EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2015
EMA/314727/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lympreva

International non-proprietary name: dasiprotimut-t

Procedure No. EMEA/H/C/002772/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
bcl	B cell lymphoma
BICR	Blinded independent central reviewer
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CHOP-R	Cyclophosphamide, doxorubicin, prednisone, vincristine with Rituxan
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRADA	Cooperative Research and Development Agreement
CRu	Complete response unconfirmed
CT	Computed tomography
CTC	Common Toxicity Criteria
CTEP	Cancer Therapy Evaluation Program
DFS	Disease free survival
DSMB	Data safety monitoring board
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EKG	Electrocardiogram
FCC	Follicular center cell
FDA	Food and Drug Administration
FL	Follicular lymphomas
FLIPI	Follicular Lymphoma Prognostic Index
FM	Follicular mixed lymphomas
FNA	Fine needle aspiration
FNHLId1	Autologous immunoglobulin follicular lymphoma idiotype vaccine (dasiprotimut T Biovest)

GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GM CSF	Granulocyte macrophage colony-stimulating factor GMP Good Manufacturing Practices
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICH	International Conference on Harmonisation
Id	Idiotypic surface Ig
IDES	Internet data entry system
IEC	Independent Ethics Committee
IFNγ	Gamma-interferon
IND	Investigational New Drug Application
IPI	International Prognostic Index
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous (ly)
IVP	Intravenous pyelogram
IWG	International Working Group
KLH	Keyhole limpet haemocyanin
LBL	Lymphoblastoid cell lines
LDH	Lactate dehydrogenase
LFT	Liver function test
MD	Maryland
MedDRA	Medical Dictionary for Regulatory Activities MRI Magnetic resonance imaging
MUGA	Multiple gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NHL	Non-Hodgkin's lymphoma
NIH	National Institute of Health
OCT	Optimal cutting temperature
ORR	Overall response rate
PACE	Prednisone, doxorubicin, cyclophosphamide, and etoposide PBMC

	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PHI	Protected health information
PI	Principal Investigator
PP	Per protocol
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
SAE	Serious adverse event
SC	Subcutaneously
SD	Stable disease
SDev	Standard deviation
SGOT	Serum glutamate oxaloacetic transaminase
SGPT	Serum glutamate pyruvate transaminase
SOC	System organ class
SPD	Sum of the products of the greatest diameters
TBI	Total body irradiation
TEAE	Treatment emergent adverse event
TIW	Three times per week
TNF	Tumour necrosis factor
US	United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biovest Europe Ltd submitted on 3 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lympreva, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004.
The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 June 2012.

Lympreva, was designated as an orphan medicinal product EU/3/06/394 on 28/08/2006. Lympreva was designated as an orphan medicinal product in the following indication: Treatment of follicular lymphoma.

The applicant applied for the following indication: Lympreva is an autologous immunoglobulin vaccine indicated for the treatment of patients with follicular non-Hodgkin' s lymphoma (FL) as first line consolidation therapy after achieving complete remission with induction therapy and is co-administered with Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF). Efficacy with induction therapy other than the PACE regimen (prednisone, doxorubicin, cyclophosphamide, etoposide) used in FL patients has been established in mantle cell lymphoma patients (MCL) with the EPOCH-R regimen (doxorubicin, etoposide, vincristine, cyclophosphamide, prednisone, rituximab). Efficacy relative to other first line consolidation therapies has not been established. Lympreva is indicated in adults.

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application. The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver and EMA Decision P/0181/2012 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

Biovest International, Inc.
8500 Evergreen Boulevard NW
Minneapolis, MN 55433
USA

Manufacturer responsible for batch release

Propak Health Ltd
3-4 Ballyboggan Industrial Estate
Ballyboggan Road, Finglas
Dublin
Ireland

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder

Co-Rapporteur: Jens Ersbøll

CHMP Peer reviewer: Arantxa Sancho-Lopez

PRAC Rapporteur: Brigitte Keller-Stanislawski

- The application was received by the EMA on 3 December 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 23 March 2014.
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 10 April 2014
- During the meeting on 25 April 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 April 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 October 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 November 2014 .
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 November 2014.
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 4 December 2014.
- During the CHMP meeting on 18 December 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.

• The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 February 2015.

• The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 March 2015.

• PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 12 March 2015.

• During the BWP meeting on 17 March 2015, the outstanding quality issues were addressed by the applicant during an oral clarification before the BWP.

• During the CHMP meeting on 24 March 2015, outstanding clinical issues were addressed by the applicant during an oral explanation before the CHMP.

• During the meeting on 23 April 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Lympreva.

2. Scientific discussion

2.1. Introduction

Problem statement

Follicular lymphoma (FL), an indolent B-cell lymphoma, accounts for 22% of non-Hodgkin's lymphomas (NHL) diagnosed worldwide. The indolent FLs include follicular small-cleaved cell (FSC) and follicular mixed (FM) lymphoma. Stage I and II patients comprise only 10-15% of all cases of FL and are best managed with radiation therapy. Eighty-five percent of newly diagnosed FL patients present with stage III or IV disease, which requires systemic therapy that has the capacity to produce high complete response rates but has failed to prolong overall survival (OS). Over the past decade, the management of lymphoma benefited from a broad range of highly-active first-line (induction) and consolidation therapies for advanced disease requiring treatment (NCCN Guidelines in Oncology, v. 1.2013).

Morphologically, FL is defined as a proliferation of malignant germinal center B cells and the relative proportion of centrocytes to centroblasts underlies the current grading scheme with, at its extremes, grade 1 FL comprising low numbers of centroblasts (0–5 per high-power field) and grade 3B FL marked by solid sheets of these same cells (Kridel et al. 2012). The hallmark t(14;18)(q32;q21) in FL results in constitutive overexpression of the BCL2 protein, allowing B cells to abrogate the default germinal center apoptotic program. Cell surface main markers include CD19, CD20, CD5, CD23 and CD10 (NCCN Guidelines in Oncology, v. 2.2014).

Patients with FL usually present with painless lymph node enlargement involving superficial lymph nodes of small to medium size, sometimes unnoticed by the patients. In some patients there may be no peripheral lymphadenopathy and abdominal or back pain is reported due to deep lymph nodes slow growth, usually in the infradiaphragmatic territories such as the retroperitoneum, the mesenteric, or the iliac areas. Primary mediastinal involvement is uncommon, as well as isolated splenic enlargement. The general status of the patient is usually preserved, with few patients presenting with B symptoms or an altered performance status. Primary involvement of extranodal areas is also very uncommon and when it happens the bone marrow is involved in 50% to 60% of the cases. Some unusual clinical presentations include particular cases with a distinct behaviour involving the gastrointestinal tract, the testis and the "in situ" FL (Goodlad et al. 2004).

Currently, approximately 70-90% of FL patients obtain remission following induction therapy; consolidation therapies as a class seek to improve the quality of response achieved with first-line regimens (Morschhauser et al. 2008), to extend remission period and prevent relapse. However, even with these improvements largely due to the addition of rituximab used as induction as well as consolidation treatment (Rummel M et al. 2009, Salles et al. 2011), therapies are not curative and median overall survival averages approximately 10 years. Given the median age at diagnosis of FL patients is about 60 years (Rohatiner and T. A. Lister, 2005), the projected ageing of the population in the Western world that will likely render FL a morbidity burden of the elderly, and the essentially symptom free status of FL patients in first remission, developing non-toxic consolidation therapeutic approaches remains highly desirable.

About the product

Lympreva is an autologous lymphoma-derived immunoglobulin (Ig) idiotype (Id)-keyhole limpet hemocyanin (KLH) conjugate active immunotherapy product manufactured from a patient's lymph node biopsy.The variable regions of the surface immunoglobulin (Ig) on a B-cell form a specific antigen binding site that is unique to each Ig and contain molecular determinants, termed idiotype (Id), which can themselves be recognized as antigens. Since B-cell malignancies are clonal proliferations of cells, the Ig variable regions on the tumour cells are distinct from other normal B cells. The idiotypic determinants of the surface Ig of a B-cell lymphoma can therefore serve as a tumour-specific antigen for therapeutic vaccine development and represent the antigen targeted by Lympreva.

The mechanism of action appears to be mediated through induction of idiotype-specific and tumour-specific T-cell responses. Antigen presenting cells (APCs) process Id-KLH and display Id/KLH peptides on Human Leukocyte Antigen (HLA) class II receptors, which lead to the activation of CD4+ T-cells. Id-specific CD4+ T-cells undergo clonal selection and induce substantial cytokine release (TNF, IFNγ, GM-CSF), activating a wide range of adaptive responses, including B-cell anti-tumour antibody production (mostly IgG_1, supposed to specifically recognize and bind autologous tumour cells), memory T-cell induction, and CD8+ T-cell (cytotoxic) responses. Trafficking of activated CD8+ T-cells leads to recognition of tumour cells via Id peptide fragments displayed on MHC-I receptors on the tumour cell surface, which results in tumour cell lysis.

The applicant applied for a marketing authorisation for the following indication: "Lympreva is an autologous immunoglobulin vaccine indicated for the treatment of patients with follicular non-Hodgkin's lymphoma (FL) as first line consolidation therapy after achieving complete remission with induction therapy and is co-administered with Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF). Efficacy with induction therapy other than the PACE regimen (prednisone, doxorubicin, cyclophosphamide, etoposide) used in FL patients has been established in mantle cell lymphoma patients (MCL) with the EPOCH-R regimen (doxorubicin, etoposide, vincristine, cyclophosphamide, prednisone, rituximab). Efficacy relative to other first line consolidation therapies has not been established. Lympreva is indicated in adults."

However during the procedure the applicant changed the applied indication to : ''Lympreva is an active immunotherapy indicated for the treatment of patients with follicularnon-Hodgkin's lymphoma (FL) as consolidation therapy after achieving complete remission with induction therapy and is co-administered with Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF). For information on the induction therapy used in clinical trials see section 5.1''.

The recommended dose is 1 mg autologous tumour-derived immunoglobulin Id coupled with KLH administered subcutaneously on day 1 and accompanied by 100 micrograms/m^2/day, or 5.6 times the 105 IU/m^2, of sargramostim (GM-CSF) administered subcutaneously on days 1-4. The recommended course of treatment is 5 doses administered over 6 months, at month 1, 2, 3, 4, and 6.

2.2. Quality aspects

2.2.1. Introduction

Lympreva is an autologous immunoglobulin idiotype (Id) active immunotherapy product designed to stimulate an immune response against Id, a tumour specific surface antigen, which leads to tumour cell lysis and elimination of residual follicular lymphoma (FL) cells. This patient-specific protein active immunotherapy product is prepared by hybridoma technology, where the patient's lymphoma cells are fused to a human-mouse heteromyeloma cell line in order to produce the tumour specific immunoglobulin Id protein. The immunoglobulin is purified from the culture supernatant by affinity chromatography, conjugated to an immunogenic carrier protein, keyhole-limpet haemocyanin (KLH) and administered together with Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) as an adjuvant.

Each single-use 2 mL vial of Lympreva contains 1 mg dasiprotimut-T per 1 mL of sterile frozen clear suspension in 0.9% sodium chloride solution.

2.2.2. Active Substance

General information

The chemical name is Follicular lymphoma-derived immunoglobulin idiotype protein conjugated to keyhole limpet haemocyanin.

Lympreva is a Follicular lymphoma-derived immunoglobulin idiotype protein conjugated to keyhole limpet haemocyanin. The active pharmaceutical ingredient in dasiprotimut-T is the patient's unique idiotype protein conjugated to keyhole limpet haemocyanin (KLH).

Dasiprotimut-T is comprised of two biological substances: an autologous immunoglobulin molecule (IgM or IgG) conjugated to KLH from the mollusc Megathura crenulata (keyhole limpet). Idiotype protein structure differs from patient to patient (lot-to-lot).

Autologous Idiotype (Id) is an immunoglobulin of the IgM or IgG isotype containing the idiotype expressed by a patient's follicular lymphoma tumour cell. The idiotype is purified from the bulk supernatant of hybridoma clone and specific to the tumour biopsy cells from which it was manufactured. Therefore physicochemical properties will vary from patient to patient. The biological activity of dasiprotimut-T is determined by its identity and purity.

KLH is a blue, copper-containing oligomeric glycoprotein from the mollusc *Megathura crenulata* (keyhole limpet). The two subunit isoforms, KLH 1 and KLH 2, associate into multiple homo-oligomeric structures. The molecular weights predicted for the KLH 1 and KLH 2 subunit isoforms from their peptide sequences are approximately 391,000 and 392,000 Daltons, respectively. Actual molecular weights are variable due to differential glycosylation of the proteins, which may account for 4% of the mass. Both isoforms contain N-acetylglucosamine, N-acetylgalactosamine, galactose, mannose, and fucose. The carbohydrates moieties are believed to be important to enhance immunogenicity of KLH. The large number of available lysine residues in KLH facilitates conjugation when used for production of conjugates.

Manufacture, characterisation and process controls

Description of manufacturing process, process controls and validation

The patient-specific component of dasiprotimut-T consists of an immunoglobulin of either an IgG or IgM isotype, which defines the specific process used to purify the Id. The purified immunoglobulins

(Id) are conjugated to keyhole limpet haemocyanin (KLH) using glutaraldehyde. The whole mixture is dialysed against physiological sodium chloride solution.

Manufacture starts with the isolation of patient tumour cells from a lymph node biopsy of a non-Hodgkin's lymphoma patient who may receive treatment with dasiprotimut-T and subsequent fusion of the cryopreserved biopsy cells with a heteromyeloma cell line.

Manufacture of dasiprotimut-T is segregated into two principle parts: (1) Production and purification of the Id (autologous immunoglobulin) and (2) conjugation of purified Id to KLH.

The patient-specific component of dasiprotimut-T consists of an immunoglobulin of either an IgG or IgM isotype, which defines the specific process used to purify the Id. The purified immunoglobulins (Id) are conjugated to keyhole limpet haemocyanin (KLH) using glutaraldehyde.

The purification process includes a series of chromatography, viral inactivation and filtration steps.

Process evaluation studies were conducted on the dasiprotimut-T manufacturing process to determine methods, operating parameters, in-process controls, and consistency of the process. The operating parameters are used in the ongoing validation studies.

Control of materials

All raw materials were sourced from approved suppliers, Certificates of Analysis were presented and TSE certificates submitted where relevant.

Patient biopsies:

A description of the handling of patient biopsies has been included in the dossier. Information on in-process testing for biopsy processing and cryopreservation is given. The procurement and testing of biopsies should be in line with the EU Directive (2004/23/EC) for tissues and cells. This therefore needs to be confirmed and specifications for testing, including virus testing of biopsies, should be presented. The patients are screened for HIV and Hepatitis B. However, according to Directive 2006/17/EC, donors should at least be tested on HIV-1, HIV-2, Hepatitis B, Hepatitis C and Syphilis. Biovest commits to perform testing in line with the Tissue and Cell Directive when the first commercial batches will be manufactured and the formal requirements in line with the Tissue and Cells Directive will be followed. To date no new biopsies have been procured, stored and tested but the plan to fulfil the requirements is acknowledged. No biopsy processing validation has been performed and the plan is to do this on an ongoing basis for commercial production or clinical trials. The cause of the failure of five patient's biopsies has been presented and is sufficiently clarified (IgG3 could not be purified (for 2 batches), failed fusion step with K6H6 cells, failed supernatant step, unable to make finished product in time).

Cell banks:

A cell banking system exists for the fusion partner cell line consisting of a MCB and WCBs. The K6H6/B5 cells were produced from a fusion of malignant lymphoid cells from a patient with nodular lymphoma with a mouse myeloma line. The source of the cells, the history and cell banking has sufficiently been described. The testing of the MCBs is found acceptable. The WCB are tested for Purity, Identity, Cell Growth, Cell Viability and Fusion capability. The WCB is also tested for its ability to fuse with human lymphocytes each time a fusion process is conducted for individual patients.

Manufacturing Process Development

Process 1

The dasiprotimut-T manufacturing process begins with a lymph node biopsy from a non-Hodgkin's lymphoma patient who may receive treatment with dasiprotimut-T. The active pharmaceutical ingredient (API) in dasiprotimut-T is the patient's unique idiotype protein conjugated to the immunogen keyhole limpet haemocyanin (KLH). Each autologous, conjugated protein constitutes a unique lot and is specific to an individual patient. This manufacturing process was used to prepare supplies for the Phase 2 and Phase 3 studies.

Process 2

The commercial manufacturing process proposed for dasiprotimut-T (Process 2) has been changed since the conduct of the BV301 Phase 3 clinical trial.

The development of the manufacturing process includes an upgraded bioreactor to provide automated control of the cell culturing steps. Purification process changes were put in place in order to reduce host cell proteins, improve process robustness and improve viral clearance resulting in higher product purity. These changes were also made to minimize lot-to-lot variability of the idiotype protein and improve manufacturing consistency. Data to date indicate that the process changes impact impurity levels, including host cell protein (HCP) levels and DNA levels. Manufacturing Process 2 has been used for development batches and reference standard generation and is the proposed process for commercial manufacture.

Characterisation:

Idiotype protein structure differs from patient to patient (lot-to-lot). According to Biovest, the autologous product is administered as one therapeutic course and therefore detailed structural characterisation of each patient-specific protein is not necessary. Although the autologous protein is an immunoglobulin, Dasiprotimut-T acts as active immunogen and not as antigen-binding monoclonal antibody. Thus, affinity/avidity and other biological characteristics that commonly define antibodies are not considered relevant for the mechanism of action. The essential properties of dasiprotimut-T are Identity, Purity and extent of Conjugation.

For characterisation analytical methods and results of studies using three batches manufactured during 2013 are described. Analytical methods comprise release methods and additional characterisation procedures.

Nucleotide sequence analysis and fusion IgH fingerprinting product was performed on patient biopsy cells and the patient hybridoma Production Clone. The amplimer strategy to amplify the same VH sequence from cDNA as well as genomic DNA template is demonstrated to be acceptable. Data to demonstrate suitability of this approach for establishing identity has been provided.

The purified Id (IgM or IgG) and KLH are conjugated via glutaraldehyde resulting in a solution containing a combination of three products: Id-KLH, Id-Id, or KLH-KLH. The Extent of Conjugation test demonstrates that Purified Id is conjugated to keyhole limpet haemocyanin. An improved method for the extent of conjugation is being developed based on immunoprecipitation and flow cytometry. A complete evaluation of extent of conjugation remained to be provided (see discussion).

Determination of potency through direct measurement of immunogenicity will not be possible as the patient's immune system is not naïve to the molecule and HLA differs from person to person. Therefore, the potency is controlled indirectly via the monitoring of identity, purity and conjugation. For this approach to be acceptable, release testing would have to be extended based on the characterisation study. In the characterisation study a biological activity study should be used to evaluate the impact of various quality parameters. Additional analytical data would have to be provided to ensure consistency of the composition of the conjugate (see discussion).

Due to the nature of the product and its inherent variability, the introduced specification set to at least 50% for Id-containing proteins also containing KLH is deemed acceptable.

The purity of the Purified Id is monitored in-process.

Possible product-related impurities have not been identified nor quantified for dasiprotimut-T.

Potential process-related impurities have been identified and methods to quantify levels of those impurities have been developed. Still few batches have been analysed and only development batches have been produced recently.

Specification

The specifications for the active substance were provided.

Validation of analytical methods was ongoing in 4 stages of development and has been completed.

Batch Analysis

Each patient-derived cell line, or autologous hybridoma, is unique relative to growth and Id secretion rates. These variations between individual hybridoma clones lead to differing culture durations (Hybridoma Expansion) and crude supernatant harvests containing a range of Idiotype protein concentrations. This can affect process performance during purification and therefore the process is closely monitored. The majority of the critical testing required takes place at or before the purified Id stage which may be acceptable only if the extent of conjugation can be monitored quantitatively. Demonstration of compliance with specifications for Critical Quality Attributes remained to be provided (see discussion).

Reference Standards

Reference Standards were designed to represent both IgG as well as IgM isotypes and to serve as references for testing of Purified Id and Id-KLH Conjugates. It has been confirmed that the reference standards originate from Process 2 material. Their suitability to work as reference standards needs to be confirmed by process validation (and comparability) data.

Container closure system

The active substance Dasiprotimut-T manufactured at Biovest (Minneapolis, MN) is filled immediately into clear glass vials to form the Lympreva Finished product. A process intermediate, Purified Id, is proposed to be held in Flexboy® bioprocessing bags for up to 7 days at 2-8°C.

It is stated that Quality Assurance for Flexboy bioprocessing bags follows applicable ISO and FDA regulations for Medical Devices. The suitability of the packaging components for Purified Id will be determined by an Extractables/Leachables study and a Photostability study by a contract laboratory.

The results of the study showing the suitability of the packaging are deemed acceptable.

Stability

Stability data demonstrate that there are no significant changes in IgM or IgG Purified Id after storage for one week at 2-8°C (parameters remained within specification limits and/or acceptance criteria). Bulk Id may be held for up to 45 days at 2-8°C or -60 to -80°C (parameters monitored remained within specification limits and/or acceptance criteria). The proposed shelf life for Purified Id is one week at a storage temperature of 5±3°C. Stability data support the proposed shelf life.

It is stated that all past stability results are being provided as developmental data to support future stability studies that will be designed to stand on their own.

Protocols for Bulk Id IgG and IgM were provided and the stability study is performed at the proposed

storage temperature (-20°C). The protocols are not deemed scientifically sound, because investigated parameters (like residual process related impurities) seem to be irrelevant (i.e. are not expected to change during storage) and relevant parameters (e.g. identity and degradation – i.e. to demonstrate an intact immunoglobulin) are not tested. Requested methods (Reduced and Non-reduced SDS-Page both followed by silver staining and Western Blotting as well as Size-exclusion HPLC) had not been implemented in either stability protocol. (see discussion)

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Lympreva is a pale yellow suspension with small white to off-white precipitates.

The composition of Lympreva is presented in the following table:

Component	**Function**	**Quality Standard**	**Quantity mg/ vial**
Id-KLH	Active Ingredient	Manufacturer's specifications	1.1 mg/vial
Sodium chloride	Diluent	USP/Ph. Eur	9.9 mg/vial

Lympreva is supplied as one individual patient-specific dose of 1.0 mL suspension contained in a clear glass vial in a pack size of five. Each vial contains 1.0 mL of autologous Lympreva. The formulation is the same as used during the clinical study.

All compendial excipients conform to EP monographs.

The finished product is administered together with Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) in one syringe. The applicant was requested to a) demonstrate that these two drugs are compatible when co-administered in one syringe, b) to establish the in use shelf life of 6 h for both Dasiprotimut-T Biovest and GM-CSF and c) to include in the SmPC the GM-CSF products for which this has been established (see discussion).

Manufacture of the product and process controls

The active substance is directly processed into finished product. The representative batch formula for Lympreva is presented (33 mg of Dasiprotimut and 9 mg NaCl/mL). The quantities of each component are based on a typical batch size of 30 vials.

The manufacturing process of the finished product consists of manual aseptic filling of the finished product in glass vials, stoppering, capping and crimping. Information on washing, sterilisation and depyrogenation of vials and stoppers has been provided.

Qualification of the aseptic filling process using media fills and evaluation of fill volume using an aseptic mock-fill has been performed and found acceptable.

Available data from IgM process validation batches have been included in the dossier as appropriate, but a complete data set including finished product testing has not yet been provided. A prospective process validation for Lympreva manufacture will be performed for six unique lots of patient-specific Lympreva. These validation batches will represent the process used for commercial manufacture and conform to the specifications set for release of Lympreva. No data from the prospective study have been attached to the dossier (see discussion).

Product specification

The specification of Lympreva was presented.

Lympreva is comprised of an autologous tumour-derived idiotype (Id) protein coupled to keyhole limpet haemocyanin (KLH). Unique product lots are manufactured for each patient. The variation from patient to patient necessitates broader specifications for certain aspects of the active substance properties than those used for non-autologous biologicals. The majority of testing is performed before the filling stage on the active substance dasiprotimut-T. Release testing for clinical batches included.

Most analytical methods proposed to release Lympreva are compendial methods.

Each batch of finished product is tested for extractable volume, requiring 5 vials. A description of the sterility test is provided.

Container closure system

Lympreva is filled into Type I, clear glass vials and sealed with a Teflon-faced rubber stopper secured with an aluminium flip-off over seal.

Container and closure integrity testing is stated to be performed as part of the stability studies on the validation batches (process validation). Sterility testing is stated to be performed as part of the initial stability studies indicated that the container/closure system remains intact and functional during storage. Confirmation of the initial results was awaited from the planned process validation studies (see discussion).

Stability of the product

Twelve months stability data are presented for eight batches of Lympreva manufactured on a pilot scale at NCI and Biovest. These were filled into the proposed commercial container/closure Type I, clear glass vials and sealed with a Teflon-faced rubber stopper secured with an aluminium flip-off over seal.

The results of the real time studies demonstrate the stability of Lympreva when stored at 12 months at -20 ± 4°C. No significant changes were observed in percent purity by SDS-PAGE and western blot, sterility, or endotoxin. All results complied with the release and/or end of life specification in place at the time of the study.

Studies assessing the stability of Lympreva were performed at multiple sites during the Phase III trial. The stability analytical studies performed were SDS-PAGE and Western Blots to assess the degree of protein degradation over time at various storage temperatures. Sterility and endotoxin assays were performed. Stability data are available up to 26 months, under various temperatures.

The early stability data are the property of NCI and a summary of these data is provided. The clinical trial batches were manufactured using Process 1, which differs from the proposed commercial process in the purification steps. The filling procedure has not changed.

The stability protocol to assess the stability of Lympreva for the commercial validation batches is provided.

The shelf life is stated to having been shortened to 6 months (from 24 months) at -20ºC. For this shortened shelf life it was confirmed that the treatment period allows such a short shelf life. Still, no data on stability of the commercial batches has been presented. Thus, adequate stability data for the finished product have not been provided and the proposed shelf life is therefore not justified with data (see discussion).

Adventitious agents

All raw materials used were sourced from approved suppliers and determined to be absent of viral and non-viral adventitious agents, including Transmissible Spongiform Encephalopathies.

Certificates of Analysis (COA) for all biological raw materials have been presented including Certificates of Suitability establishing compliance with monographs of the European Pharmacopoeia (CEP) and materials of animal origin in compliance with Directive 75/318/EEC (Tables A-C) are provided. Non-irradiated Fetal Calf Serum is no longer used in the cell culture. TSE certificates were provided.

The viral clearance studies have not been finalised. The viral safety for the IgM process is deemed insufficient. Results for the IgG virus clearance studies were still awaited.

Data in support of microbiological safety derive from in-process controls and testing of the biopsy. However, virus testing fully in compliance with EU Directives 2004/23/EC and 2006/17/EC has not been performed on the biopsies to date (see discussion).

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Points that have been resolved or partly resolved at time of opinion are:

- The formal requirements in line with the Tissue and Cells Directive (2004/23/EC) will be followed (e.g. procurement, storage, testing, shipping, labelling). To date no new biopsies have been procured, stored or tested. The plan is to fulfil the requirements and to conduct biopsy-processing validation on an on-going basis. The protocol for biopsy processing validation has been presented and is acceptable. Biopsy processing validation will be done on an ongoing basis for commercial production or clinical trials. .

- Biopsy processing and handling have been outlined and validation reports for fusion and clone selection have been presented. Pending results from process validation batches and the comparability study, along with clinical batch data, are supposed to support batch analysis.

- Analytical procedures have been validated with reference to ICH Q2(R1) and requests for clarifications and updates of procedures have been responded to and found acceptable.

- Two tests for finished product release testing have been added. Validation of the assays was sufficiently shown.

- The protocol of the IgG viral clearance study is considered adequate, but the study has not been completed. The results on the Master Cell Bank testing program are pending. Even though TSE certificates were not required at the time of MCB#1 establishment and suitable gamma-irradiation of BSA for MCB#2 establishment cannot be assured, the justification can be accepted due to the testing for bovine viruses and mycoplasma as well as further testing of the MCB.

Oral Clarification on Quality Outstanding Issues at BWP (14/04/15):

An oral presentation was given by the Applicant concerning the unresolved major issues identified. From the presentation in which no new data were presented it is clear the applicant is working very focussed on resolving the outstanding issues and this work was acknowledged. Time frames were presented for the different outstanding issues and respective updates regarding ongoing studies were also presented at CHMP. Most validation studies are claimed to be finished in the near future. It was however considered that the results of these studies need to be assessed and found acceptable before a positive opinion can be given. The issue concerning validation of the biopsy processing was discussed after the oral presentation which resulted in a modified conclusion on the unresolved issue on biopsy procurement / storage / testing and validation according to the Tissue and Cells directive.

At time of opinion there are the following major issues related to the quality aspects of the product and their potential impact on efficacy and safety:

Full access to pertinent information from the supplier can be considered as assured but the definition of KLH as starting material is ambiguous and not endorsed. Neither manufacturing process nor analytical methods have been validated and Critical Process Parameters (CPPs) have not been laid down or justified. Completed stability studies on KLH in line with ICH-recommendations are lacking and shelf life as well as storage conditions for vialled KLH (to be supplied to the user) have not been addressed. Stability data presented are incomplete and the battery of analytical methods is too limited.

Several tests for characterisation have not been qualified (see discussion).

Data from comparability assessment between Process 1 (clinical trials material) and Process 2 (commercial process) are deemed insufficient.

Process-related impurities are insufficiently controlled because the removal is not validated and specifications are based on incomplete data.

Demonstration of CQA's being within specifications despite large yield differences due to variability between individual batches should have been provided. Reference is made to EMA/CHMP/BWP/187338/2014 ('Process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission').

Correct and scientifically sound stability protocols were lacking. For Bulk Id IgG and IgM further tests (e.g. reduced and non-reduced SDS-PAGE using silver staining and Western Blotting, size exclusion HPLC and other tests for control of Id protein) besides the proposed ones are required.

Adequate stability data (collected with validated methods) for finished product manufactured with the commercial process have not been provided. A six-month shelf life has been implemented as a conservative estimate and the shelf life will be extended when stability data are generated.

Results of compatibility studies supporting the instructions for use (co-administration of Lympreva and GM-CSF in one syringe; in use shelf life) and handling in the SPC have been requested. The requested study is still pending, thus the issue is persisted and was included as a MO at D180 due to the risk of implications on safety and efficacy of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for Dasiprotimut-T is currently not approvable from the quality point of view since major objections still remain that preclude a recommendation for a positive opinion.

The outstanding Major Quality Objections are as following:

- The quality of the critical intermediate KLH was insufficiently guaranteed. The CTD section dealing with the critical intermediate KLH is deemed deficient and incomplete. A major issue was the lack of process validation.
- The manufacturing process lacked full process validation and sufficient control of bioburden.
- Viral clearance and viral inactivation data for the IgM and IgG processes was insufficient and therefore, a final conclusion on viral safety cannot be drawn.
- Comparability between material from the manufacturing process used for clinical batches and

material from the commercial manufacturing process had not been demonstrated as studies were incomplete.

- Process related impurities are insufficiently controlled as specifications with associated actual limits were not defined and analytical methods for their determination were not validated.
- Characterisation data are incomplete and several characterisation tests had not been qualified.
- Critical Quality Attributes should be within specifications, despite large yield differences due to variability between batches, this has not been demonstrated.
- Stability: Stability for bulk IgM and IgG during shelf life had not been demonstrated. In addition, stability for the medicinal product manufactured with the commercial process had not been demonstrated.
- Compatibility of the product with regards to the instructions for use and handling in the proposed Summary of product characteristics (co-administration of Lympreva and GM-CSF in one syringe; in use shelf life) had not been demonstrated.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical part of this application is based on published literature and no additional study reports have been submitted by the Applicant. All pharmacological experiments were proof of concept studies and were not GLP-compliant.

Scientific advice has not been sought for the non-clinical aspects of Lympreva.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Pharmacologic data were generated in murine models using tumour-specific Ig (idiotype, or Id) clonally expressed by B-cell lymphomas as unique tumour-specific antigens. The models used were the 38C13 B cell lymphoma, the BCL1 lymphoma, and the lymphoma 141 models.

An overview of the published non-clinical proof of concept studies presented for the application on Lympreva is shown in Table 1.

Table 1: Overview of relevant primary pharmacodynamics studies

Type of Study	Reference	Objective	Species/Strain	Test article	Method of administration
Proof of concept	(Kaminski et al. 1987)	Assess optimal conditions of immunization	Mouse / C3H/HeN	50 mcg free 38C13-Id; 50 mcg 38C13-Id-KLH	i.p.
Proof of concept	(Campbell et al. 1987)	Assess whether 38C13-Id-KLH protects against tumour challenge	Mouse / C3H/HeN	50 mcg 38C13-Id-KLH in FCA, boosted with same dose in PBS 2 weeks later	i.p.
Proof of concept	(Campbell et al. 1988)	Assess therapeutic effects of 38C13-Id-KLH after lethal tumour inoculation	Mouse / C3H/HeN	50 mcg 38C13-Id-KLH in SAF-1, boosted 1 and/or 2 weeks later	s.c.
Proof of concept	(Campbell et al. 1990)	Assessing humoral and cellular requirements for anti-tumour immunity	Mouse / C3H/HeN	50 mcg 38C13-Id-KLH in SAF-1, boosted 1 and/or 2 weeks later	s.c.
Proof of concept	(Kwak et al. 1996)	Assess cytokines / GM-CSF for enhancement of T-cell mediated immune response	Mouse / C3H/HeN	50 mcg 38C13-Id-KLH (s.c., i.p.) or 25 mcg 38C13-Id-KLH (i.d.), with and without cytokines	s.c., i.p., i.d. (footpad)
Proof of concept	(Heyfets et al. 2002)	Determination of idiotype-specific T cell response	Mouse / C3H/eB	25 mcg 38C13-Id-KLH in CFA[1], two weeks later boosted with similar dose in IFA	s.c.
Proof of concept	(George et al. 1988)	Assess whether vaccination has a tumour inhibiting effect and protects against tumour challenge	Mouse / Balb/C	50 mcg BCL1 IgM or 50 mcg BCL1 IgM-KLH	s.c.
Proof of concept	(Sugai et al. 1974)	Assess whether vaccination has a tumour inhibiting effect and protects against tumour challenge	Mouse / B/W	1 mg IgM 141, 104E or human IgM or bovine serum albumin in FCA (total dose, given as 3 weekly or biweekly injections)	s.c. (multiple sites)

[1] CFA: complete Freund's adjuvant, IFA: incomplete Freund's adjuvant

38C13 B cell lymphoma

Immunization of animals with isolated Id protein (i.e., Id from 38C13, a B-cell lymphoma of C3H origin) resulted in the induction of Id-specific resistance to the tumour growth (Kaminski et al., 1987). 38C13 Idiotype was isolated from ascites fluid of mice inoculated with the rescue hybridoma 38C13/A1-2, which secretes abundant quantities of the 38C13 IgM protein. After intraperitoneal (IP) administration of purified Id, no detectable antibody to idiotype was induced. Due to the weak

immunogenicity of the 38C13 IgM protein alone, immunisation with 38C13 conjugated with the immunogen keyhole limpet haemocyanin (KLH) was tested and resulted in high titres of anti-Id antibodies.

When mice were lethally challenged with tumour cells IP, mice receiving the Id-KLH experienced 90% long term survival as compared with a 20% survival rate for mice receiving an irrelevant (not tumour-derived) IgM conjugated to KLH, demonstrating idiotype-specific immunization. With tumour challenges of 1000 cells and 10,000 cells, the group receiving the Id-KLH demonstrated survival rates of 50% and 20%, respectively. However, of mice receiving the irrelevant IgM-KLH, none survived long-term with either tumour cell number challenge. It was found that the Id-KLH conjugate could produce tumour immunity and antibody responses if it was administered at least one week prior to tumour challenge. The effect of free Id protein on the immunity induced by Id-KLH was investigated and it was found that free Id blocked immunity; however, once free Id fell to a sufficiently low level, immunity was again induced.

Campbell et al. (1987) examined the humoral and cellular immune responses elicited by Id immunisation. Survival significantly improved in mice groups receiving KLH-conjugated 38C13 idiotype protein compared with mice immunized with an unrelated IgM. Tumours developed in all control animals, while 30% of immunized mice remained tumour free for >120 days. Without KLH as a carrier, 38C13-Id did not confer resistance to tumour challenge and yielded only one long-term survivor. These results provided further support that KLH is needed to generate an adequate immune response to the 38C13 Id protein.

Use of idiotype immunotherapy in a therapeutic-like setting in which some tumour debulking would be expected with chemo- or radiotherapy, was investigated by Campbell et al.(1988), After administration of immunotherapy in the form of idiotype immunisation, mice treated with Id-KLH again demonstrated a significant prolongation on survival as compared with untreated animals. The results showed that Id immunotherapy alone or in combination with chemotherapy can be effective against established B cell tumours.

The roles of humoral and cellular anti-tumour immune responses were investigated in the 38C13 model (Campbell et al. 1990; Heyfets et al. 2002; Kwak et al. 1996). Id-specific T cells had not been found in earlier studies. As survival of T cell subset depleted mice was still significantly longer than the mice immunized with control IgM, it was hypothesized that an antibody dependent mechanism and not T cell responses were most likely responsible for the survival benefit. From tumour implantation experiments (Campbell et al. 1990) it was concluded that humoral responses as well as cellular immunity, which may be needed to produce an adequate humoral response or to lyse tumour directly, are important for resistance to tumour growth.

To determine the effect of a compromised immune system on Id immunotherapy, Kwak et al. (1990) investigated the use of idiotype immunization in the bone marrow transplant setting. Initial experiments showed that lethally irradiated mice transplanted with syngeneic marrow can mount a response to KLH as early as 3 weeks post-transplant. Near full resistance to tumour challenge was restored in mice at 5 weeks post bone marroe transplant. Anti-Id antibody response could be boosted by a second immunization two weeks later, but this did not result in any additional protection against tumour.

Based on the known pleiotropic effects of GM-CSF, including augmentation of antigen presentation, enhancement of T cell proliferation, and induction of MHC Class II expression on monocytes, the ability of GM-CSF to enhance the immune response after Id vaccination was tested in the 38C13 model (Kwak et al. 1996). Mice receiving recombinant murine GM-CSF and challenged with 38C13 tumour cells two weeks after immunization demonstrated significantly prolonged survival as compared with mice not receiving GM-CSF. GM-CSF administered subcutaneously (SC) appeared more effective than systemic (IP) administration, and, interestingly, the effect was found with relatively low doses of GM-CSF and lost with higher doses. Whereas GM-CSF enhanced survival for

38C13-Id vaccinated mice, it did not enhance survival for mice administered control IgM-KLH; thus GM-CSF appeared to enhance specific anti-Id immunity.

The involvement of a T cell component to the benefit conferred by GM-CSF was investigated by Kwak et al. (1996). Mice were vaccinated with 38C13-Id-KLH plus GM-CSF for four days, depleted of their CD4+ or CD8+ T cells and challenged with 38C13 tumour cells three weeks after immunization. Consistent with previous experiments, the protective effect of 38C13-Id-KLH was augmented by GM-CSF as compared with Id-KLH alone. Depletion of either CD4+ or CD8+ T cells resulted in abrogation of the beneficial effect of GM-CSF, indicating that the protective effect of GM-CSF combined with Id-KLH immunization was dependent on CD4+ and CD8+ T cells. Depletion of CD4+ T cells did not influence the beneficial effect of Id-KLH vaccine alone; however, depletion of CD8+ T cells did abrogate the beneficial effect of Id-KLH vaccination without GM-CSF, indicating that the mechanism of action of Id-KLH immunization may be mediated through CD8+ T cells even in the absence of GM-CSF.

An increase in the frequency of Id-specific IFNγ secreting T cells was demonstrated in mice immunized two times with syngeneic 38C13 tumour-derived Ig-KLH (Heyfets et al. 2002). Depletion of T cell subsets demonstrated that both CD4+ and CD8+ T cells were involved in the response to Id. The same immunization schedule resulted in high levels of anti-Id antibodies and anti-Id antibody production was evident already after a single immunization, suggesting a slow onset of the cellular response compared to the humoral response.

BCL1 mouse model

George et al. (1988) used a slower-growing model of lymphoma, the BCL1 mouse model, to attempt to come closer to mimicking human disease; the lymphoma grows more slowly than the 38C13 model, allowing for immunization of animals after tumour establishment in the spleen. Instead of varying the time from tumour inoculation, the investigators varied the numbers of tumour cells in the inoculum, which results in replacement of normal spleen cells with tumour cells at different times and allows discernment of the timing of protective immunization. Mice were immunized with BCL1 IgM or BCL1 IgM-KLH and long-term survival was found to be dependent on the number of tumour cells inoculated. In a subsequent study, conjugation of KLH to BCL1 IgM led to a more rapid production of antibodies.

Lymphoma 141 model

Sugai et al. (1974) investigated the ability of another tumour idiotype, from a spontaneously arising malignant lymphoma murine model in B/W mice (lymphoma 141), to serve as a tumour specific antigen. They first demonstrated the presence of idiotypic determinants on the protein with an immunofluorescent assay using rabbit serum raised to the protein. Results from inhibition experiments showed that purified IgM from the lymphoma 141 cells inhibited binding of the rabbit anti-Id antibodies, whereas an immunoglobulin from another tumour line, MOPC104E, had no effect. When mice were immunized with a human monoclonal IgM from a patient with Waldenstrom's macroglobulinaemia, and challenged with 1 x 105 lymphoma 141 cells, 15/16 mice died by day 35. In contrast, four out of five mice immunized with the lymphoma 141 idiotype had only a small tumour nodule on day 35.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies have been conducted with Dasiprotimut-T (see discussion on non-clinical aspects).

Safety pharmacology programme

Safety pharmacology studies were not performed (see discussion on non-clinical aspects)..

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were not performed (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

Pharmacokinetic studies were not submitted (see discussion on non-clinical aspects).

Toxicology

Single dose toxicity

No single-dose toxicity studies were submitted (see discussion on non-clinical aspects).

Repeat dose toxicity

No repeat-dose toxicity studies were submitted (see discussion on non-clinical aspects).

Genotoxicity

No genotoxicity studies were submitted (see discussion on non-clinical aspects).

Carcinogenicity

No carcinogenicity studies were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No reproductive and developmental studies were submitted (see discussion on non-clinical aspects).

Toxicokinetic data

N/A

Local Tolerance

No local tolerance studies were submitted (see discussion on non-clinical aspects).

Other toxicity studies

N/A

2.3.4. Ecotoxicity / environmental risk assessment

No ERA was submitted (see discussion on non-clinical aspects).

2.3.5. Discussion on non-clinical aspects

Id immunotherapy was associated with prevention or slowing the growth of syngenic tumour challenge in a number of B cell lymphoma models (38C13, BCL1 and lymphoma 141. The addition of the KLH carrier protein added to the Id immunogenicity. The addition of GM-CSF at low i.p. doses showed enhanced protective anti- tumour immunity.

In vitro data generated from immunized animals showed the formation of anti-Id antibodies after vaccination. The serum titres of such antibodies were also correlated to survival. Serum from immunized animals was also able to induced ADCC against the syngenic tumour. A specific T cells response against the Id antigen was also shown by a decrease in tumour protection in immunised, T cell depleted, animals after tumour challenge. Also, upon prime-boost immunisation IFNg producing T cells could be detected upon Id-antigen stimulation. In addition, mice with a compromised immune system (lethally irradiated and transplanted) were able to survive tumour challenge after receiving Id immunisation.

Pharmacokinetic studies have not been performed and are generally not required for tumour immunotherapy products or adjuvants in accordance with the Guideline on the evaluation of anticancer medicinal products in man Rev. 4".
The product applied for holds an autologous Id-antigen conjugated to the KLH adjuvant specifically produced for every individual patient. Thus, every batch will be different in terms of the antigenic amino acid sequence. Therefore, conventional toxicology studies are neither appropriate nor relevant.

To use homologues murine Id-antigens for toxicity testing could potentially have provided data on the safety profile of the product (local tolerance, systemic effects), however such data could also be questioned due to the autologous nature of the human product. Nevertheless, taking the general safety profile of tumour immunotherapy products and the available clinical data in to account, it is concluded that additional animal toxicology studies are not required.

As to the carrier protein, KLH, the applicant did not include any discussion or data on its toxicological properties, but rely on clinical data to substantiate safety. GM-CSF has been used in the past extensively in the clinic. Thus, from a non-clinical point of view additional non-clinical toxicology studies with GM-CSF are not required.

Environmental risk assessment has not been submitted in accordance with the guidance on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) which specifically exempts amino acids, peptide and proteins from the need for a detailed environmental assessment.

2.4. Conclusion on the non-clinical aspects

Overall, the non-clinical overview of the published literature was considered adequate.

2.5. Clinical aspects

2.5.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2: Overview of clinical studies

Study Centres, Dates, Status, and Enrolment Goals	Study Population and Dosing Regimen	Number of Enrolled Patients and Treatment Duration	Patient Demographics	Primary and Secondary Efficacy Endpoint(s)
BV301: Pivotal, Phase 3, Randomized, Double-blind, Active-control Study				
Study Centres Location (N): USA (13); Russia (4) **Study Start/End Date:** Jan-00/ Apr-08 **Study Status:** Study stopped Total enrollment:234 Enrolment goal: 629	**Study Population:** Male or female treatment-naive patients with follicular lymphoma (stage IIx, III, or IV and Grade I, II, or IIIa) and surface IgM or IgG phenotype with a monoclonal heavy and light chain. Following induction therapy, patients must have achieved CR/CRu before receiving vaccine. **Dosing Regimen:** Following induction chemotherapy, vaccine administered at Months 1, 2, 3, 4, and 6: • Dasiprotimut-T Biovest (0.5 mg Id+0.5 mg KLH) sc on Day 1with 100µg/m^2/day GM-CSF on Day 1-4 • 0.5 mg KLH sc on Day 1with 100µg/m^2/day GM-CSF on Day 1-4	**Enrolment (Number randomized/vaccinated):** Dasiprotimut-T Biovest=118/59 Control=76/41 Total=234 **Treatment duration:** Total treatment duration=6 months	**Gender:** 95 (Male) 82 (Female) **Median Age (Range):** 49 (19-80)	**Primary efficacy endpoint:** Disease free survival from the date of randomization until relapse or last follow-up **Secondary efficacy endpoints:** • To determine the ability of Dasiprotimut-T Biovest to produce a molecular CR in patients in clinical CR, but with polymerase chain reaction (PCR) evidence of residual disease after standard chemotherapy; • To determine the impact of Dasiprotimut-T Biovest immunization on molecular DFS in FL patients; • To evaluate the ability of Dasiprotimut-T Biovest to generate an immune response against autologous tumor; • determine and compare the overall survival (OS) of patients randomized to receive either treatment assignment
NCI T93-0164: Supportive Phase 2, Randomized, Open-label, Parallel Group Study				
NCI T93-0164 **Study Centres Location (N):** NCI (1) **Study Start/End Date:** Oct-93/Febr-10	**Study Population:** Male or female treatment-naive patients with follicular lymphoma (stage III or IV) with surface IgM, IgG, IgA phenotype with a monoclonal heavy and light chain. Following induction therapy, patients must have achieved CR	**Enrolment (Number randomized/vaccinated):** Dasiprotimut-T Biovest with 100µg/m^2/day GM-CSF=25 Dasiprotimut-T Biovest with 500µg/m^2/day GM-CSF=13/12	**Gender:** 28 (Male) 14 (Female) **Median Age (Range):** 46 (24-66)	**Primary efficacy endpoint:** Complete molecular response rate in patients with clinical complete response rate from chemotherapy who are still bcl-2 positive post-chemotherapy and become bcl-2 negative after vaccination therapy **Secondary efficacy endpoints:** • To determine which of the 2 granulocyte-

Study Centres, Dates, Status, and Enrolment Goals	Study Population and Dosing Regimen	Number of Enrolled Patients and Treatment Duration	Patient Demographics	Primary and Secondary Efficacy Endpoint(s)
Study Status: Study completed Total enrolment: 42 Enrolment goal: 42	before receiving vaccine. **Dosing Regimen:** Following induction chemotherapy, vaccine administered at Months 1, 2, 3, 4, and 6: • Dasiprotimut-T Biovest (0.5 mg Id+0.5 mg KLH) sc on Day 1with 100µg/m^2/day GM-CSF on Day 1-4 • Dasiprotimut-T Biovest (0.5 mg Id+0.5 mg KLH) sc on Day 1with 500µg/m^2/day GM-CSF on Day 1-4	Total=42 **Treatment duration:** Total treatment duration=6 months		macrophage colony-stimulating factor (GM-CSF) doses (100 vs. 500 µg/m^2/day) is a more biologically active vaccine adjuvant, as measured by the endpoints in the primary objectives described above • To determine the impact of Dasiprotimut-T Biovest immunization on disease free survival (DFS) of patients achieving a complete response (CR) with chemotherapy
NCI 1033: Bridging Phase 2, Single-arm, Open-label Study				
NCI 1033 **Study Centres Location (N):** NCI (1) **Study Start/End Date:** **Jun-00/Aug 03** **Study Status:** Study completed	**Study Population:** Male or female treatment-naive patients with mantle cell lymphoma (blastic variant included, all stages) **Dosing Regimen:** Following induction chemotherapy, vaccine administered at Months 1, 2, 3, 4, and 6: • Dasiprotimut-T Biovest (0.5 mg Id+0.5 mg KLH) sc on Day 1with 100µg/m^2/day GM-CSF on Day 1-4	**Enrolment (Number randomized/vaccinated):** Dasiprotimut-T Biovest=26/24 **Treatment duration:** Total treatment duration=6 months	**Gender:** 19 (Male) 7 (Female) **Median Age (Range):** 56 (22-73)	**Primary efficacy endpoint:** Progression free survival from the start of chemotherapy until progression or death. **Secondary efficacy endpoints:** • To assess the response rate and toxicity of EPOCH-R in previously untreated mantle cell lymphoma • To assess the use of molecular markers of mantle cell lymphoma, including PCR- based methodologies for detection of bcl-1 and IgH rearrangements (*data not analyzed*) • To obtain cDNA microarray profiling of untreated mantle cell lymphomas (*data not analyzed*)

2.5.2. Pharmacokinetics

No pharmacokinetic studies have been submitted.

2.5.3. Pharmacodynamics

The pharmacodynamics of Lympreva has been studied in relation to the following clinical studies: a phase 2 clinical study in patients with advanced-stage follicular NHL in first complete remission (CR)

(NCI T93-0164), and a phase 2 bridging study in mantle cell lymphoma (MCL) patients in first remission achieved with a rituximab combination chemotherapy induction regimen (NCI 1033).

Mechanism of action

No clinical pharmacodynamic studies were submitted.

Primary and Secondary pharmacology

The primary pharmacology has been studied using various biomarkers of immune response. The immune response endpoints investigated in these studies include: Humoral anti-Id response, Proliferative anti-Id response, Increase in tumour specific cytolytic T-lymphocytes precursors (CTLp) frequency, Tumour-specific direct cytotoxicity, Tumour-specific cytokine production, Id-specific cytokine production.

In both studies 5 immunizations were administered at month 1, 2, 3, 4, and 6. Each immunization consisted of subcutaneous injections administered over 4 days: (Id-KLH with GM-CSF on Day 1 and GM-CSF on Days 2-4). The dose of Id-KLH was 0.5 mg Id conjugated to 0.5 mg KLH and administered subcutaneously on day 1. Immune responses were available for 20/42 enrolled patients in study NCI T93-0164 and for 23/26 enrolled patients in study NCI 1033. The pharmacodynamic biomarker responses are summarized in Table 3.

Table 3: Immune response data from 2 phase 2 studies

Critical Aspects of Study Design and Endpoints	NCI T93-0164 (Bendandi 1999)	NCI 1033 (Neelapu 2005; Grant 2011; Dunleavy 2012)
Study population (N/ histology/ prior therapy)	20/ FL/ Treatment naïve	23/ MCL/ Treatment naive
Vaccine adjuvant	GM-CSF 100 µg/m2/day vs. 500 µg/m2/day	GM-CSF 100 µg/m2/day
Vaccine schedule (month)	0, 1, 2, 3, 5	0, 1, 2, 3, 5
Vaccine dose	0.5 mg Id conjugated to 0.5 mg KLH	0.5 mg Id conjugated to 0.5 mg KLH
Time to vaccine (months)	12.3 to 17.7	2.1 to 8.3
Disease status at vaccine	20 CR	22 CR 1 PD
Anti-Id Ab (N/ %)	15 (75)	7(30)
Anti-Id Ab kinetics	ND	Detected after 4th-5th vaccine (concomitant to post-rituximab B-cell recovery)
Tumor-specific cytokine release	19 (95%) patients Duration 6+ to 18+ months • TNFα: median 825 pg/mL; range 92- 2,453 pg/mL • INFγ: median 121 pg/mL; range 50-290 pg/mL • GM-CSF: median 112 pg/mL; range 53- 372 pg/mL	20 (87) patients Detected after 3rd vaccine (concomitant to total B-cell depletion post-rituximab) • TNFα: median 1.65 pg/mL; range 0-37.8 pg/mL • INFγ: median 4.75 pg/mL; range 0-63.1 pg/mL • GM-CSF: median 4.3 pg/mL; range 0-56.3 pg/mL
Id-specific cytokine release (N/ %)	ND	13(57)
Tumor-specific direct cytotoxicity	Substantial tumor-specific lysis of autologous FL targets mediated by post-immune CD8+ T-cells	Tested in 1 patient: 27% post-vaccine tumor-specific lysis compared to 2% for pre-vaccine
T-cell precursor frequency (N/ %)	ND	9 (39) patients had significant increase in frequency post-vaccine compared to pre-vaccine

In the study of patients not receiving rituximab, immune responses were available for 20/42 enrolled patients. CD4+ and CD8+ cytokine were induced in 19/20 patients while humoral Id-responses demonstrated in 15/20 of patients; in the study with patients pre-treated with rituximab, CD4+ and

CD8+ cytokine responses were induced in 87% of the treated patients, while humoral Id-responses were demonstrated in 30% of the patients.

2.5.4. Discussion on clinical pharmacology

The pharmacodynamics of Lympreva has been investigated in two clinical studies by assessment of various biomarkers of immune response.

2.5.5. Conclusions on clinical pharmacology

Additional clinical pharmacology studies for Lympreva are not required.

2.6. Clinical efficacy

2.6.1. Dose response studies

No dose/response studies were performed.

2.6.2. Main study

Study BV301

Methods

Study BV301 was a a phase 3, double-blind, controlled, multicenter randomized trial of patient-specific active immunisation with Lympreva (an autologous immunoglobulin follicular lymphoma idiotype immunotherapy fused with KLH) with local GM-CSF in first complete remission, compared to a control consisted only of carrier (KLH) and adjuvant (GM-CSF), in patients with indolent, Stage IIx, III, or IV follicular lymphoma (FL) in first CR/CRu (CR unconfirmed) achieved with PACE (prednisone, doxorubicin, cyclophosphamide, and etoposide).

Study Participants

Inclusion criteria

Patients had to meet the following criteria:

1. Tissue diagnosis of FL with surface IgM or IgG phenotype with a monoclonal heavy and light chain as determined by flow cytometry.. The histology of the lymph node biopsy as evaluated by the NCI should be Follicular Center Cell (FCC) Grade I, II, or IIIa (FSC lymphoma, FM, or follicular large cell lymphoma with centrocytes).

2. Stage II with bulky adenopathy (> 5 cm in diameter), Stage III or IV lymphoma.

3. Patients should be chemotherapy naive-patients and may have received prednisone (<2 months of therapy).

4. Previous treatment with radiation alone (□ 2 sites) was permissible.

5. A single peripheral lymph node > 2 cm size accessible for biopsy/harvest or an abdominal lymph node > 2 cm that was accessible for laparoscopic biopsy. Patients with lymphoma cells circulating in the peripheral blood, malignant pleural effusions, or malignant ascites may have been eligible if adequate lymphoma cells were present (> 109).

6. ECOG performance status < 2, unless the performance was directly related to disease and therefore should have improved with therapy.

7. Life expectancy of > 1 year.

8. Serum creatinine < 1.5 mg/dl unless secondary to lymphoma.

9. Bilirubin ≤ 1.5 mg/dl unless secondary to lymphoma or Gilbert's disease. SGOT/SGPT < 3.5 x upper limit of normal.

10. Ability to give informed consent. Ability to return to clinic for adequate follow-up for the period that the protocol requires.

Exclusion criteria

Any patient who met any of the following criteria was excluded:

1. Any amount of radiation exceeding 2 sites, including prior total body irradiation (TBI).

2. Presence of antibodies to human immunodeficiency virus (HIV), hepatitis B surface antigen or other active infectious process.

3. Pregnancy or lactation.

4. A history of unrelated (non-lymphomatous) neoplasm within the past 10 years other than non-melanoma skin cancer or in-situ cervix cancer. Patients with a prior diagnosis of malignancy more than 10 years may have entered into the study at the discretion of the PI.

5. Unwilling to give informed consent.

6. Failure to meet any of the eligibility criteria.

7. Any medical or psychiatric condition that, in the opinion of the protocol chairman, would compromise the patient's ability to tolerate this treatment.

8. Patient with primary or secondary central nervous system (CNS) lymphoma (current or previously treated) was not eligible.

Treatments

Segment A: Within 30 days of the date of Segment A registration, patients were to receive induction chemotherapy with PACE (Prednisone, Doxyrubicin, Cyclophosphamide, and Etoposide) until they achieved their best response. Each complete responder was to have received a minimum of 6 cycles before therapy was discontinued. Patients who achieved a CR/CRu were to enter on the vaccination part of the protocol and randomized. Patients with less than a CR/CRu or with PD were to be taken off of the study. Only 8 cycles of chemotherapy with adriamycin and 10 total cycles of chemotherapy were allowed.

The dose and schedule for each PACE chemotherapy 28-day cycle are described in Table 4.

Table 4: PACE chemotherapy doses and schedule per cycle (Study BV301)

Day 1	Day 8	Day 14	Day 29
Cyclophosphamide 650 mg/m^2	Cyclophosphamide 650 mg/m^2		Start of next cycle$^{\alpha}$
Doxorubicin 25 mg/m^2	Doxorubicin 25 mg/m^2		
Etoposide VP-16 120 mg/m^2	Etoposide VP-16 120 mg/m^2		
Prednisone 40 mg/m^2, daily x 14 (i.e., Days 1 to 14)			

$^{\alpha}$At least 6 cycles were administered.

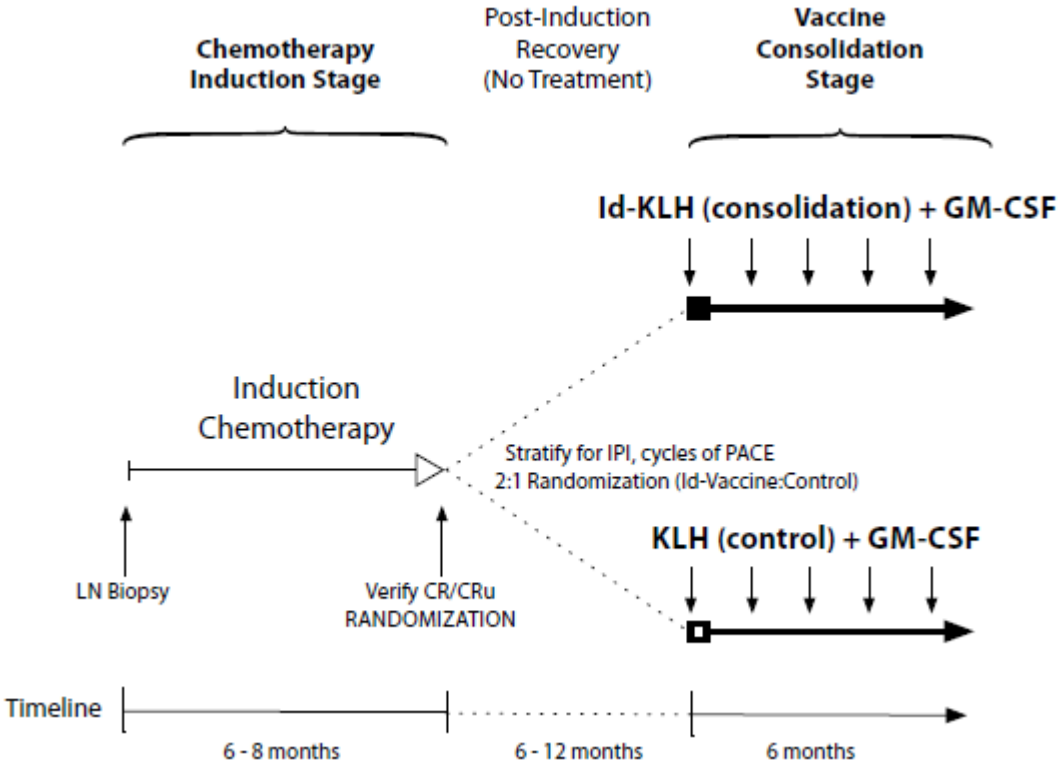
Segment B :Six months (up to a maximum period of 12 months) after the completion of induction chemotherapy, all patients who had not relapsed were randomized and planned to receive a series of

5 subcutaneous injections at 1, 2, 3, 4 and 6 months according to doses described in Table 5, as shown in Figure 1.

Table 5: Vaccination Therapy Schedule and Doses (Study BV301)

Group	Day 1	Day 2	Day 3	Day 4
Active	1 mg Id KLH / 100 μg/m²/day GM-CSF	100 μg/m²/day GM-CSF	100 μg/m²/day GM-CSF	100 μg/m²/day GM-CSF
Control	1 mg KLH-KLH / 100 μg/m²/day GM-CSF	100 μg/m²/day GM-CSF	100 μg/m²/day GM-CSF	100 μg/m²/day GM-CSF

Figure 1: Design of Study BV301



Objectives

The primary objective was to evaluate efficacy and safety by assessing significant prolongation of clinical Disease-Free Survival (DFS) following Lympreva + GM-CSF when compared to DFS following administration of KLH + GM-CSF, in FL patients achieving a CR with standard dose chemotherapy.

Secondary objectives included the following: to determine the ability of Id-vaccine to produce a molecular CR in patients in clinical CR, but with PCR evidence of residual disease after standard chemotherapy; to determine the impact of Id immunization on molecular DFS in FL patients; to evaluate the ability of Id vaccine to generate an immunology response against autologous tumour; to determine and compare the overall survival of patients randomized to receive either treatment arm; to evaluate the safety of a series of 5 immunization injections administered with GM-CSF as adjunct therapy over a 6 month period.

Outcomes/endpoints

The primary endpoint was the clinical Disease-Free Survival, defined as duration from randomization to relapse or last follow-up.

Secondary endpoints included the following:

Molecular CR (defined as the proportion of patients achieving a molecular CR (CR + PCR negative) after vaccination among those with a CR/CRu and PCR evidence of residual disease before vaccination);

Molecular DFS defined as the duration of molecular DFS after randomization in FL patients achieving a CR but with PCR evidence of residual disease before vaccination;

Rate of immune response against the autologous tumour; defined as the proportion of patients who achieve an immunologic response against the autologous tumour;

Overall survival defined as the time from randomization to the date of death due to any reason or last follow-up.

Sample size

The following assumptions are used to estimate the sample size of the study:

• 85% of patients entered onto the trial and administered PACE chemotherapy are expected to achieve a complete remission (CR) or CRu. Updated enrollment data from the clinical trial suggest that the actual proportion of patients achieving CR/CRu from PACE chemotherapy is higher than originally assumed (i.e. 80 – 85% vs. 66% as described in protocol version P).

• 87% of patients entered onto the trial and administered CHOP-R chemotherapy are expected to achieve a complete remission (CR) or CRu.

• CHOP-R was not used in the first years of accrual and it is currently assumed for power calculation purposes that a fixed proportion of patients entered onto the trial will use CHOP-R in the later 2 years of the recruitment period (75%).

• The median disease-free survival for patients with follicular lymphoma treated with GM-CSF alone after PACE chemotherapy is expected to be 3.5 years.

• The median disease-free survival for patients with follicular lymphoma treated with GM-CSF alone after CHOP-R chemotherapy is expected to be 6.9 years.

• This study will utilize an intent-to-treat design and all patients will be analyzed as they were randomized.

• Sample size calculations will be performed based on simulations assuming an intent-to-treat analysis, equal hazards (1.0 hazard ratio) for the first 8 months (when treatments are expected to be the same in both randomized arms), and then a hazard ratio of 2.0 after 8 months.

• A two-sided hypothesis test at the alpha=0.01 level will be used to ensure a stringent evaluation.

• A 2:1 randomization favoring Id-KLH vaccine will be used to gain more information about the effects of vaccine in this group of patients.

Based on the above, 563 patients were planned to be enrolled and receive PACE as first line chemotherapy treatment (Segment A) so that 375 patients (Segment B) could be randomized at a 2:1 rate to the vaccine (Lympreva+GM-CSF) arm (n=250) or to the control (KLH-KLH+GM+CSF) arm (n=125).

However, during the 08 April 2008 DMC meeting, it was recommended that enrollment be discontinued before reaching the intended sample size.

Randomisation

Patients were randomised immediately after completion of chemotherapy to be allocated to active or control arm with a ratio of 2:1, respectively. Randomization was stratified by number of

chemotherapy cycles (<8 vs. ≥8), and IPI (International Prognostic Index) risk group (levels 0, 1 and 2 vs. levels 3 and 4).

Blinding (masking)

This was a double-blinded study.

Statistical methods

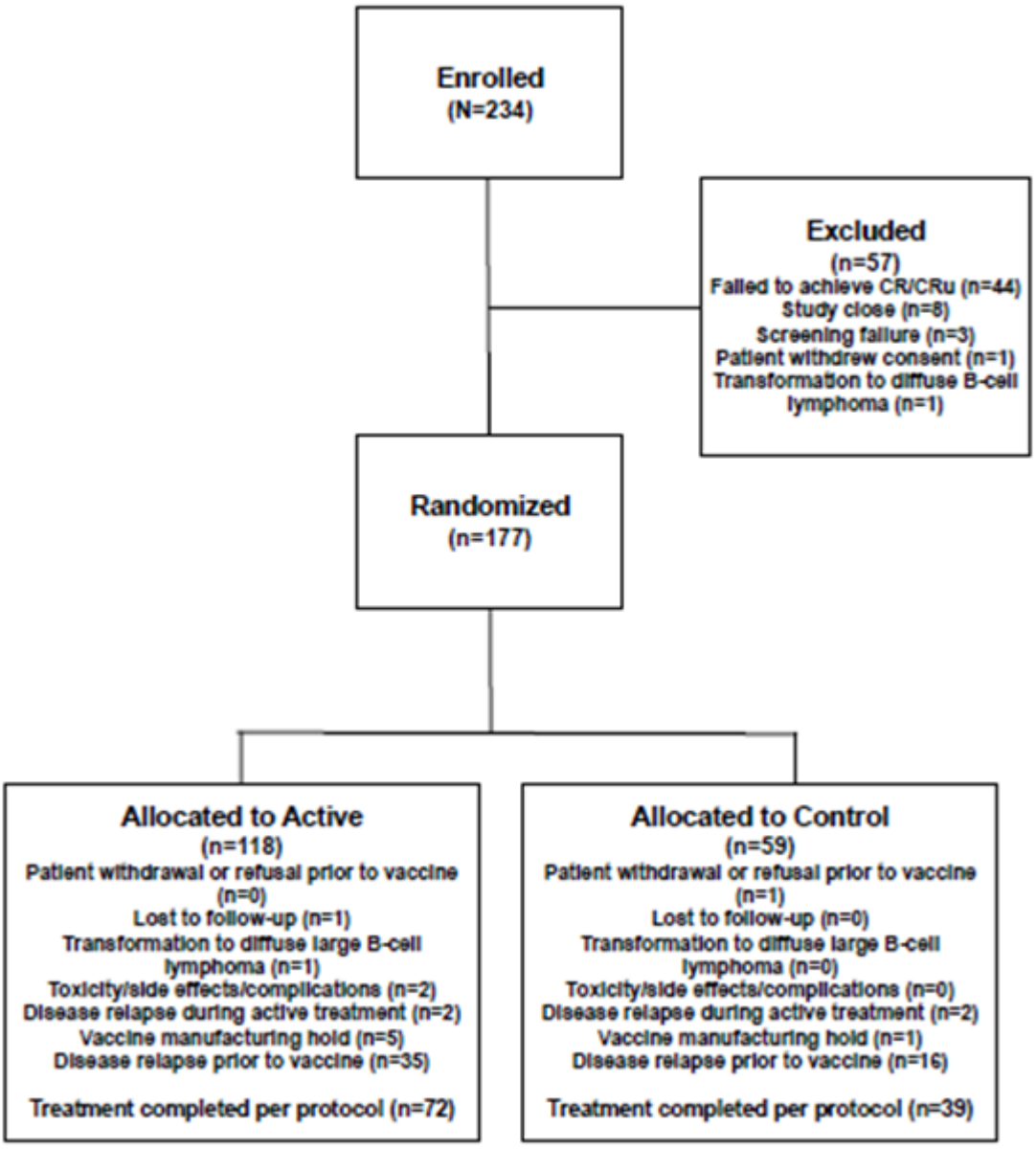
A 2-sided test was planned at a Type I error rate of 0.01 for the primary efficacy analysis of this study. All other statistical analyses were to be performed using a 2-sided hypothesis test at the overall 5% level of significance and a 95% confidence interval (CI). No adjustment for Type I error was planned for multiple comparisons if applicable. Since there were no multiple comparisons planned in this study, adjustments for multiple comparisons were not made. A row denoted "Missing" was included in count tabulations where necessary to account for dropouts and missing values. The denominator for all percentages was the number of patients in that treatment within the population of interest. Missing data were not imputed.

Patients who received additional chemotherapy and/or radiation therapy after randomization were considered to be off-study and did not receive the vaccine. Patients who relapsed after randomization but prior to vaccination did not receive the vaccine but were included in the intent-to-treat (ITT) population as censored observations and were followed for survival. Patients randomized to receive the Lympreva for whom the Lympreva could not be made received the KLH control vaccine and were analyzed according to the study arm they were randomized.

The population used for the primary analyses include patients that underwent vaccination (patients who achieved CR/CRu after induction with PACE and underwent randomisation between active and control vaccination.

Results

Participant flow



Recruitment

The trial was conducted from 14 January 2000 (first patient enrolled) to 16 October 2007 (last patient completed). A total of 17 centres in US, Russia and Ukraine were involved.

Conduct of the study

Major protocol deviations and violations are reported in Table 6.

Table 6: Major Protocol Deviations and Violations (ITT Population, Study BV301)

	N	%
Major Protocol Deviations		
Assessment Deviations	32	18.1
Deviation Other, Minor	12	6.8
Major Protocol Violations		
Dosing Violations	4	2.3
Inclusion/ Exclusion Criteria Violations	1	0.6
Other Violations	14	7.9

ITT population includes all patients who were randomized to one of the treatment arms, as randomized.
Percentage indicates number of patients with a protocol deviation or violation from the ITT population.

A total of 19 amendments were made to the protocol between 02 August 2000 and 14 March 2007. The major ones are summarised below.

Amendment 3 (14 July 2001) included an update to provide a more stringent evaluation of the primary efficacy endpoint and generate a more robust outcome as follows: a 2-sided hypothesis test at the alpha=0.01 level was implemented; the sample size was increased from 450 to 563 total enrolled patients; patients randomized to the Id-KLH arm for whom vaccine could not be made were to receive KLH control and be analyzed as randomized. Overall survival was added as a secondary endpoint. A provision was added to clarify that only patients who maintained their CR/CRu would receive vaccinations. It was also specified that vaccination therapy must be administered at a Consortium site, and that only randomized patients who had relapsed would receive vaccinations.

Amendment 5 (24 July 2001) expanded the eligibility criteria to include patients with Stage II with bulky adenopathy, and patients with tumour histology of FL Grade IIIa.

Amendment 8 (22 April 2003) included changes regarding the following: additional sources of lymphoma cells for vaccine production (i.e., peripheral blood, pleural effusion, and ascites); additional methods of tissue procurement (i.e., mini-laparotomy for abdominal nodes not accessible via biopsy), a clarification of relapse criteria using tissue diagnosis.

Amendment 10 (03 December 2003): PACE chemotherapy modifications included a Prednisone dose reduction from 60 mc/m^2 to 40 mg/m^2, and the specification that dexamethasone use while on PACE regimen was not permitted.

Amendment M (10 May 2004) was the first amendment after the IND transfer from NCI to Biovest, and reflected the changed responsibilities, administrative changes in study conduct, and removal of irrelevant information.

Amendment R (no version date) changed the expected CR/CRu rate from PACE chemotherapy from 66% to 80-85% based on the observed response rate in the patients enrolled in the study, which resulted in a sample size reduction from 563 to 460.

Amendment T (14 March 2007): addition of the CHOP-R regimen as an induction therapy. The choice of induction therapy regimen was at the discretion of the PI or the treating physician. In addition to the changes driven by the CHOP-R addition, several protocol changes were included as follows: the requirement to collect bone marrow aspirates for molecular analyses was removed throughout as their value was reassessed as less reliable than that of peripheral blood samples; added requirement for collection of peripheral blood for T-cell assays and serum and peripheral blood for storage; the requirement for chest X-rays during the screening visits was removed; the option for Fine Needle aspiration (FNA) for relapsed disease determination was removed. Ten patients were enrolled under Amendment T.

Baseline data

Baseline demographic and disease characteristics are summarized in Table 7.

Table 7. Demographics and Baseline Characteristics (ITT Population, Study BV301)

	Active (N=118)		Control (N=59)		All Patients (N=177)		
Characteristic	N	%	N	%	N	%	P†
Gender							0.338
Male	60	50.8	35	59.3	95	53.7	
Female	58	49.2	24	40.7	82	46.3	
Age							0.586
Mean (SD)	49.7 (9.9)		50.1 (9.8)		49.8 (9.9)		
Median	49.7		50.0		49.9		
Min, Max	19.2, 80.1		30.2, 69.2		19.2, 80.1		
Age category							0.861
<50 years	60	50.8	30	50.8	90	50.8	
50-59 years	40	33.9	19	32.2	59	33.3	
60-69 years	15	12.7	10	16.9	25	14.1	
70-79 years	2	1.7	0	0.0	2	1.1	
≥80 years	1	0.8	0	0.0	1	0.6	
Race/Ethnicity							0.797
White	104	88.1	52	88.1	156	88.1	
Black	5	4.2	5	8.5	10	5.6	
Hispanic or Latino	4	3.4	1	1.7	5	2.8	
Asian	4	3.4	0	0.0	4	2.3	
American Indian or Alaskan Native	1	0.8	0	0.0	1	0.6	
Other	0	0.0	1	1.7	1	0.6	
Stage at study enrollment							0.219
Stage II	2	1.7	1	1.7	3	1.7	
Stage III	40	33.9	13	22.0	53	29.9	
Stage IV	76	64.4	45	76.3	121	68.4	
Histology							0.749
Follicular Mixed Lymphoma	64	54.2	34	57.6	98	55.4	
Follicular Small Cleaved Cell Lymphoma	54	45.8	25	42.4	79	44.6	
ECOG Performance Status							1.000
0	94	79.7	46	78.0	140	79.1	
1	23	19.5	12	20.3	35	19.8	
2	1	0.8	1	1.7	2	1.1	

FLIPI risk group							0.559
Low Risk (0,1)	65	55.1	28	47.5	93	52.5	
Intermediate Risk (2)	39	33.1	22	37.3	61	34.5	
High Risk (3,4,5)	13	11.0	9	15.3	22	12.4	
Missing	1	0.8	0	0.0	1	0.6	
IPI risk group							1.000
Low or Low-Intermediate (0,1,2)	105	89.0	53	89.8	158	89.3	
High-Intermediate or High (3,4,5)	13	11.0	6	10.2	19	10.7	
Tumor isotype							0.360
IgD	1	0.8	1	1.7	2	1.1	
IgG	55	46.6	23	39.0	78	44.1	
IgM	61	51.7	33	55.9	94	53.1	
IgM/IgG	1	0.8	2	3.4	3	1.7	
Number of chemotherapy cycles							1.000
<8	60	50.8	29	49.2	89	50.3	
≥8	58	49.2	30	50.8	88	49.7	

ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; FLIPI = Follicular Lymphoma International Prognostic Index; Ig = Immunoglobulin
† Comparison performed with two-sided Fisher Exact Test for categorical variables; otherwise, a Wilcoxon Rank Sum Test for mean level comparisons.
Active = dasiprotimut-T Biovest + GM-CSF; Control = KLH-KLH + GM-CSF
ITT population includes all patients who were randomized to one of the treatment arms, as randomized.

Numbers analysed

Patient populations of the Study BV301 are reported in Table 8.

Table 8: Patient Population Definition and Enrollment (Study BV301)

Population	Definition	Total Number in Defined Population	Enrollment per Treatment group Active/ Control
All Enrolled	All patients screened and enrolled in Segment A. Patients screened and pre-registered for lymph node biopsy were not included.	N = 234	N/A
ITT Population	All patients who were randomized to one of the treatment groups (in Segment B) - regardless of whether or not they received study drug - and analyzed according to the treatment assigned.	N = 177	118†/ 59
PP Population	All patients randomized to one of the treatment groups, excluding those with major protocol violations and for whom vaccine could be made, and analyzed according to the treatment received.	N = 97	62/35
Safety Population	All patients exposed to treatment (in Segment B) - i.e., received at least on dose of study drug (either active [Dasiprotimut-T+GM-CSF] or control [KLH-KLH+GM-CSF]) and analyzed according to the treatment received.	N = 117	71/46†

Active = Dasiprotimut-T Biovest+GM-CSF; Control = KLH-KLH+GM-CSF; GM-CSF = granulocyte macrophage colony-stimulating factor; KLH = keyhole limpet haemocyanin
† Includes 5 patients randomized to vaccine but received control

Outcomes and estimation

Primary endpoint: Disease-free Survival

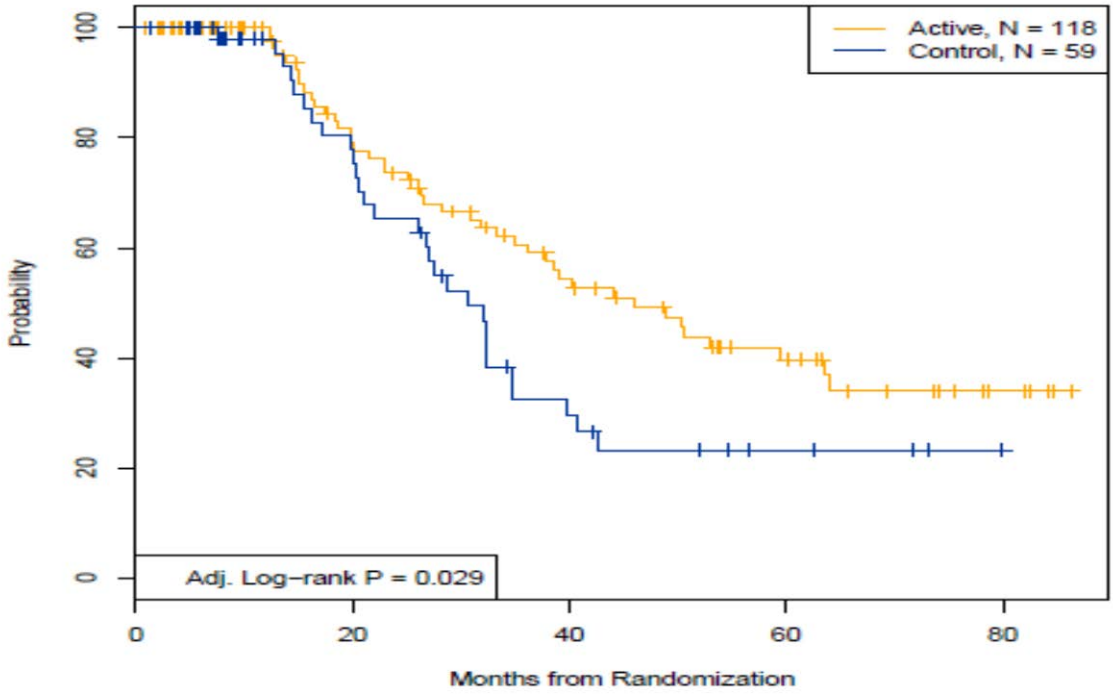
In the ITT population, results in term of median DFS are shown in Table 9 and Figure 2. Patients who relapsed prior to receiving vaccine were treated as censored observations.

Table 9: Duration of Clinical Disease-Free Survival Controlled for FLIPI Risk Group and Number of Chemotherapy Cycles, censoring untreated patients (ITT Population, Study BV301)

	Active (N=118)	Control (N=59)	P-value
Log-rank test			**0.029**
Median, months	46.0	30.6	
95% CI	36.2-63.9	26.2-39.8	
Length of follow-up: min-max (median, months)	4.2-92.0 (55.2)	5.7-90.7 (56.6)	
Number of events	43	29	
Number censored	75	30	

ITT population includes all patients who were randomized to one of the treatment arms, as randomized.
Active = dasiprotimut-T Biovest + GM-CSF; Control = KLH-KLH + GM-CSF

Figure 2: Kaplan-Meier Estimation of Clinical Disease-Free Survival Controlled for FLIPI Risk Group and Number of Chemotherapy Cycles, censoring untreated patients (ITT Population, Study BV301)

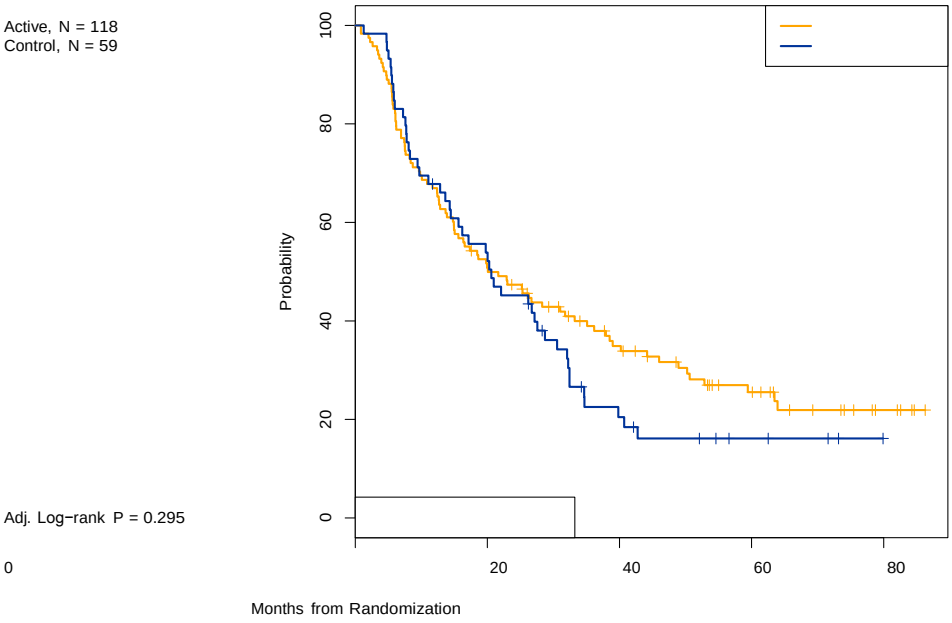


Median DFS results when all events occurring after randomization are counted are reported in Table 10 and Figure 3.

Table 10: Duration of Clinical Disease-Free Survival Controlled for FLIPI Risk Group and Number of Chemotherapy Cycles, Untreated Patients as Events (ITT Population, Study BV301)

	Active (N=118)	Control (N=59)	P-value
Log-rank test			0.295
Median, months	20.1	20.6	
95% CI	15.0-35.1	14.5-30.6	
Length of follow-up: min-max (median, months)	4.2-92.0 (55.2)	5.7-90.7 (56.6)	
Number of events	85	47	
Number censored	33	12	

Figure 3: Kaplan-Meier Estimation of Clinical Disease-Free Survival Controlled for FLIPI Risk Group and Number of Chemotherapy Cycles, Untreated Patients as Events (ITT Population, Study BV301)



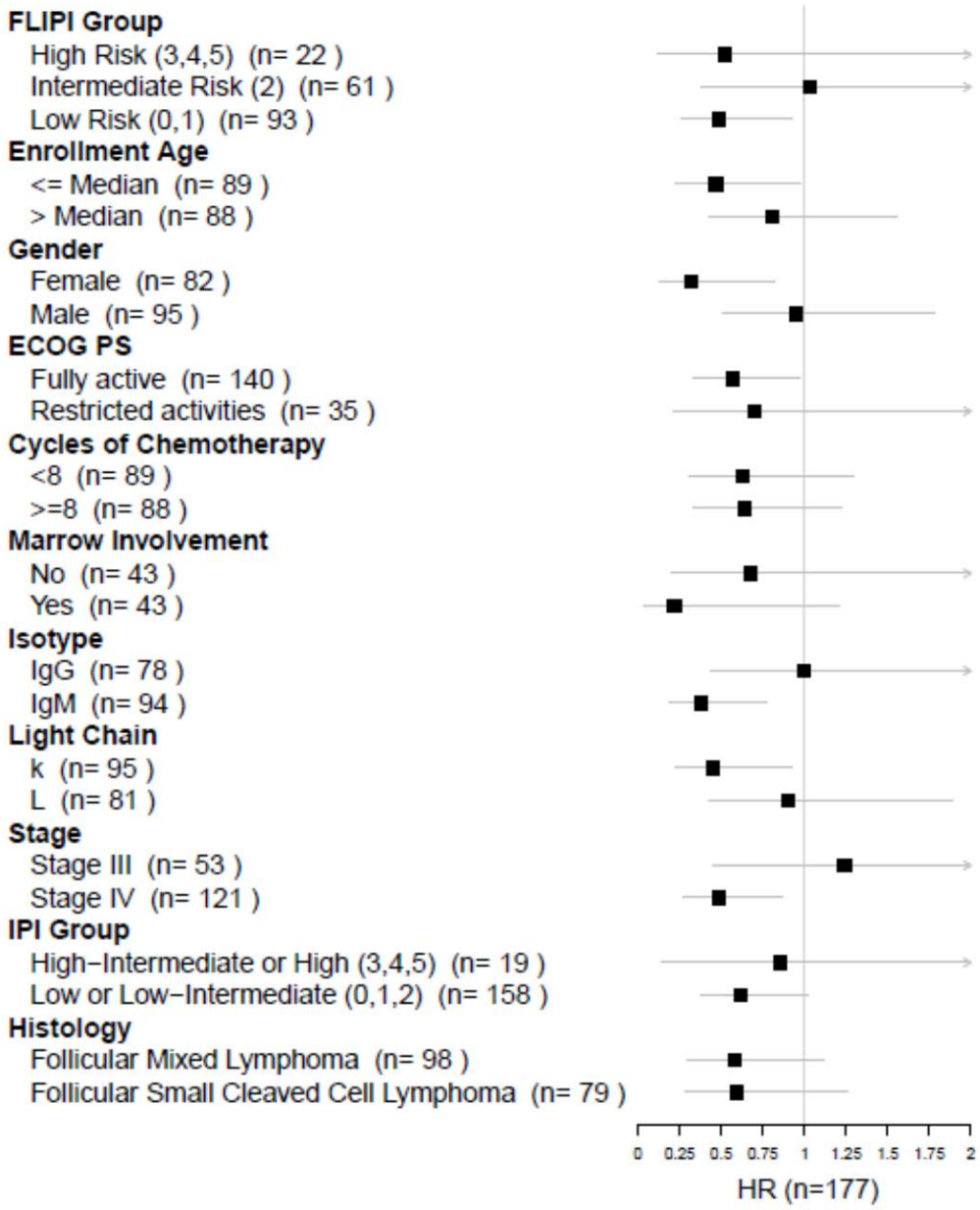
Secondary key endpoint: Overall Survival

In the ITT population, because the follow-up duration of the study is not long enough median OS was not reached in either treatment arm (data not shown).

Ancillary analyses

Subgroup analyses for DFS (censoring events occurring before vaccination) are shown in Figure 4.

Figure 4: Forest Plot of DFS by Subgroups (ITT Population, Study BV301)



Duration of Clinical DFS in IgM Patients with untreated patients as events and censoring patients that did not receive the study drug is reported in Table 11 and Table 12, respectively.

Table 11: Duration of Clinical Disease-Free Survival in IgM Patients, Controlled for FLIPI Risk Group and Number of Chemotherapy Cycles with Untreated Patients as Events (ITT Population, Study BV301)

	Active (N=61)	Control (N=33)	P-value
Log-rank test			0.366
Median, months	16.6	21.0	
95% CI	12.4-46.0	16.2-32.2	
Length of follow-up: min-max (median, months)	4.2-87.1 (55.0)	5.7-90.7 (53.4)	
Number of events	43	28	
Number censored	18	5	

ITT population includes all patients who were randomized to one of the treatment arms, as randomized.
Active = Dasiprotimut-T Biovest + GM-CSF; Control = KLH-KLH + GM-CSF

Table 12: Duration of Clinical Disease-Free Survival in IgM Patients, Controlled for FLIPI Risk Group and Number of Chemotherapy Cycles censoring untreated patients (ITT Population, Study BV301)

	Active (N=61)	Control (N=33)	P-value
Log-rank test			**0.004**
Median, months	52.9	28.7	
95% CI	40.2-NR	21.0-39.8	
Length of follow-up: min-max (median, months)	4.2-87.1 (55.0)	5.7-90.7 (53.4)	
Number of events	17	20	
Number censored	44	13	

ITT population includes all patients who were randomized to one of the treatment arms, as randomized.
Active = Dasiprotimut-T Biovest + GM-CSF; Control = KLH-KLH + GM-CSF
NR = Not Reached

FLIPI Risk Groups

DFS within FLIPI groups with untreated patients as events and censoring patients that did not receive the study drug is reported in Table 13 and Table 14, respectively.

Table 13: Duration of Clinical Disease-Free Survival within FLIPI Risk Groups Counting Untreated Patients as Events (ITT Population, N= 177 - Study BV301)

	Active (N=117)	Control (N=59)	P-value
Overall Log-rank test			0.394
High (3,4,5)			
Log-rank test			0.904
Median, months	19.9	20.6	
95% CI	5.7-NR	15.6-NR	
Length of follow-up: min-max (median, months)	4.2-88.1 (57.5)	27.3-81.9 (59.3)	
Number of events	10	8	
Number censored	3	1	
Intermediate (2)			
Log-rank test			0.887
Median, months	14.9	8.8	
95% CI	8.4-33.2	7.6-27.6	
Length of follow-up: min-max (median, months)	7.4-87.1 (50.2)	5.7-86.7 (56.6)	
Number of events	31	17	
Number censored	8	5	
Low (0,1)			
Log-rank test			0.292
Median, months	28.3	27.1	
95% CI	17.3-50.2	19.7-39.8	
Length of follow-up: min-max (median, months)	7.5-92.0 (58.2)	9.7-90.7 (57.1)	
Number of events	43	22	
Number censored	22	6	

Table 14: Duration of Clinical Disease-Free Survival within FLIPI Risk Groups censoring untreated Patients (ITT Population, N= 177 - Study BV301)

	Active (N=117)	Control (N=59)	P-value
Overall Log-rank test			0.042
High (3,4,5)			
Log-rank test			0.204
Median, months	52.9	30.6	
95% CI	20.1-NR	16.2-NR	
Length of follow-up: min-max (median, months)	4.2-88.1 (57.5)	27.3-81.9 (59.3)	
Number of events	4	6	
Number censored	9	3	
Intermediate (2)			
Log-rank test			0.849
Median, months	36.2	27.6	
95% CI	21.7-NR	21.0-NR	
Length of follow-up: min-max (median, months)	7.4-87.1 (50.2)	5.7-86.7 (56.6)	
Number of events	14	6	
Number censored	25	16	
Low (0,1)			
Log-rank test			0.026
Median, months	50.2	32.1	
95% CI	37.9-NR	26.2-42.7	
Length of follow-up: min-max (median, months)	7.5-92.0 (58.2)	9.7-90.7 (57.1)	
Number of events	24	17	
Number censored	41	11	

Gender

Results in terms of DFS within gender when counting patients not receiving active study drug as events and when the untreated patients are censored are summarized in Table 15 and Table 16, respectively.

Table 15: Duration of Clinical Disease-Free Survival with Untreated Patients as Events within Gender (ITT Population, N= 177- Study BV301)

	Active (N=118)	Control (N=59)	P-value
Overall Log-rank test			0.416
Female			
Log-rank test			0.056
Median, months	20.8	15.0	
95% CI	12.6-52.9	9.4-27.1	
Length of follow-up: min-max (median, months)	7.4-87.1 (54.9)	9.7-90.7 (57.1)	
Number of events	38	21	
Number censored	20	3	
Male			
Log-rank test			0.634
Median, months	20.1	27.6	
95% CI	14.9-36.2	20.0-39.8	
Length of follow-up: min-max (median, months)	4.2-92.0 (56.2)	5.7-86.7 (54.6)	
Number of events	47	26	
Number censored	13	9	

ITT population includes all patients who were randomized to one of the treatment arms, as randomized.
Active = Dasiprotimut-T Biovest + GM-CSF; Control = KLH-KLH + GM-CSF
NR = Not Reached

Table 16: Duration of Clinical Disease-Free Survival within Gender (ITT Population, N= 177- Study BV301)

	Active (N=118)	Control (N=59)	P-value
Overall Log-rank test			0.110
Female			
Log-rank test			**0.032**
Median, months	63.9	27.1	
95% CI	44.2-NR	19.7-NR	
Length of follow-up: min-max (median, months)	7.4-87.1 (54.9)	9.7-90.7 (57.1)	
Number of events	17	10	
Number censored	41	14	
Male			
Log-rank test			0.598
Median, months	37.9	32.4	
95% CI	26.7-59.4	26.7-42.7	
Length of follow-up: min-max (median, months)	4.2-92.0 (56.2)	5.7-86.7 (54.6)	
Number of events	26	19	
Number censored	34	16	

ITT population includes all patients who were randomized to one of the treatment arms, as randomized.
Active = Dasiprotimut-T Biovest + GM-CSF; Control = KLH-KLH + GM-CSF
NR = Not Reached

An additional alternative analysis of DFS was submitted. This analysis of DFS considers the time that the vaccine became available as Time 0.

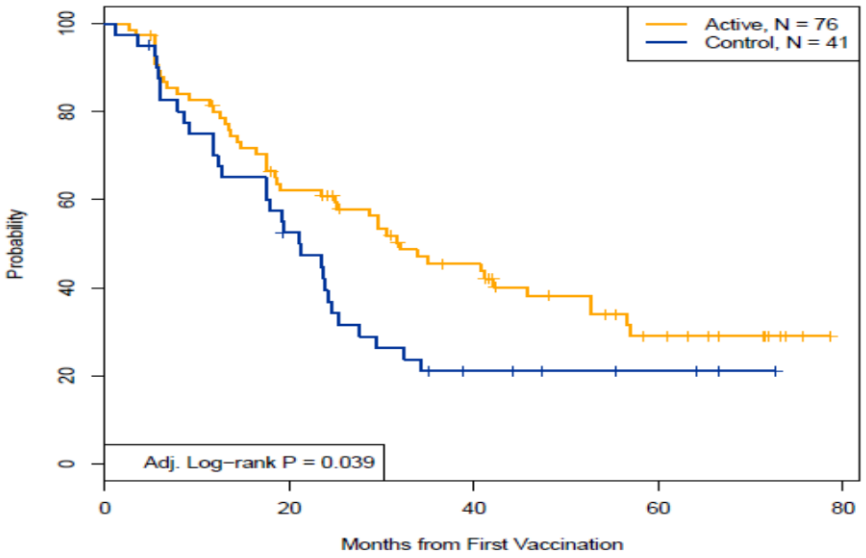
Table 17 provides the summary of DFS analysis that excludes pre-study treatment time. Figure 5 shows the survival curves. The p-value from the log-rank test, adjusted for strata, is 0.039 and the estimated hazard ratio is 0.61 (CI: 0.38-0.98).

Table 17: Duration of Clinical Disease-Free Survival Controlled for FLIPI Risk Group and Number of Chemotherapy Cycles, Untreated Patient-time Excluded (ITT Population, N= 177, Study BV301)

	Active (N=76)	Control (N=41)	P-value
Log-rank test			0.039
Median, months	32.0	21.1	
95% CI	24.9-52.7	17.4-27.6	
Length of follow-up: min-max (median, months)	4.9-81.8 (53.6)	4.8-83.2 (48.1)	
Number of events	47	31	
Number censored	29	10	

ITT population includes all patients who were randomized to one of the treatment arms, as randomized.
Active = Dasiprotimut-T Biovest + GM-CSF; Control = KLH-KLH + GM-CSF

Figure 5: Clinical Disease Free Survival from First Vaccination, Controlling for FLIPI Risk Group and Number of Chemotherapy Cycles (ITT Population, N=117, Study BV301)



Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18. Summary of Efficacy for trial BV301

Title: Randomized Trial of Patient-specific Vaccination with Conjugated Follicular Lymphoma-Derived Idiotype (FNHLId1) with Local GM-CSF in First Complete Remission			
Study identifier	BV301		
Design	Randomized, double-blind, controlled, multicenter study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months not applicable Median follow-up: 56.6 months	
Hypothesis	Superiority		
Treatments groups	Active (Id-KLH + GM-CSF)		0.5 mg isotype-matched Id conjugated to 0.5 mg KLH vaccine SC (Day1) + 100 mcg/m^2/day GM-CSF SC (Days 1 to 4) at 1, 2, 3, 4 and 6 months (vaccinations started ≥6 months after completion of induction chemotherapy); 118 patients randomized
	Control (KLH-KLH + GM-CSF)		1 mg KLH-KLH vaccine SC (Day1) + 100 mcg/m^2/day GM-CSF SC (Days 1 to 4) at 1, 2, 3, 4 and 6 months; 59 patients randomized
Endpoints and definitions	Primary endpoint	Disease Free Survival (DFS)	Duration from randomization to relapse or last follow-up
	Secondary endpoint	Overall survival (OS)	Time from randomization to the date of death due to any reason or last follow-up.
Database lock	30-June-2008		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) population. All randomized patients: 177		
Descriptive statistics and estimate variability	Treatment group	Active (Id-KLH + GM-CSF)	Control (KLH-KLH + GM-CSF)
	Number of subject	118	59
	Median DFS (months)	46.0	30.6
	95% CI	(36.2-63.9)	(26.2-39.8)
	Median OS (months)	90.2	NR
	95% CI	(90.2-NR)	(NR-NR)
Effect estimate per comparison	Primary endpoint	Comparison groups	Active vs Control
		Hazard Ratio	0.58
		95% CI	(0.35, 0.95)
		P-value (log-rank)	0.029
	Secondary endpoint	Comparison groups	Active vs Control
		P-value	0.680
Notes	Stratification factors: number of chemotherapy cycles (<8 vs. ⩾8), and IPI risk group (levels 0, 1 and 2 vs. levels 3 and 4).		

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive studies

Study NCI T93-0164

NCI T93-0164 was a phase 2 randomized (ratio 1:1), parallel-group, open-label study of Id-KLH vaccine administered with 2 different adjuvant doses (100 or 500 µg/m^2 granulocyte-macrophage

colony-stimulating factor [GM-CSF]) as a series of 5 vaccinations over 6 months in follicular lymphoma (FL) patients with complete clinical remission or minimal residual disease status after induction chemotherapy (first patient dose of chemotherapy: 28 October 1993; study termination date: 22 February 2010).

Forty-two adult patients with Stage III or IV lymphoma and no previous treatment for FL (except for treatment with radiation alone less than total body irradiation) were enrolled. They had tissue diagnosis of follicular small cleaved cell, or follicular mixed lymphoma with surface IgM, IgG, or IgA phenotype with a monoclonal heavy and light chain; a single peripheral lymph node of at least 2 cm size accessible for biopsy/harvest; Karnofsky status ≥ 70% and life expectancy of > 1 year; serum creatinine ≤1.5 mg/dL (unless felt to be secondary to lymphoma), bilirubin≤1.5 mg/dL (unless felt to be secondary to lymphoma or Gilbert's disease), aspartate aminotransferase (AST/SGOT) or alanine aminotransferase (ALT/SGPT)≤3.5 x upper limit of normal (ULN).

Patients were treated with ProMACE chemotherapy (cyclophosphamide, doxorubicin, etoposide, and prednisone) to best response and were then randomized to 1 of 2 doses of GM-CSF (500 or 100 µg/m^2/day) to be administered with 0.5 mg of Lympreva (autologous Id-KLH) vaccine.

The primary objectives were to induce cellular and humoral immunity against the unique idiotype (Id) expressed on the surface of patients' B-cell lymphomas and to determine the ability of Id immunization to eradicate bcl-2 positive tumour cells from the bone marrow as detected by polymerase chain reaction (PCR). The secondary objectives included the disease free survival (DFS) of patients achieving a complete response (CR) with chemotherapy.

The primary endpoint was molecular complete remission, rate, defined as the percentage of patients who achieved a clinical complete remission to induction therapy but still had cells in their blood from the malignant clone detectable by polymerase chain reaction (PCR) at the end of induction therapy, and who then become PCR negative after the administration of immunotherapy.

Complete molecular remissions were detected in 73% of the evaluable patients, and were maintained for a median of 18+ months after vaccination (range: 8+ to 32+ months). At a median follow-up of 165.7 months (13.82 years), median DFS in the efficacy set was 62.5 months (95% CI 31.3, NR): 84.9 months in patients who received 100 µg/m^2/day GM-CSF [n=13] vs. 46.8 months in patients who received 500 µg/m^2/day GM-CSF [n=12] (p=0.411).. Comparisons of complete remission rates and disease free survival rates between the two GM-CSF dose groups did not reach statistical significance.

Study NCI 1033

NCI 1033 was a single centre, phase 2, single arm, open-label study of Lympreva vaccine administered with 100 µg/m^2/day granulocyte-macrophage colony stimulating factor (GM-CSF) as a series of 5 vaccinations over 6 months in untreated Mantle Cell Lymphoma patients who achieved minimal residual disease with combination chemotherapy (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone [EPOCH]) with rituximab (EPOCH-R). First patient dose of EPOCH-R: 23 June 2000; date of last follow-up: 24 August 2011.

Adults patients with tissue diagnosis of mantle cell lymphoma, previously untreated with cytotoxic chemotherapy (local radiation or a short course of steroids for control of symptoms admitted) were enrolled for the study. Patients may have all stages of disease, lymph node of ≥ 2 cm accessible for biopsy/harvest or > 1000/µl of circulating tumour cells in the blood, ECOG performance status ≤ 3, adequate major organ function (serum creatinine 1.5 mg/dl or creatinine clearance > 60 ml/min; bilirubin < 2 mg/dl (total) except < 5 mg/dl in patients with Gilbert's syndrome as defined by > 80% unconjugated; ANC > 1000 and platelets > 100,000) unless impairment due to organ involvement by

lymphoma. No active symptomatic ischemic heart disease, myocardial infarction or congestive heart failure within the past year was admitted.

Patients received EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxyrubicin, rituximab) chemotherapy for 6 cycles, followed by 5 vaccinations with Dasiprotimut- T Biovest. Vaccine treatment was started at least 12 weeks and no more than 12 months after completion of chemotherapy. Each vaccine consisted of Lympreva vaccine administered on Day 0. The vaccine was administered together with 100 µg/m^2/day GM-CSF on Days 0-3 as an immunological adjuvant.

Primary objectives were to assess progression free survival (primary endpoint: PFS for at least 4 weeks after EPOCH-R completion, with 36 months) and the tumour specific T-cell response.

Median PFS was 24.1 months (95% CI: 21.12 – 31.05). The results of the clinical response analysis results are reported in Table 19.

Table 19: EPOCH-R Clinical Response (Study NCI 1033)

	Total (All Patients) (N = 26)	95% Confidence Interval
Response to EPOCH-R Therapy		
CR	24 (92%)	76% - 98%
CRu	0 (0%)	0% - 13%
PR	2 (8%)	2% - 24%
SD*	0 (0%)	0% - 13%
PD	0 (0%)	0% - 13%

Abbreviations: CR = complete response; CRu = complete response unconfirmed; EPOCH-R = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; PD = progressive disease; PR = partial response; SD = stable disease Note: Percentages are calculated based on the number of patients who had at least one valid assessment. The 95% CI was calculated using a binomial distribution.

2.6.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant submitted one pivotal phase III study (BV301), one supportive phase II study (NCI T93-0164) and one bridging phase II study (NCI 1033) in mantle cell lymphoma.

The pivotal study was a double-blinded, randomised, two-arm, multicenter and place-controlled phase III study. However, due to the introduction of rituximab and other changes, accrual rates were low and the study was terminated prematurely. Consequently, the planned sample size of 540 patients could not be reached.

In Study BV301, of the 234 patients with previously untreated follicular lymphoma enrolled 177 (75.6%) who achieved CR/CRu after PACE chemotherapy were randomized to blinded vaccine therapy (Lympreva+GM-CSF or KLH-KLH+GM-CSF). A majority of patients who were not randomized were withdrawn due to failure to achieve CR. The study population had a mean and median age significantly younger (by approximately 10 years) than population based reports on FL. A total of 118 patients were randomized to Lympreva+GMCSF, of whom 72 patients completed treatment per protocol. Fifty-nine patients were randomized to KLHKLH+ GM-CSF, of whom 39 patients completed treatment per protocol. The arms were well balanced considering age, lymphoma stage and IPI risk group (FLIPI risk groups were introduced post-hoc and were also reasonably well balanced between the two arms).

The intensive induction regimen (PACE) needed to induce CR from FL before vaccination has not been compared with standard of care treatments at time of study initiation especially with regard to the use of anti CD20 antibodies, the mainstay of current clinical practice. Therefore, “bridging” of clinical efficacy of Dasiprotimut-T to regimens other than that used in the BV 301 study is not possible.

Efficacy data and additional analyses

In the pivotal study BV301, median DFS was 46.0 months for patients in the active treatment group versus 30.6 months for patients in the control treatment group (HR=0.029, 95% CI [0.35, 0.95], (log-rank p value=0.029). However, this difference in DFS between the two arms is limited to the subpopulation that underwent vaccination and it was calculated by including only patients who achieved CR/CRu after induction with PACE (ie, study treatment 1) and underwent randomisation (2:1) between active and control vaccination (ie, study treatment 2). Disease relapse prior to vaccine was the primary reason for patients being censored in either active or treatment arm (83.3% and 88.9%, respectively). The CHMP raised a major objection about this analysis considering questionable the DFS benefit from a methodological and clinical perspective. Based on this, a new analysis representing all events recorded in the ITT population has been submitted by the applicant. In the new DFS analysis the benefits seen for the patients in the active vaccination arm were considerably diminished. The Kaplan-Meier estimated median duration of DFS was 20.1 months vs. 20.6 months in the active arm and control arm, respectively (adjusted log-rank p 0.295).

More than 50% of the patients had FLIPI score of 0-1 and only 12% had FLIPI score 3-5. From a conventional perspective, the need for therapy may thus be questioned in a non-trivial proportion of the population and the induction regimen (PACE) must be regarded as experimental and of high intensity with unproven positive B/R, especially in these patients.

The small supportive study NCI T93-1064 reports biologically active immune responses demonstrated in larger and smaller subgroups of the enrolled patients, but the influence on clinical parameters such as DFS and OS remain elusive. Furthermore, the results clearly imply that an immune response to tumour Id, whether humoral or cellular, does not entail long term survival or cure.

Finally, the study NCI 1033 in MCL showed that both cellular and, to a limited extent, humoral immune responses could be elicited in the MCL patients after achieving CR on chemoimmune therapy. However, there was a lack of standardization of definitions used for meaningful immune responses in this study compared to the earlier study NCI T90-1064. This study provides no strong supportive evidence for the FL indication.

2.6.4. Conclusions on the clinical efficacy

No significant difference in DFS was shown between subjects randomised to active vs. control vaccination (log-rank p-value 0.295), and the same was observed for all subgroups analysed. Therefore, efficacy for Dasiprotimut-T has not been demonstrated in the pivotal study.

In addition, notwithstanding the fact that efficacy has not been established, the intensive induction regimen (PACE) used to induce CR from FL before vaccination is not standard of care. There are no data to show clinical efficacy of Dasiprotimut-T with induction regimens used in current clinical practice. In view of the important differences between the PACE regimen and the current regimens that include CD20 antibodies, it is not possible to generalise the effect observed between regimens.

2.7. Clinical safety

The safety analysis of of Lympreva was based on the pooled population (Summary Safety Population, N=179) of the following 3 different groups, from the studies BV301 (safety population: 71 subjects with active vaccination and 46 controls, with FL), NCI T93-0164 (safety population: 37 subjects with FL treated with active vaccination) and NCI 1033 (safety population: 26 subjects with MCL treated with active vaccination):

- Lympreva with 100 mcg/m^2 GM-CSF group, including all patients who received blinded or unblinded vaccinations in this formulation from the BV301, NCI T93-0164 and NCI 1033 studies (N=115);
- Lympreva with 500 mcg/m^2 GM-CSF group, including all patients from Study NCI T93-0164 who received vaccinations in this formulation (unblinded) (N=18);
- The KLH-KLH control with 100 mcg/m^2 GM-CSF group, including all patients from Study BV301 who received this vaccination formulation (blinded) (N= 46).

Adverse events (AEs) were collected during vaccine administration and up to 30 days after last vaccine dose.

Patient exposure

In the BV301 study, median duration of vaccine therapy was 4.7 months and ≥94% subjects received the complete 5 course planned vaccination in both arms. In the NCI 1033 study median duration of vaccine therapy was 4.7 months (92% of patients received 5 vaccinations) and in the NCI T93-0164 study therapy was administered for a mean 4.6 months (92% of subjects received 5 vaccinations).

Overall, mean duration of vaccine exposure was 4.7 months across all studies.

Adverse events

The most common TEAE in the Summary Safety Population was injection site reaction, which was reported for 129 patients (72.1%): 78 (67.8%) patients in the Lympreva with GM-CSF 100 µg/m^2 treatment group, 11 patients (62.2%) in the Lympreva with GM-CSF 500 µg/m^2 treatment group, and 40 patients (87.0%) in the KLH-KLH with GM-CSF 100 µg/m^2 control group. Of the 351

vaccinations administered, 286 (81.5%) vaccinations demonstrated erythema, 210 (59.8%) vaccinations demonstrated induration and 5 (1.5%) demonstrated ulceration.

Following injection site reactions, the next most common TEAEs were fatigue (85 patients, 47.5%), myalgia (74 patients, 41.3%), and arthralgia (64 patients, 35.8%). The additional following TEAEs had an incidence of >20% for the overall Summary Safety Population: headache, pruritus, erythema, and nausea.

In the Lympreva with GM-CSF 100 µg/m^2 treatment group, 26.9% of patients experienced TEAEs of severity ≥Grade 3. TEAEs with a severity ≥Grade 3 experienced by >1% of the patients from the overall safety population were: Neutrophil count decreased, White blood cell count, Lymphocyte count decreased, Anaphylactic reaction, Arthralgia, Diarrhoea, Dyspnoea, Headache, Induration, Injection site reaction, Pain, Sinusitis, Urticaria, and Vomiting.

- Study BV301 (FL)

An overview of Treatment Emergent Adverse Events is presented in Table 20.

Table 20: Overview of Treatment-Emergent Adverse Events from Newer CRF (Safety Population, N=117 – Study BV301)

Subjects, n (%)	Active (N=71)	Control (N=46)	Overall (N=117)
With at least 1 TEAE	51 (71.8)	35 (76.1)	86 (73.5)
With at least 1 serious TEAE	6 (8.5)	6 (13.0)	12 (10.3)
With at least 1 TEAE related to Vaccine	33 (46.5)	24 (52.2)	57 (48.7)
With at least 1 TEAE related to GM-CSF	37 (52.1)	25 (54.3)	62 (53.0)
With at least 1 NCI CTCAE Grade 3/4 TEAE related to Vaccine	5 (7.0)	1 (2.2)	6 (5.1)
With at least 1 NCI CTCAE Grade 3/4 TEAE related to GM-CSF	5 (7.0)	1 (2.2)	6 (5.1)
With at least 1 serious TEAE related to Vaccine	3 (4.2)	2 (4.3)	5 (4.3)
With at least 1 serious TEAE related to GM-CSF	3 (4.2)	2 (4.3)	5 (4.3)
With at least 1 NCI CTCAE Grade 5 TEAE related to study drug*	0 (0.0)	0 (0.0)	0 (0.0)
With at least 1 TEAE related to study drug* leading to dose reduction	0 (0.0)	0 (0.0)	0 (0.0)
With at least 1 TEAE related to study drug* leading to temporary regimen interruption	1 (1.4)	1 (2.2)	2 (1.7)
With at least 1 TEAE related to Vaccine leading to temporary regimen interruption	0 (0.0)	1 (2.2)	1 (0.9)
With at least 1 TEAE related to GM-CSF leading to temporary regimen interruption	1 (1.4)	1 (2.2)	2 (1.7)
With at least 1 TEAE related to Vaccine leading to permanent regimen interruption	1 (1.4)	0 (0.0)	1 (0.9)
With at least 1 TEAE related to GM-CSF leading to permanent regimen interruption	1 (1.4)	0 (0.0)	1 (0.9)
Deaths on Study§	0 (0.0)	0 (0.0)	0 (0.0)

* Study drug here relates to either dasiprotimut-T Biovest + GM-CSF or KLH + GM-CSF.

§ Death on study defined here are deaths occurring during vaccine administration or within 30 days from last vaccine administration.

Active = dasiprotimut-T Biovest + GM-CSF; Control = KLH-KLH + GM-CSF

GM-CSF = granulocyte macrophage colony-stimulating factor, KLH = keyhole limpet hemocyanin, TEAE = Treatment-emergent adverse event, NCI CTC = National Cancer Institute Common Terminology Criteria

Safety Population includes all randomized subjects who received at least one dose of active or control vaccine as treated.

Treatment Emergent Adverse Events by Body System and Preferred Term are reported in Table 21.

Table 21: Overall Treatment Emergent Adverse Events Reported by ≥ 5% of Patients in Either Treatment Group, by Body System and Preferred Term (Safety Population, N= 117 – Study BV301)

	Active (N=71)		Control (N=46)		All Patients (N=117)		
SOC/Preferred Term	n	%	n	%	n	%	P†
Vascular disorders							
Flushing	8	11.3	2	4.3	10	8.5	0.312
Hot flush	5	7.0	2	4.3	7	6.0	0.703
Hypertension	4	5.6	1	2.2	5	4.3	0.647
Hypotension	4	5.6	1	2.2	5	4.3	0.647
Surgical and medical procedures							
Skin and subcutaneous tissue disorders							
Pruritus	15	21.1	11	23.9	26	22.2	0.821
Hyperhidrosis	11	15.5	3	6.5	14	12.0	0.243
Rash maculo-papular	6	8.5	4	8.7	10	8.5	1.000
Urticaria	6	8.5	2	4.3	8	6.8	0.478
Palmar-plantar erythrodysaesthesia syndrome	2	2.8	3	6.5	5	4.3	0.380
Respiratory, thoracic and mediastinal disorders							
Cough	11	15.5	4	8.7	15	12.8	0.398
Dyspnoea	5	7.0	4	8.7	9	7.7	0.737
Rhinitis allergic	2	2.8	5	10.9	7	6.0	0.110
Reproductive system and breast disorders							
Renal and urinary disorders							
Pollakiuria	5	7.0	0	0.0	5	4.3	0.155
Psychiatric disorders							
Depression	4	5.6	1	2.2	5	4.3	0.647
Hallucination	3	4.2	3	6.5	6	5.1	0.678

Nervous system disorders							
Headache	28	39.4	15	32.6	43	36.8	0.557
Depressed level of consciousness	6	8.5	2	4.3	8	6.8	0.478
Peripheral sensory neuropathy	2	2.8	3	6.5	5	4.3	0.380
Dizziness	1	1.4	4	8.7	5	4.3	0.077
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Musculoskeletal and connective tissue disorders							
Myalgia	29	40.8	17	37.0	46	39.3	0.703
Arthralgia	25	35.2	17	37.0	42	35.9	0.847
Bone pain	15	21.1	10	21.7	25	21.4	1.000
Back pain	8	11.3	2	4.3	10	8.5	0.312
Muscular weakness	3	4.2	3	6.5	6	5.1	0.678
Musculoskeletal pain	0	0.0	3	6.5	3	2.6	0.058
Metabolism and nutrition disorders							
Hyperglycaemia	10	14.1	1	2.2	11	9.4	**0.048**
Decreased appetite	5	7.0	2	4.3	7	6.0	0.703
Investigations							
White blood cell count decreased	5	7.0	1	2.2	6	5.1	0.401
Injury, poisoning and procedural complications							
Contusion	2	2.8	3	6.5	5	4.3	0.380
Infections and infestations							
Infection	7	9.9	2	4.3	9	7.7	0.480
Sinusitis	0	0.0	3	6.5	3	2.6	0.058
Immune system disorders							
Hypersensitivity	3	4.2	4	8.7	7	6.0	0.431
General disorders and administration site conditions							
Injection site reaction	68	95.8	40	87.0	108	92.3	0.152
Fatigue	40	56.3	24	52.2	64	54.7	0.706
Pyrexia	16	22.5	10	21.7	26	22.2	1.000
Non-cardiac chest pain	11	15.5	5	10.9	16	13.7	0.587
Pain	9	12.7	5	10.9	14	12.0	1.000
Chills	6	8.5	10	21.7	16	13.7	0.054
Influenza like illness	6	8.5	2	4.3	8	6.8	0.478
Chest pain	5	7.0	3	6.5	8	6.8	1.000
Oedema	4	5.6	0	0.0	4	3.4	0.153
Unevaluable event	3	4.2	3	6.5	6	5.1	0.678
Injection site pain	0	0.0	3	6.5	3	2.6	0.058
Gastrointestinal disorders							
Nausea	16	22.5	11	23.9	27	23.1	1.000
Diarrhoea	12	16.9	4	8.7	16	13.7	0.275
Dyspepsia	12	16.9	4	8.7	16	13.7	0.275
Abdominal pain	11	15.5	4	8.7	15	12.8	0.398
Vomiting	8	11.3	3	6.5	11	9.4	0.524
Constipation	6	8.5	0	0.0	6	5.1	0.080
Stomatitis	4	5.6	0	0.0	4	3.4	0.153
Eye disorders							
Ear and labyrinth disorders							
Cardiac disorders							
Blood and lymphatic system disorders							

Fisher's exact test was used for group comparisons.
MedDRA v. 16.0 was used to code adverse events.
Active = dasiprotimut-T Biovest + GM-CSF; Control = KLH-KLH + GM-CSF

Treatment Emergent Adverse Events by Severity are shown in Table 22:

Table 22: Summary of Treatment-emergent Adverse Events Reported by ≥ 10% of Patients in Either Treatment Group by Severity (Safety Population – Study BV301)

	Mild		Moderate		Severe	
Body System/ Adverse Event, n (%)	**Active** (N=71)	**Control** (N=46)	**Active** (N=71)	**Control** (N=46)	**Active** (N=71)	**Control** (N=46)
Vascular Disorders						
Flushing	8 (11.3)	2 (4.3)	0	0	0	0
Skin and Subcutaneous Tissue Disorders						
Pruritus	15 (21.1)	10 (21.7)	1 (1.4)	2 (4.3)	0	0
Hyperhidrosis	11 (15.5)	2 (4.3)	1 (1.4)	1 (2.2)	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	10 (14.1)	2 (4.3)	1 (1.4)	2 (4.3)	0	0
Nervous System Disorders						
Headache	26 (36.6)	14 (30.4)	7 (9.9)	5 (10.9)	1 (1.4)	1 (2.2)
Musculoskeletal and Connective Tissue Disorders						
Myalgia	28 (39.4)	15 (32.6)	5 (7.0)	4 (8.7)	0	0
Arthralgia	24 (33.8)	13 (28.3)	5 (7.0)	7 (15.2)	1 (1.4)	1 (2.2)
Bone pain	12 (16.9)	4 (8.7)	3 (4.2)	7 (15.2)†	0	0
Metabolism and Nutrition Disorders						
Hyperglycaemia	9 (12.7)	0	1 (1.4)	1 (2.2)	0	0
General Disorders and Administration Site Conditions						
Injection site reaction	61 (85.9)	37 (80.4)	21 (29.6)	17 (37.0)	1 (1.4)	0
Fatigue	37 (52.1)	24 (52.2)	10 (14.1)	2 (4.3)	1 (1.4)	0
Pyrexia	15 (21.1)	10 (21.7)	3 (4.2)	0	0	0
Pain	9 (12.7)	5 (10.9)	1 (1.4)	0	0	1 (2.2)
Non-cardiac chest pain	8 (11.3)	3 (6.5)	5 (7.0)	3 (6.5)	0	0
Chills	6 (8.5)	10 (21.7)	1 (1.4)	0	0	0
Gastrointestinal Disorders						
Nausea	14 (19.7)	11 (23.9)	3 (4.2)	3 (6.5)	0	0
; Diarrhoea	11 (15.5)	4 (8.7)	1 (1.4)	1 (2.2)	1 (1.4)	0
Dyspepsia	11 (15.5)	2 (4.3)	1 (1.4)	2 (4.3)	1 (1.4)	0
Abdominal pain	9 (12.7)	3 (6.5)	3 (4.2)	1 (2.2)	1 (1.4)	0

Safety population includes all patients randomized to one of the treatment groups and who received at least one dose of active or control vaccine, as treated.
Active = Dasiprotimut-T Biovest+GM-CSF; Control = KLH-KLH+GM-CSF
GM-CSF = granulocyte macrophage colony-stimulating factor; KLH = keyhole limpet hemocyanin
†P = 0.048; Fisher's exact test was used for group comparison.

Adverse Events of special interest

Injection site reactions

All patients who received Lympreva with GM-CSF reported injection site reactions during the course of the therapy. In 81.7% of patients, injection site reactions were mild or moderate. The most common reactions were erythema (72.2%), induration (66.1%), pruritus (43.5%), and pain (20%).

In the control trial, erythema reactions between 1 and 10 cm were reported in 62% of patients during the duration of the treatment. The incidence of erythema reactions increased progressively during the first four immunizations (48.8% at the first vaccine, 80% at the second vaccine, 87.5% at the third and fourth vaccine, and 84.7% at the fifth vaccine). Induration reactions between 1 and 10 cm were reported in 49.5% of patients. The incidence of induration reactions increased progressively during the first four immunizations (23.7% at the first vaccine, 64.5% at the second vaccine, 67.1% at the third vaccine, 78.4% at the fourth vaccine, and 62.5% at the fifth vaccine). Ulceration reactions were reported in 8.4% of patients. Size of ulceration reactions were reported as follows: 1.4% measured >10 cm, 2.8% measured 1-10 cm, and 4.2% measured <1 cm.

In the controlled trial, severe (grade 3) induration was reported each in 1.4% of patients.

Such injection site reactions are known to be associated distinctly with GM-CSF and the KLH component of Lympreva. In patients who experience a reaction suggestive of sensitization, the Dasiprotimut- T and GM-CSF must be administered in separate syringes and at distant injection sites.

Hyperglycaemia

In the study BV301, 10 patients in the active treatment group versus 1 patient in the control treatment group reported at least 1 TEAE hyperglycaemia. Two of them (1 each in the active and control treatment groups) had an ongoing history of diabetes.

None of the patients with treatment-emergent hyperglycaemia had dosing changes, interruptions or discontinuations due to the events.

Secondary malignancies

Eight of the 10 patients reporting secondary malignancies in the study BV301 were on active treatment (11.3%, control arm 4.3%); in 2 of these, two different malignancies were reported (adenocarcinoma of the liver + squamous cell carcinoma; melanoma + B cell leukemic malignancy). One case of AML occurred in the active treatment arm and one case of MDS/AML occurred in the control arm. No pattern in terms of histology or temporal trend was noted.

- Study NCI 1033 (MCL)

An overview of Treatment Emergent Adverse Events in Study NCI 1033 is presented in Table 23.

Table 23: Overall Summary of Treatment-Emergent Adverse Events (Safety Set, – Study NCI 1033)

Variable	During EPOCH-R Therapy	During Vaccination Therapy
Number of Subjects	26	25
Number of subjects with one or more TEAE, n (%)	26 (100 %)	22 (88 %)
Number of TEAEs	1420	134
Number of subjects with one or more serious TEAE, n (%)	2 (7.69 %)	1 (4 %)
Number of serious TEAEs	2	3
Number of subjects with one or more related TEAE, n (%)	26 (100 %)	18 (72 %)
Number of related[a] TEAEs	1387	71
Number of subjects with one or more serious and related [a] TEAE, n (%)	2 (7.69 %)	1 (4 %)
Number of serious and related TEAEs	2	3
Number of TEAEs leading to study drug discontinuation	12	0
Number of subjects with one or more TEAE leading to study drug discontinuation, n (%)	2 (7.69 %)	0 (0 %)

During vaccine therapy the following Treatment Emergent Events by Preferred Term were reported in ≥8% of subjects (= in ≥2 patients): neutrophil count decreased (36%), platelet count decreased (8%), WBC decreased (32%), lymphocyte count decreased (36%), ALP increased (8%), AST increased (8%), diarrhoea (12%), arthralgia (8%), fatigue (8%), anaemia (12%), hyperglycaemia (24%), and hypomagnesaemia (12%).

Treatment Emergent Adverse Events by Severity are shown in Table 24.

Table 24: Treatment Emergent Adverse Events During Vaccine Therapy by Severity (Safety Set – Study NCI 1033)

SOC, PT, n(%)	Vaccine Grade 1 (N = 25)	Vaccine Grade 2 (N = 25)	Vaccine Grade 3 (N = 25)	Vaccine Grade 4 (N = 25)
Overall				
Subjects with any events	18 (72%)	12 (48%)	11 (44%)	6 (24%)
Investigations				
Investigations , Any	9 (36%)	10 (40%)	7 (28%)	5 (20%)
Aspartate aminotransferase increased	2 (8%)	0 (0%)	0 (0%)	0 (0%)
Blood alkaline phosphatase increased	2 (8%)	0 (0%)	0 (0%)	0 (0%)
Platelet count decreased	2 (8%)	0 (0%)	0 (0%)	0 (0%)
White blood cell count decreased	2 (8%)	4 (16%)	2 (8%)	4 (16%)
Alanine aminotransferase increased	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Blood bilirubin increased	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Blood creatine phospholcinase increased	1 (4%)	0 (0%)	0 (0%)	0 (0%)
International normalised ratio increased	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Neutrophil count decreased	1 (4%)	1 (4%)	4 (16%)	5 (20%)
Lymphocyte count decreased	0 (0%)	7 (28%)	4 (16%)	0 (0%)
Metabolism and nutrition disorders				
Metabolism and nutrition disorders , Any	10 (40%)	1 (4%)	1 (4%)	0 (0%)
Hyperglycaemia	5 (20%)	1 (4%)	0 (0%)	0 (0%)
Hypomagnesaemia	2 (8%)	0 (0%)	1 (4%)	0 (0%)
Decreased appetite	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Hypercalcaemia	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Hypermagnesaemia	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Hypoalbuminaemia	1 (4%)	0 (0%)	0 (0%)	0 (0%)
General disorders and administration site conditions				
General disorders and administration site conditions , Any	5 (20%)	1 (4%)	0 (0%)	0 (0%)
Fatigue	2 (8%)	0 (0%)	0 (0%)	0 (0%)
Non-cardiac chest pain	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Oedema	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Pain	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Unevaluable event	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal and connective tissue disorders , Any	3 (12%)	0 (0%)	0 (0%)	0 (0%)
Arthralgia	2 (8%)	0 (0%)	0 (0%)	0 (0%)
Bone pain	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Blood and lymphatic system disorders				
Blood and lymphatic system disorders , Any	3 (12%)	0 (0%)	0 (0%)	0 (0%)
Anaemia	3 (12%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal disorders				
Gastrointestinal disorders , Any	4 (16%)	0 (0%)	0 (0%)	0 (0%)
Diarrhoea	3 (12%)	0 (0%)	0 (0%)	0 (0%)
Abdominal pain	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders				
Nervous system disorders , Any	2 (8%)	0 (0%)	1 (4%)	0 (0%)
Headache	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Peripheral sensory neuropathy	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Peripheral motor neuropathy	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Vascular disorders				
Vascular disorders , Any	2 (8%)	0 (0%)	0 (0%)	0 (0%)
Flushing	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Hypotension	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Respiratory, thoracic and mediastinal disorders				
Respiratory, thoracic and mediastinal disorders , Any	1 (4%)	0 (0%)	1 (4%)	0 (0%)
Cough	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Dyspnoea	0 (0%)	0 (0%)	1 (4%)	0 (0%)

Skin and subcutaneous tissue disorders				
Skin and subcutaneous tissue disorders , Any	1 (4%)	2 (8%)	0 (0%)	0 (0%)
Pruritus	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Alopecia	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Rash maculo-papular	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Urticaria	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Endocrine disorders				
Endocrine disorders , Any	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Hypothyroidism	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Immune system disorders				
Immune system disorders , Any	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Anaphylactic reaction	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Infections and infestations				
Infections and infestations , Any	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Infection	0 (0%)	0 (0%)	0 (0%)	1 (4%)

Serious adverse event / deaths / other significant events

Serious Adverse Events

In the pooled data, during vaccine treatment or within 30 days of the last vaccine therapy, a total of 17 (9.5%) patients experienced an SAE. Of these 17 patients, 9 were in the Lympreva with GM-CSF 100 µg/m^2 treatment group (7.8% of the treatment group) and 8 were in the KLH-KLH with GM-CSF 100 µg/m^2 control group (17.4% of the control group).

In study BV301, SAEs were reported in 8 patients in each study arm: in 11% of patients in the active arm and 17% in the control arm. A summary of Serious Adverse Events is reported on Table 25.

Table 25: Summary of Serious Adverse Events Other than Death (Safety Set – Study BV301)

MedDRA Preferred Term / Reported Term	Relationship to Study Drug / GM-CSF	Cycle / Day / Grade	Outcome / Action Taken with Study Drug
Active (Dasiprotimut-T Biovest+GMCSF)			
Vomiting / Vomiting	Unrelated / NA	6 / NA / 3	Resolved / No change
Anaphylactic reaction / Allergic reaction/ hypersensitivity (including drug fever)	Possible / Possible	4 / 1 / 3	Resolved / Permanently stopped
Non-cardiac chest pain / Chest pain	Possible / Possible	1 / 8 / 2	Resolving / No change
Infection / Infection without neutropenia	Unlikely / Unlikely	4 / 16 / 2	Unresolved / No change
Chest pain / Cardiovascular/general other (specify)	Unlikely / Unlikely	3 / 1 / 2	Resolved / No change
Anxiety / Mood alteration-anxiety, agitation	Unrelated / Unrelated	4 / 36 / 1	Resolved / No change
Urticaria / Urticaria (hives, welts, wheals)	Probable / Probable	4 / 7 / 3	Resolved / No change
Cough / Cough	Unlikely / Unlikely	4 / 21 / 2	Resolved / No change
Infection / Infection without neutropenia	Unrelated / Unrelated	2 / 9 / 2	Resolved / No change
Bone pain / Bone pain	Possible / Possible	2 / 9 / 2	Resolved / No change
Control (KLH-KLH+GM-CSF)			
Herpes zoster / Site of shingles at L chest area - grade 2	Unlikely / Unlikely	2 / NA / 2	Resolving / No change
Supraventricular tachycardia / supraventricular arrhythmia	NA / NA	2 / NA / 3	NA / NA
Infection / Infection without neutropenia	Unrelated / Unrelated	4 / 57 / 2	Resolved / No change
Blood cholesterol increased / Hypercholesterolemia	Unrelated / Unrelated	4 / 37 / 1	Unresolved / No change
Dyspnoea / Dyspnea (shortness of breath)	Probable / Probable	4 / 1 / 3	Resolved / No change
Compression fracture / musculoskeletal fracture	Unlikely / Unlikely	4 / 27 / 3	Resolved / No change
Cystitis interstitial / Pain - other (specify)	Unrelated / Unrelated	1 / 21 / 3	Resolved / No change
Sudden hearing loss / Auditory/hearing (specify)	Unrelated / Unrelated	2 / 16 / 2	Unresolved / No change
Bone pain / Bone pain	Possible / Possible	2 / 9 / 2	Unresolved / No change

Safety population includes all patients randomized to one of the treatment groups and who received at least one dose of active or control vaccine, as treated.
CNS = central nervous system; CRF = case report form; F = female; GM-CSF = granulocyte macrophage colony-stimulating factor; KLH = keyhole limpet hemocyanin; M = male; NA = not assigned by site investigator

Additionally, one patient experienced the following Grade 4 TEAEs in Study BV301: myocardial infarction (Cycle 2) and acute myeloid leukaemia (Cycle 6).

In NCI 1033 study, 1 patient had SAEs during vaccine therapy, including PTs neutrophil count decreased (Grade 4), WBC decreased (Grade 4) and dyspnoea (considered related to asthma); the neutropenia occurred 6 months after completed EPOCH-R therapy (6 courses, CR) and approximately 2 months after the first dose of vaccine, and lasted for at least 2 months before resolution during ongoing vaccine therapy at unchanged dosing.

Deaths

In the Summary Safety Population, no patients died while on study (i.e., at time of first dose or later) or within 30 days of the last dose of study drug.

Laboratory findings

Clinical laboratory evaluations, vital signs and physical findings were not monitored during treatment in Lympreva clinical studies. Clinically significant abnormalities were to be reported as AEs.

Safety in special populations

In the Summary Safety Population, Grade 3-4 events were reported in 10/17 patients (59%) aged ≥60 years and in 26/98 patients (27%) aged <60 years.

Grade 3-4 events were experienced in 35% of female patients versus 25% of male patients.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

In the Study BV301, 1 patient in the treatment arm discontinued permanently the therapy due to severe anaphylactic reaction (Cycle 4) and no one in the control arm. Additionally, 1 patient was noted in the CRF as discontinuing from the study due to "toxicity/side effects"; no specific TEAE was noted with an action taken of permanently discontinuation; however the patient did experience serious TEAEs. One patient in the active treatment group experienced 2 events (arthralgia and osteoporosis) that led to the study drug being temporarily stopped; similarly, 1 patient in the control treatment group had an event of muscle spasms which led to temporary interruption of the study drug.

In Study NCI 1033 and NCI T93-0164 no patients discontinued due to TEAEs.

Post marketing experience

N/A

2.7.1. Discussion on clinical safety

Data on safety in the intended indication and dose was primarily derived from the randomised study BV301 with support from the uncontrolled studies NCI T93-0164 in FL and NCI 1033 in MCL. However, the pooling strategy (n=115 vs 46 controls) applied by the Applicant was not considered acceptable without justification, mainly due to the inclusion of the MCL rituximab-exposed group, and the assessment has primarily focused on the BV301 study in FL and the study1033 in MCL.

As a consequence of the study design the randomised data principally allows estimation of Dasiprotimut-T toxicity upon combination with KLH and GM-CSF, but does not inform on KLH and GM-CSF toxicity over background morbidity. Thus, depiction of the causative toxicity profile of the active vaccination part of the combination is challenging.

Injection site reaction has been the most frequently reported adverse reaction, including induration, erythema, pruritus and pain. The other most commonly reported adverse reactions during treatment were oedema, flushing, chills, myalgia, arthralgia, fatigue, headache, chest pain, hypersensitivity, dizziness, and decreased lymphocyte count. These reactions were generally mild or moderate, reversible and manageable. It should be noted that all these events are compatible with the known side effect profile of GM-CSF. Anticipated toxicities from GM-CSF administration are expected to be mild. Potential toxicities include fever, chills, myalgias, arthralgias, nausea, vomiting, diarrhea, dyspnea, tachycardia, arrhythmia, elevation of liver function tests, elevation of blood urea nitrogen (BUN) and creatinine. However, local skin reactions, such as erythema and induration, may be

observed and must be carefully noted.

Toxicity specifically related to the active component of the vaccine appears limited, but, when taking into account data obtained in both studies, may include a risk for hyperglycaemia and decreased white blood cells.

Immunocompromised patients, such as patients with detectable anti-HIV antibodies, hepatitis B surface antigen, or other active infectious processes, were excluded from clinical trials due to potential interferences with the development of an immune response to the tumour antigen. Lympreva has not been evaluated in HIV positive patients, nor in patients on antiretroviral therapy. Lympreva has not been evaluated in patients with a history of hepatitis B exposure

Serious adverse reactions associated with therapy with Lympreva with GM-CSF include anaphylactic reaction, urticaria, neutrophil count decreased, white blood cell count decreased, bone pain, cough, and dyspnoea. Except for the anaphylactic reaction which occurred after the fourth immunization and resulted in treatment discontinuation, these serious reactions were reversible and did not affect the course of therapy.

In the controlled trial, 1.7% of patients discontinued treatment with Lympreva due to adverse reactions.

Although grade ≥3 events were reported in 30% of patients in the pooled active vaccination group, and SAEs occurred, discontinuation rate due to AE was low (1 or 2 patients in BV301 and none in NCI 1033) and no patient died due to AE. Therefore, the toxicity associated with Lympreva was generally considered clinically manageable, but the report of one patient with an injection-related ulceration of >10 cm is worrisome.

Leukopenia was noted in patients under active vaccine treatment, including neutropenia and lymphocytopenia. While confounded by previous exposure to rituximab in the MCL study, these cytopenias were also reported numerically more frequent in the active arm vs the control arm of study BV301.

There was one case of leukoencephalopathy in the active arm, but no conclusions can be drawn based on this single event. Nonetheless, the Applicant had addressed this issue in the proposed RMP.

In BV301, 8 of the 10 patients reporting secondary malignancy were on active treatment. No pattern in terms of histology or temporal trend was noted. An increased incidence of secondary malignancies is expected in the present study population. However, as the incidence was numerically distinctly higher in the active treatment arm, secondary malignancies are included as a potential risk in the RMP.

In terms of external validity of the safety data, the general median age at diagnosis in FL of approximately 60 years is not reflected in the study populations of BV301 or NCI T93-0164, in which age at time of study enrolment was ≥60 years in only 16% and 8%, respectively. Further, the majority of patients presented with low risk disease and in the pooled population (n=115) only 12 patients had an ECOG PS of 1 while all others with data available had an ECOG PS of 0. Although low patient numbers exclude a reasonably robust evaluation of safety by age, it is noted that grade 3-4 events occurred numerically more common patients ≥60 years of age (10/17 patients (59%) aged ≥60 years vs in 26/98 patients (27%) aged <60 years). Therefore, the characterisation of the toxicity profile associated with active vaccination specifically in the general main target FL population cannot be considered robust.

Another issue relates to the capture of data on clinical laboratory evaluations and vital signs and physical findings. Such data was not monitored at baseline and during treatment in the clinical studies except for clinically significant abnormalities to be reported as AEs. This makes evaluation of safety issues difficult. Safety in patients with renal or hepatic impairment, or of non-white ethnicity, remains to be determined.

Long-term safety after active immunotherapy is lacking.

Lympreva has a minor influence on the ability to drive and use machines.

There have been no reports of overdose with Lympreva. Lympreva has been administered in clinical trials only in the currently recommended dose.

2.7.2. Conclusions on the clinical safety

The toxicity of active vaccination treatment seems to be dominated by the GM-CSF component but may also include a risk for leukopenia, including neutropenia and lymphocytopenia, and hyperglycaemia. Although deemed generally clinically manageable, with low rates of discontinuations due to AE, one patient was reported with an injection-related ulceration of >10 cm and there was a numerical increase in secondary malignancies in the active treatment arm. There was one case of leukoencephalopathy in the active arm, but no conclusions can be drawn based on this single event. Nonetheless, the Applicant had addressed this issue in the proposed RMP. Issues challenging the internal and external validity of the database have been identified.

2.8. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.9. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.10. Product information

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to agree on the Product Information at this time.

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable for the packaging part only by the QRD

Group for the following reasons:

The Group agreed an English only packaging based on the applicant's justification; however, the PL should be in the national language.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

3. Benefit-Risk Balance

Benefits

Beneficial effects

No significant difference in DFS was shown between subjects randomised to active vs. control vaccination (log-rank p-value 0.295), and the same was observed for all subgroups analysed. Therefore, efficacy for Lympreva has not been demonstrated in the pivotal study.

Uncertainty in the knowledge about the beneficial effects

Major concerns have been raised on the design of the trial and more specifically on the definition of the population used for the primary analysis, which may introduce bias. The difference in DFS between the two arms is limited to the subpopulation that underwent vaccination and it was calculated by including only patients who achieved CR/CRu after induction with PACE and underwent randomisation between active and control vaccination.

Notwithstanding the fact that efficacy has not been established, the intensive induction regimen (PACE) used to induce CR from FL before vaccination is not standard of care. There are no data to show clinical efficacy of Lympreva with induction regimens used in current clinical practice. In view of the important differences between the PACE regimen and the current regimens that include CD20 antibodies, it is not possible to generalise the effect observed between regimens.

Risks

Unfavourable effects

Injection site reaction has been the most frequently reported adverse reaction, including induration, erythema, pruritus and pain. The other most commonly reported adverse reactions during treatment were oedema, flushing, chills, myalgia, arthralgia, fatigue, headache, chest pain, hypersensitivity, dizziness, and decreased lymphocyte count. These reactions were generally mild or moderate, reversible and manageable. It should be noted that all these events are compatible with the known side effect profile of GM-CSF. Toxicity specifically related to the active component of the vaccine appears limited, but, when taking into account data obtained in both studies, may include a risk for hyperglycaemia and decreased white blood cells.

Serious adverse reactions associated with therapy with Lympreva with GM-CSF include anaphylactic reaction, urticaria, neutrophil count decreased, white blood cell count decreased, bone pain, cough, and dyspnoea. Except for the anaphylactic reaction which occurred after the fourth immunization and resulted in treatment discontinuation, these serious reactions were reversible and did not affect the course of therapy. One patient experienced an injection-related ulceration of >10 cm.

In the controlled trial, 1.7% of patients discontinued treatment with Lympreva due to adverse reactions.

Uncertainty in the knowledge about the unfavourable effects

In BV301, 8 of the 10 patients reporting secondary malignancy were on active treatment. No pattern in terms of histology or temporal trend was noted. However, as the incidence was numerically distinctly higher in the active treatment arm, secondary malignancies were included as a potential risk in the RMP.

With only 16% and 8% of patients ≥60 years of age in study BV301 and NCI T93-0164, respectively, and only 12/115 patients in the pooled population with ECOG PS 1 (none with PS 2), the characterisation of the toxicity profile associated with active vaccination specifically in the general main target FL population, with a median age at diagnosis of approximately 60 years, cannot be considered robust. Thus, the external validity of the safety data might be questionable; especially as grade 3-4 events were numerically more common in patients ≥60 years of age.

However, given the assumption that immune-related reactions directly associated with the drug hardly can be expected to increase with age, it could have been considered acceptable to collect safety data in an older population as a post-approval commitment as part of the RMP.

There was one case of leukoencephalopathy in the active arm, but no conclusions can be drawn based on this single event. Nonetheless, the Applicant had addressed this issue in the proposed RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

DFS is an accepted outcome measure of adjuvant therapy in patients with FL in remission after induction therapy. A favourable effect, however, has not been demonstrated. In addition, there are no data to show clinical efficacy of Lympreva with induction regimens used in current clinical practice.

Although grade ≥3 events were reported in 30% of patients in the pooled Lympreva group, and SAEs occurred, discontinuation rate due to AE was low. Therefore, the toxicity associated with Lympreva is generally considered clinically manageable.

Benefit-risk balance

Discussion on the benefit-risk balance

A number of the Major Objections related to the quality of the product remain. Although much work had been done by the Applicant, there are still outstanding issues that are critical for this type of finished product and its manufacturing process. There are limited possibilities for control of the finished product due to the properties of the active substance, the limited batch size (about 20-30 vials) and that each batch is patient specific with the autologous immunoglobulin component. In view of these circumstances it is crucial that the manufacturing process is validated and capable to deliver a consistent product for which safety can be ensured with validated aseptic process. This was not demonstrated.

In the absence of established clinical efficacy and quality, the benefit-risk balance cannot be considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Lympreva in the treatment of patients with follicular non-Hodgkin's lymphoma (FL) as consolidation therapy after achieving complete remission with induction therapy and is co-administered with Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) the CHMP considers by consensus that the quality and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The quality of the critical intermediate KLH was insufficiently guaranteed. The CTD section dealing with the critical intermediate KLH is deemed deficient and incomplete. A major issue was the lack of process validation.
- The manufacturing process lacked full process validation and sufficient control of bioburden.
- Viral clearance and viral inactivation data for the IgM and IgG processes was insufficient and therefore, a final conclusion on viral safety cannot be drawn.
- Comparability between material from the manufacturing process used for clinical batches and material from the commercial manufacturing process had not been demonstrated as studies were incomplete.
- Process related impurities are insufficiently controlled as specifications with associated actual limits were not defined and analytical methods for their determination were not validated.
- Characterisation data are incomplete and several characterisation tests had not been qualified.
- Critical Quality Attributes should be within specifications, despite large yield differences due to variability between batches, this has not been demonstrated.
- Stability: Stability for bulk IgM and IgG during shelf life had not been demonstrated. In addition, stability for the medicinal product manufactured with the commercial process had not been demonstrated.
- Compatibility of the product with regards to the instructions for use and handling in the proposed Summary of product characteristics (co-administration of Lympreva and GM-CSF in one syringe; in use shelf life) had not been demonstrated.
- There are significant and unresolved concerns regarding the design of the pivotal study BV301. The analyses of the efficacy results did not sufficiently demonstrate the efficacy of the product and do not support of a marketing authorisation.
- The clinical efficacy of Lympreva in FL after induction with anti-CD20 antibodies, the mainstay of current clinical practice, has not been demonstrated.

REFERENCES

1. Campbell, M.J., Carroll, W., Kon, S., Thielemans, K., Rothbard, J.B., Levy, S., Levy, R., 1987. Idiotype vaccination against murine B cell lymphoma. Humoral and cellular responses elicited by tumour-derived immunoglobulin M and its molecular subunits. Journal of immunology 139, 2825-2833.

2. Campbell, M.J., Esserman, L., Levy, R., 1988. Immunotherapy of established murine B cell lymphoma. Combination of idiotype immunization and cyclophosphamide. Journal of immunology 141, 3227-3233.

3. Campbell, M.J., Esserman, L., Byars, N.E., Allison, A.C., Levy, R., 1990. Idiotype vaccination against murine B cell lymphoma. Humoral and cellular requirements for the full expression of antitumour immunity. Journal of immunology 145, 1029-1036.

4. George, A.J., Folkard, S.G., Hamblin, T.J., Stevenson, F.K., 1988. Idiotypic vaccination as a treatment for a B cell lymphoma. Journal of immunology 141, 2168-2174.

5. Goodlad JR, MacPherson S, Jackson R, Batstone P, White J., 2004. Extranodal follicular lymphoma: a clinicopathological and genetic analysis of 15 cases arising at non-cutaneous extranodal sites. Histopathology 44, 268–276.

6. Heyfets, A., Haimovich, J., Hollander, N., 2002. Determination of idiotype-specific T cells in idiotype-vaccinated mice. Immunology letters 80, 207-213.

7. Kaminski, M.S., Kitamura, K., Maloney, D.G., Levy, R., 1987. Idiotype vaccination against murine B cell lymphoma. Inhibition of tumour immunity by free idiotype protein. Journal of immunology 138, 1289-1296.

8. Kwak, L.W., Campbell, M.J., Zelenetz, A.D., Levy, R., 1990. Combined syngeneic bone marrow transplantation and immunotherapy of a murine B-cell lymphoma: active immunization with tumour-derived idiotypic immunoglobulin. Blood 76, 2411-2417.

9. Kwak, L.W., Young, H.A., Pennington, R.W., Weeks, S.D., 1996. Vaccination with syngeneic, lymphoma-derived immunoglobulin idiotype combined with granulocyte/macrophage colony-stimulating factor primes mice for a protective T-cell response. Proceedings of the National Academy of Sciences of the United States of America 93, 10972-10977.

10. F. Morschhauser et al. “Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma.” In: Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26.32 (2008), pp. 5156–64.

11. A. Z. Rohatiner and T. A. Lister. “The clinical course of follicular lymphoma.” In: Best practice & research. Clinical haematology 18.1 (2005), pp. 1–10.

12. Mathias J. Rummel et al. “Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial.” eng. In: Lancet (Feb. 2013).

13. G. A. Salles et al. “Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial.” eng. In: Lancet 377.9759 (Jan. 2011), pp. 42–51.

14. Sugai, S., Palmer, D.W., Talal, N., Witz, I.P., 1974. Protective and cellular immune responses to idiotypic determinants on cells from a spontaneous lymphoma of NZB-NZW F1 mice. The Journal of experimental medicine 140, 1547-1558.