosed with RRHL between 01 January 2010 and 31 December 2013 (Group 2)***
Costs	*Costs will be reported for:* • *Frontline chemotherapy ± RT treatment (per patient per cycle)* *Overall HL-related costs will be reported, as well as the costs associated with adverse event management* *The costs associated with each frontline treatment will be calculated from the resource use parameters (listed in Table 12 [above]) using country-specific reference costs*	*Costs will be reported for:* • *Salvage therapy (per patient per cycle)* • *ASCT (per patient per procedure [from start of stem cell mobilization to reinfusion of cells])* • *Allogeneic stem cell transplantation (per patient per procedure)* • *Brentuximab vedotin in the non-ASCT setting (per patient per cycle)* • *Brentuximab vedotin in the post-ASCT setting (per patient per cycle)* • *Each post-ASCT chemotherapy regimen (per patient per cycle)* *For each treatment, overall HL-related costs will be reported, as well as the costs associated with adverse event management* *Allocation of costs (as for patients receiving frontline HL treatment)*