Clinical Study Protocol

EU PAS Number: EUPAS36934

Title: Brentuximab Vedotin Administration Registry and Outcomes Study in Polish CTCL Patients (BV-BALTIC study)

Study Number: Brentuximab-5014

Document Version and Date: Version 1.0, 13 Jun 2020

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

Non-Interventional Study Protocol

Title: Brentuximab vedotin administration registry and outcomes study in Polish CTCL patients.

Short title: BV-BALTIC study

Study ID: Brentuximab-5014

Protocol version: 1.0

Sponsor: Takeda Pharma Sp. z o.o.
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Study phase: IV

Date of version 1.0 **of protocol:** 13 Jun 2020

1 Administrative information

1.1 Contacts

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

Data Management, CRO (advice on e-CRF)	[redacted] The CRO, Biostat Sp. z o.o., ul. Kowalczyka 17, 44-206 Rybnik [redacted]
Medical advice on compound & study	[redacted] Takeda Polska sp. z o.o. Warszawa Ul Prosta 68 Tel: [redacted] [redacted]
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Medical [redacted]	[redacted] Takeda Polska sp. z o.o. Warszawa Ul Prosta 68 Tel: [redacted] [redacted]

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

[redacted]	Date	Takeda Pharma sp z o.o.	Date
The CRO, Biostat Sp. z o.o.			
Takeda Pharma sp z o.o.	Date	Takeda Pharma sp z o.o.	Date

INVESTIGATOR SIGNATURE PAGE

I confirm that I have read and that I understand this protocol and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects 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.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events as defined in this protocol.

Signature of Investigator Date

<Investigator Name (print or type)>

<Investigator's Title>

<Location of Facility (City, State/Provence)>

<Location of Facility (Country)>

STUDY SUMMARY

Name of Sponsor(s): Takeda Pharma sp z o.o.	**Compound/Product:** Brentuximab vedotin/Adcetris
Title of Protocol: Brentuximab vedotin administration registry and outcomes study in Polish CTCL patients. BV-BALTIC study	
Study Number: Brentuximab-5014	**Phase:** IV
Study Design: BV-BALTIC is a prospective, multicenter, observational, open-label study designed to document the management and clinical outcome of brentuximab vedotin in cutaneous T-cell lymphomas (CTCL) patients based on local real-world data in Poland. There is no predefined sample size.	
Primary Objectives: 1. To determine objective skin response (measured by mSWAT) which lasted 4 months or longer (sORR4). 2. To measure best Overall skin response, (BsORR - Best overall skin response rate) measured by mSWAT.	
Secondary Objectives: 1. To determine PFS according to progression confirmed by physician. 2. Clinical and demographic characteristics of CTCL patients (disease subtypes – MF, pcALCL; skin symptoms, time from symptoms presentation to diagnosis) 3. To determine duration of response (DOR) in patients who completed treatment. Duration will be measured 6 months after EOT in patients who achieved objective response.	
Exploratory Objectives: [redacted]	
Subject Population: Adult CTCL patients eligible to receive treatment with brentuximab vedotin (BV) in the scope of Drug Program in Poland between 2020-2022	
Number of Subjects: All adult patients included in BV CTCL Drug Program between Oct 2020 and Oct 2022.	**Study Sites:** The study is planned to be conducted in approx. 10 sites in Poland. The sites in BV-BALTIC study will be hospitals and clinics administrating BV in the frames of CTCL Drug Program.
Dose Level(s): Brentuximab vedotin to be administered in accordance to SmPC and Drug Program.	**Route of Administration:** Brentuximab vedotin to be administered intravenously in accordance to SmPC.
Duration of Study: Overall Study Duration: 42 months Enrolment period: 24 months Treatment: up to 16 cycles (48 weeks) Follow-up: 6 months post treatment cessation	

Main Criteria for Inclusion:

1. Adult (aged ≥18) CTCL patients included in brentuximab vedotin CTCL Drug Program.
2. Patients willing to participate in the study and signed ICF.

Main Criteria for Exclusion:

1. Patients currently participates or plans to participate in any interventional clinical trial.
2. Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.

Statistical Considerations: Data will be summarized using standard descriptive statistics. For primary and secondary endpoints percentages will be calculated and presented with 95% confidence intervals. For secondary endpoints survival analysis using Kaplan-Meier method will be used. Subgroups will be compared using appropriate statistical tests: Chi-square or Fisher test (for categorical data), Student t-test or U Mann-Whitney test for numeric data. Decision on test selection will be based on verification of test assumptions.

Sample Size Justification: There is no predefined sample size, and all data collected during BV-BALTIC study will be considered for analytical purposes. Alternative analyses may employ sample sizes based upon sub-populations.

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Appendix 1 Data collection overview

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List of Abbreviations and Definition of Terms

Abbreviation or special term	Explanation
AE	adverse event
BV	brentuximab vedotin
CR	complete response
CRO	Contract Research Organization
CTCL	cutaneous T-cell lymphoma
DP	Drug Program
eCRF	electronic case report form
EFS	event free survival
FSFV	first subject first visit
FSLV	first subject last visit
HRQoL	health related quality of life
ICF	Informed Consent Form
LSFV	last subject first visit
LSLV	last subject last visit
MF	mycosis fungoides
mSWAT	modified severity weighted assessment form
sORR4	Objective skin response rate lasting at least 4 months
BsORR	Best overall skin response rate
pcALCL	primary cutaneous anaplastic large cell lymphoma
PD	progressive disease
PFS	progression free survival
PR	partial response
SAP	statistical analysis plan
SD	stable disease
SmPC	summary of product characteristics
TP	time to progression
TTR	time to response

2 Introduction

CTCL diagnosis and treatment remains a complex and highly site-depended area based on site's experience and specific patient flow between sites. The disease should be an area of multidisciplinary approach of hematologists, dermatologists and oncologists (Wilcox, 2016). Patterns of treatment stay variable as some agents are not reimbursed and others might be used by selected specialists only (Sokolowska-Wojdylo *et al.*, 2016). Given above characteristic of CTCL treatment and referral, particularly in advanced stages, the treatment patterns seem to be poorly understood in Poland.

Currently advanced stages of CTCL can be treated with methotrexate, interferon or bexarotene, however many patients are not responding nor tolerating above mentioned medicines (Willemze *et al.*, 2018). Therefore, it is expected that brentuximab vedotin (BV), that will be reimbursed soon, will significantly affect current proceedings in the sites. These expectations are facilitated by excellent outcomes of phase III ALCANZA trial in which BV was used to treat CTCL (Prince *et al.*, 2017).

The aim of this study is to assess BV treatment outcomes in CTCL Polish patients who will undergo therapy in the scope of the Drug Program. Main BV-BALTIC goals are to describe patients' characteristics and BV treatment effectiveness and safety. Equally interesting will be collection of data on CTCL treatment patterns, having in scope sites specificity, multidisciplinary approach and availability of other agents at local market. The data collected in the course of BV treatment in CTCL Drug Program may be used for future submissions with the Ministry of Health.

3 Study Objective(s)

3.1 Objective(s)

3.1.1 Primary Objectives

1. To determine objective skin response (measured by mSWAT) which lasted 4 months or longer (sORR4).
2. To measure best overall skin response, (BsORR - Best overall skin response rate) measured by mSWAT.

3.1.2 Secondary Objective(s)

1. To determine PFS according to progression confirmed by physician.
2. Clinical and demographic characteristics of CTCL patients (disease subtypes – MF, pcALCL; skin symptoms, time from symptoms presentation to diagnosis)
3. To determine duration of response (DOR) in patients who completed treatment. Duration will be measured 6 months after EOT in patients who achieved objective response.

3.1.3 Exploratory Objective(s)

[redacted]

[redacted]

4 Study Administrative Structure

4.1 Study Sites

The study is planned to be conducted in approx. 10 sites in Poland. The sites in BV-BALTIC study will be hospitals and clinics administarting brentuximab vedotin in the frames of Drug Program.

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

4.2 Sponsor Personnel

Sponsor will keep a record of all relevant Sponsor personnel that will be responsible for study oversight.

4.3 Contract Research Organisation (CRO)

The CRO, Biostat Sp. z o.o., ul. Kowalczyka 17, 44-206 Rybnik, Poland will be in charge of data management, Statistical Analysis Plan, analysis and generation of a study report. Data management tasks will be conducted according to the CRO's SOPs. Sponsor or CRO will also be in charge of relevant document submission to Independent Ethics Committee (IEC). Details of the tasks and responsibilities are regulated in the contract between the Sponsor and the CRO. The CRO will keep a record of all involved CRO personnel.

5 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 to use of the subject's data and to collect data from patients' questionnaires.

5.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and any local regulations. Special attention will be paid to data protection. Special attention will be paid to data protection as described in Directive 95/46/EC.

The Sponsor and/or the appointed CRO will ensure that the protocol, any amendments and the Subject Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements. The sponsor is responsible for meeting the ICH requirement for yearly updates to the IECs/IRBs, if applicable.

5.2 Independent Ethics Committee / Institutional Review Board and Authorities

IEC/ IRB

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, patients questionnairies, eCRF printout.

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 (if appicable)
- notification of the end-of-study
- a summary of the study results

The Sponsor or the appointed CRO 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.

5.3 Subject Information and Written Informed Consent

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 (and if applicable, the 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 which 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 and parent 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.

6 Study Design and Plan

This study is a 'non-interventional study' as defined in Directive 2001/20/EC and will follow the guidelines for GPP.

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.
- Brentuximab vedotin is prescribed in accordance with the terms of the marketing authorisation(s)
- The prescription of brentuximab vedotin is clearly separated from the decision to include the subject in the study

Prospective, observational (non-interventional), multicentre study with consecutive patients aged ≥ 18 enrolled between October 2020 and October 2022 with cutaneous T-cell lymphoma fulfilling inclusion criteria to Drug Program.

Data collection is scheduled in line with Drug Program visits and will not cause any further obligations for the patients except of signing ICF and filling patients' questionnaires.

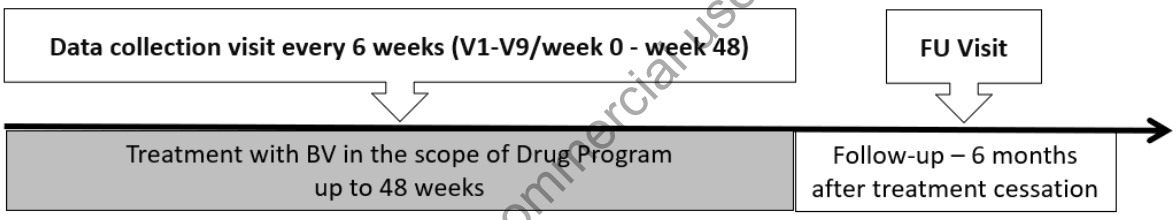

Fig.1 Study design

There are 9 visits scheduled during the treatment period (week 0, week 6, week 12, week 18, week 24, week 30, week 36, week 42 and week 48) (Fig. 1). There is planned one follow-up visit 6 months post treatment cessation. Follow-up will be conducted on patients who completed all 16 cycles of treatment with response/remission or achieved response/remission, however treatment was stopped due to intolerance.

6.1 Study Schedule

Planned Start of Study:	Oct 2020
Planned collection of first data point:	Oct 2020
Planned End of Study:	Jun 2024
Planned collection of the last data point:	Apr 2024
Planned completion of the Study Report:	Dec 2024

The Sponsor 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.

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

6.2 Discussion of Study Design

BV-BALTIC is a non-interventional study (NIS), designed to generate real-world evidence (RWE), complement and provide additional insight to the data produced through clinical trials. NIS are critical for assessing utilization, treatment patterns, comparative effectiveness and safety, and providing overall value demonstration, as well as informing on important therapeutic findings to help guide treatment decisions and real-world use. Having in regards that in BV-BALTIC study, patient's data are gathered and collected during routine clinical care, there will be single arm only with no control (no randomization). Potential source of bias in non-interventional cohort studies is well-known and it is equal to BV-BALTIC study, however prospective nature of the study, multi-centres involved and consecutive patients to be enrolled, must be highlighted as factors distinguishing BV-BALTIC study.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. Patients included in BV CTCL Drug Program between Oct 2020 and Oct 2022 and receiving treatment according to the Summary of Product Characteristics for Adcetris.

4. Male or female subjects, aged ≥ 18 years.

6.3.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Currently participates or plans to participate in any interventional clinical trial.
2. Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.

Subjects should be included in the study only once.

Data erroneously collected from subjects for which written consent is not available, will not be included in or will be deleted from the database.

6.4 Treatments

Non-interventional/observational – no treatments/pharmacotherapy are instructed by the study protocol.

6.5 Premature Termination or Suspension of Study or Investigational Site

6.5.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the brentuximab vedotin and may have serious impact on treatment effectiveness or patients safety.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.5.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP/GPP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.5.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

6.6 Study Plan

	Visit1 (Week 0)	Visit 2 (Week 6)	Visit 3 (Week 12)	Visit 4 (Week 18)	Visit 5 (Week 24)	Visit 6 (Week 30)	Visit 7 (Week 36)	Visit 8 (Week 42)	Visit 9 (Week 48)	FU Visit, (week 74)	Early Termination visit
Informed consent	X										
Data collection (for details see section 8.4.1)	X	X	X	X	X	X	X	X	X	X	X
Safety reporting	X	X	X	X	X	X	X	X	X	X	X

7 Safety Reporting

7.1 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 AE can therefore be any unfavorable and unintended sign (including 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 the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Health care provider, places the subject/patient at immediate risk of death (a life threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one

of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

Product Quality Issues

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

Special Situation Reports

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 authorization, also known as “off-label”
- Use of falsified medicinal product

A SSR should be reported even if there is no associated AE.

Relationship of an AE to studied drug(s)

- **Related (Yes):** An AE that follows a reasonable temporal sequence from administration of the medication, vaccine or device (including the course after withdrawal of the medication), or for which a casual relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the medication, vaccine or device, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
- **Not related (No):** An AE that does not follow a reasonable temporal sequence from administration of the medication, vaccine or device and/or that can reasonably be explained by other factors, such as underlying disease, complications, concomitant drugs and concurrent treatments. The investigator must make an assessment of causality using the above definition. Causality cannot be assumed in the absence of the investigator's assessment.:

7.2 Collection and notifying of Adverse Events, Special Situation Reports and Product Quality Issues to Takeda Pharmacovigilance

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQI where the event/issue pertains to a Takeda product (or unbranded generic), such information should be notified to the local Takeda Pharmacovigilance department within 1 working day for SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

8 Data Quality Control and Assurance

8.1 Quality Control

A web-based application (eCRF) will be used for entering data into the BV-BALTIC database, allowing for remote data entry at hospital/investigator centers. The users will access the BV-BALTIC database via a web browser. A dedicated database server stores all the information collected from the clinics participating in BV-BALTIC study. The database server is managed by an independent external service provider to ensure that the data are kept secure and confidential during data collection, transfer and storage.

The BV-BALTIC eCRF is described in the eCRF manual, which will be provided to each participating center and can be accessed within the database. Immediate questions or problems with the data entry that are not addressed in the eCRF manual may be directed to representatives of Takeda/Biostat (CRO). Note that this study has core variables that must be completed in the registry in order for a specific visit data entry to be considered "complete." Please see Appendix 1 for the list of core variables.

In order to ensure good quality, patient source data should be available by direct access, at individual centers, for the routine monitoring visits done by Takeda designated contract research organization. It is important that the responsible BV-BALTIC investigator and other relevant personnel are available during these monitoring visits, and that sufficient time is allocated. BV-BALTIC study will also be monitored remotely by designated CRO. The nature and frequency of the monitoring will be dependent on the number of patients enrolled at each individual center and will be presented in dedicated Monitoring Plan.

8.2 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.

8.3 Inspection by IRB/IEC

Representatives from IRB/IEC 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. The Inspector must be reminded up front that consent to access to personal data has not been obtained from the participants in this study.

8.4 Data Management

Biostat (CRO) is responsible for Data Management. Data Management will be carried out according to a Data Management Plan, which 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.

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 time frame 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, date of birth, gender.

8.4.1 Data Collection Tools and Flow

The Study Sites will receive access to Electronic Data Collection System (EDC) allowing for collection of eCRF from Takeda/Biostat. Sites will receive training and have access to a manual for appropriate CRF completion. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should follow the requested language standard.

The Study Site Responsible must sign off the complete data set for each subject, confirming the collected data. ADR data reported according to section 7 and data on serious AE/ADR reactions collected according to section 6 should be signed off separately by a physician who may or may not be involved in the study. The eCRFs will be submitted electronically to Biostat and will be handled in accordance with study Data Management Plan. Data will be periodically transferred electronically from the Biostat to Takeda, and the Biostat's standard procedures will be used to handle and process the electronic transfer of these data. At the end of the study, participating investigators will receive the data related to patients from his or her site in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records. Acknowledgement of receipt of the data is required.

The eCRFs and correction documentation will be maintained in the EDC system audit trail.

System backups for data stored by Biostat and records retention for the study data will be consistent with the Takeda and CRO standard procedures. Biostat will comply with the Takeda's procedures regarding archiving and record management.

9 Statistical Methods and Determination of Sample Size

Statistical analysis will be performed by Biostat Sp. z o. o. following the principles of the Guidelines ICH Topic E3 and ICH Topic E9 as well as Biostat's SOPs. The statistical analysis will be performed using the R statistical software (Version 3.5 or later; R Foundation for Statistical Computing; Vienna, Austria).

This section describes the statistical analyses as foreseen at the time of planning the study. 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 Statistical Analysis Plan (SAP) before completion of data collection. All later deviations and / or alterations will be summarised in the Clinical Study Report.

All data collected will be analyzed descriptively. Standard descriptive statistic methods will be applied including number of patients, arithmetic mean, standard deviation, upper and lower quartiles, minimum, median and maximum. For categorical variables tables of frequencies (absolute and relative frequencies) will be presented. Number of patients for whom data is missing will be provided where appropriate.

The safety endpoints will be presented as incidence rate calculated using person-time analyses. Reported adverse events and comorbidities will be coded using MedDRA dictionary (version current at the time of study initiation) and all adverse event summaries will present preferred terms and System Organ Class. Where appropriate 95% confidence intervals will be provided. Detailed description of study populations, including rules for inclusion and exclusion to a given popuation, data analysis and results presentation will be provided in a statistical analysis plan (SAP), a separate document provided by the CRO prior to final database lock.

9.1 Statistical Analysis Plan

This study is observational and epidemiological methods will be employed for data analyses. Descriptive analysis will be performed of all collected data (listed in **Error! Reference source not found.** and Appendix 1 Data collection overview), except variables collected only for the purpose of data cleaning.

The main outcomes of the study are:

- Proportion of subjects with objective skin response (measured by mSWAT) which lasted 4 months or longer (sORR4) as determined by Physician. Objective response is defined as either Complete or Partial response (see Appendix 2: Response assessment)
- Proportion of subjects with either: Complete Response (CR), Partial response (PR), Stable disease (SD) or Progressive disease (PD) as best response at any time between initiation and cessation of the treatment as determined by Physician (Best Skin Response, BsORR, measured by mSWAT - BsORR).
- Incidence rate of adverse events and serious adverse events reported from the date of first use of BV (treatment emergent adverse events; TEAE).

Secondary outcomes of the study are:

- Progression free survival - defined as a time from first use of BV until progressive disease (as determined by physician, based on mSWAT assessment) or death from any cause.
- Duration of response – defined as a time between first response (either CR or PR) and progressive disease (or death from any cause) that occurs after end of BV treatment in Drug Program.

ADRs reported in the study as well as ADRs reported directly to authorities and to Takeda International Drug Safety according to Section 7 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).

For primary and secondary endpoints appropriate percentages will be presented with 95% confidence intervals. For secondary endpoints survival analysis using Kaplan-Meier method will be used. In addition, analyses in following subgroups are planned:

- Responders versus non responders
- Disease subtypes – MF versus pcALCL.

Subgroups will be compared using appropriate statistical tests: Chi-square or Fisher test (for categorical data), Student t-test or U Mann-Whitney test for numeric data. Decision on test selection will be based on verification of test assumptions.
Due to interim analysis O'Brien-Fleming approach will be used for controlling the type I error – significance level will be equal to 0.0054 for the interim analysis and 0.0492 for the final analysis.

For details of the statistical analyses please refer to the Statistical Analysis Plan.

9.2 Interim Analyses

Interim analysis to be performed when the observation of patients recruited up to half of recruitment period (12 months) is completed (about 30 months from the start of the study). The results from Interim Analysis will be published in a medical journal. All primary, secondary and exploratory analyses will be performed. As mentioned, O'Brien-Fleming approach will be used, and significance level will be set to 0.0054.

9.3 Determination of Sample Size

There is no predefined sample size, and all data entered into BV-BALTIC study database will be considered for analytical purposes.
Nevertheless, a potential for enrolment during recruitment period indicates that approximately 40 consecutive patients fulfilling inclusion criteria and not meeting exclusion criteria will be recruited and observed. In case of proportions, such as sORR4, a maximum width of 95% confidence interval (CI) for proportion will be 29.6%.
Alternative analyses may employ sample sizes based upon sub-populations.

10 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 one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalised.

11 Publication, Disclosure, and Clinical Trial Registration Policy

The Sponsor aims to have the results of this study published.

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

Takeda may post the results of the study on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

12 Archiving of Study Documentation

During the course of the study the Site Responsible must as a minimum file the below essential documents in the Study Site File:

- Written agreement between the Sponsor representative – CRO, Study Site and Investigator.
- The study protocol and any amendments
- 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), including the original signed Forms
- The list of participating subjects
- Written IEC / IRB approval
- The completed CRFs
- The progress reports

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.

13 References

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14 Appendices

Appendix 1 Data collection overview

1. Subject demographics
    a. gender
    b. age
    c. height, body weight, BMI,
    d. ECOG PS
    e. voivodship (area) of residence
    f. Name of site at which the subject is treated
2. Comorbidities, if present; any comorbidity may be specified.
3. Clinical characteristics of CTCL
    a. Disease subtype (MF or pcALCL)
    b. Disease stage at diagnosis (TMNB).
    c. Time from symptom presentation to diagnosis -
    d. Time since initial diagnosis
    e. Time since progression on last therapy (excl. RT) or time since relapse.
    f. Current treatment, if present.
    g. Speciality of physician who made the diagnosis.
4. Skin-related characteristics at inclusion to drug program.
    a. Body Surface Area (BSA)
    b. BSA by lesion type
    c. mSWAT
    d. Skin symptoms
5. Prior therapy
    a. Prior skin directed therapy (multiple entries possible)
        i. Type
        ii. Duration
        iii. Outcome
        iv. Specialty of prescribing physician
    b. Prior radiotherapy (multiple entries possible)
        i. Duration
        ii. Type (local, total)
        iii. Dosage
        iv. Frequency of administration
        v. Target location
        vi. Outcome
        vii. Specialty of prescribing physician
    c. Prior systemic therapy (multiple entries possible)
        i. Type

ii. Duration
iii. Number and duration of cycles
iv. Outcome, reason for discontinuation
v. AEs
vi. specialty of prescribing physician

d. Stem cell transplant (multiple entries possible)
i. Type (allogeneic, autologous)
ii. Date
iii. CTCL subtype
iv. TMNB stage

e. Surgery (multiple entries possible)
i. Date
ii. Type
iii. Setting
iv. CTCL subtype
v. TMNB stage
vi. Specialty of prescribing physician.

6. Concomitant medications and procedures monitored from qualification to Drug Program till discontinuation of treatment to any reason.

7. Current treatment with brentuximab vedotin
a. mSWAT score
b. Number of doses received so far,
c. Reason for dose delay if occurred
d. Infusion reaction if occurred
e. Nodal and visceral involvement if present at baseline
f. AE/SAE if occurred
g. Place of BV administration
i. ambulatory,
ii. hospital
iii. one day care,

8. Biomarkers:
a. complete blood count with differential count;
b. aminotransferase (AspAT, AlAT) and total bilirubin levels;
c. creatinine level

Appendix 2: Response assessment

1. mSWAT

The mSWAT assessment tool will be used for MF and pcALCL and will be performed as specified in the Drug Programme. The mSWAT score calculation method and skin lesion definitions for MF and pcALCL are provided below.

Body region	% BSA in Body region	Assessment of Involvement in Patient's Skin		
		Patch[a]	Plaque[b]	Tumor[c]
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		x1	x2	x4
Subtotal of lesion BSA x Weighting factor				

mSWAT score equals summation of each column line.

Abbreviations: BSA = body surface area; mSWAT = modified Severity Weighted Assessment Tool.

a) Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.

b) Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

c) Any solid or nodular lesion ≥1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

The mSWAT score will be calculated as follows:
Sum of %TBSA from all body regions affected by patches x severity-weighting factor of 1
+ Sum of %TBSA from all body regions affected by plaques x severity-weighting factor of 2
+ Sum of %TBSA from all body regions affected by tumors x severity-weighting factor of 4
= Total mSWAT (maximum score = 400)

2. Response in skin

Response	Definition
Complete Response (CR)	100% clearance of skin lesions[a]
Partial response (PR)	50%-99% clearance of skin disease from baseline No new tumors in patients without tumors at baseline (MF) No new tumors (pcALCL)
Stable disease (SD)	< 25% increase to < 50% clearance in skin disease from baseline No new tumors in patients without tumors at baseline (MF)
Progressive disease (PD)[b]	≥ 25% increase in skin disease from baseline, or Loss of response: in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score, or New tumors in patients without tumors at baseline (MF)
Relapse	Any disease recurrence in those with complete response

Response criteria for MF are per Olsen 2011 (Olsen *et al.*, 2011) **and for pcALCL per Kempf 2011** (Kempf *et al.*, 2011)**.**

a) A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed on a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome, the response should be considered a partial response only.

b) Whichever criterion occurs first.

Appendix 3 National Drug Program

BRENTUXIMAB VEDOTIN IN THE TREATMENT OF PATIENTS WITH CUTANEOUS T-CELL LYMPHOMA (ICD-10: C84)

<table>
<tr><th colspan="3">SCOPE OF GUARANTEED MEDICAL SERVICE</th></tr>
<tr><th>MEDICAL SERVICE RECIPIENTS</th><th>DOSE REGIMEN OF ACTIVE SUBSTANCES IN THE PROGRAMME</th><th>DIAGNOSTIC TESTS PERFORMED AS PART OF THE PROGRAMME</th></tr>
<tr>
<td>1. Programme inclusion criteria:

Patients meeting all the following criteria are eligible for treatment with brentuximab vedotin under the drug programme:
a) age ≥ 18 years,
b) performance status of 0-2 according to the Zubrod-WHO or ECOG classification;
c) patients with histopathologically confirmed cutaneous T-cell lymphoma (mycosis fungoides – MF or primary cutaneous anaplastic large cell lymphoma – pcALCL),
d) immunohistochemically confirmed presence of the CD30 antigen in at least one of collected biopsies of MF lesions or one biopsy of lesions in pcALCL,
e) disease stage of IB or above for MF, according to the TNMB staging system (ISCL and EORTC classifications),
and one of the following criteria:
a) disease progression in the course of prior systemic treatment confirmed during at least two consecutive medical visits or
b) unacceptable (stage 3 or 4 according to the WHO classification) and recurrent, despite dosage adjustment, toxicity of prior systemic treatment or
c) disease recurrence after a period of remission caused by prior systemic treatment.
2. Determination of the duration of treatment under the programme.
The duration of treatment under the programme is determined by the physician on the basis of the programme inclusion and exclusion criteria. Patients may receive up to 16 treatment cycles.
3. Programme exclusion criteria:
1) hypersensitivity to brentuximab vedotin or to any of the product ingredients;
2) toxicity necessitating treatment discontinuation in accordance with the current Summary of Product Characteristics;</td>
<td>Dosage:

Dosage of brentuximab vedotin in the treatment of cutaneous T-cell lymphoma in accordance with the current Summary of Product Characteristics.</td>
<td>1. Tests to determine eligibility for the treatment with brentuximab:
1) medical interview and physical examination (including optional dermatological examination);
2) complete blood count with differential count;
3) aminotransferase (AspAT, AlAT) and total bilirubin levels;
4) creatinine level;
5) TNMB and mSWAT testing;
6) chest and abdominal computed tomography (CT) scan or chest X-ray and abdominal ultrasound;
7) documenting the presence of the CD30+ antigen in the lymphoma tissue by immunohistochemical testing;
8) ruling out of pregnancy – in the case of women of childbearing potential
2. Treatment monitoring:
1) examinations and tests performed before each administration of the medicine:
a. medical interview and physical examination (including optional dermatological examination);
b. complete blood count with differential count;
c. creatinine level;
d. aminotransferase (AspAT, AlAT) levels; total bilirubin level;
2) the mSWAT scale must be completed once every two months;
3) performance of follow-up imaging examinations, as clinically necessary.
3. Programme monitoring:
1) collecting in the patient's medical record the data on treatment monitoring and presenting those data each time at a request of the controllers of the National Health Fund (NFZ);</td>
</tr>
</table>

3) disease progression in the course of treatment, where a period of two-month follow-up is required to confirm progression; 4) administration of 16 treatment cycles; 5) appearance of comorbidities that are a contraindication to treatment continuation; 6) pregnancy, breast-feeding period.		2) completing the data contained in the register (of the Therapeutic Programme Monitoring System, SMPT) accessible via the internet application made available by the Voivodeship Branch of the National Health Fund (OW NFZ), with the frequency consistent with the programme description and at the end of treatment; 3) transferring reporting and accounting information to the NFZ: the information is transferred to the NFZ in the paper or electronic form, in line with the requirements published by the National Health Fund.