17 September 2020
EMA/CHMP/624882/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Phelinun

International non-proprietary name: melphalan

Procedure No. EMEA/H/C/005173/0000

Note

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

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List of abbreviations

AE	Adverse event
ALL	Acute lymphoblastic leukaemia
allo-SCT	Allogenic stem cell transplantation
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AraC	Cytarabine
ASCT	Autologous stem cell transplantation
BM	Bone marrow
Bu	Busulfan
CHMP	Committee for Medicinal Products for Human use
CMV	Cytomegalovirus
Cy	Cyclophosphamide
DFS	Disease free survival
DLT	Dose-limiting toxicity
DSC	Differential Scanning Calorimetry
DVS	Dynamic Vapour Sorption
EBMT	European Group for Blood and Marrow Transplantation
EC	European Commission
EFS	Event free survival
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FAI	Fludarabine, cytarabine, and idarubicin
FBM	Fludarabine- bis-chlorethyl-nitroso-urea/ carmustine –melphalan;
FFS	Failure free survival
Flu	Fludarabine
GMP	Good Manufacturing Practice
GR	Graft rejection
GvHD	Graft versus host disease
GvT	Graft versus tumour
HL	Hodgkin’s lymphoma
HLA	Human leukocyte antigen
HPLC	High performance liquid chromatography
HSCT	Haematopoietic stem cell transplantation
i.v.	Intravenous
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
JMML	Juvenile myelomonocytic leukemia
KF	Karl Fischer titration
LDPE	Low Density Polyethylene
L-PAM	L-phenylalanine mustard
MAA	Marketing authorization application
MAC	Myeloablative conditioning
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Mel	Melphalan
MM	Multiple myeloma
NCI	National Cancer Institute
NHL	Non-Hodgkin’s lymphoma
NMA	Non myeloablative
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NRM	Non-relapse mortality
OS	Overall survival
PBSC	Peripheral blood stem cell
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
RH	Relative Humidity
RIC	Reduced intensity conditioning
RMP	Risk management plan
RR	Response rate
SCID	Severe combined immunodeficiency

SCT	Stem cell transplantation
SmPC	Summary of product characteristics
SOC	System organ class
TBI	Total body irradiation
TRM	Transplant-related mortality
TSE	Transmissible Spongiform Encephalopathy
UCB	Umbilical cord blood
URD	Unrelated donor
UV	Ultraviolet
VOD	Veno-occlusive disease
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ADIENNE S.r.l. submitted on 11 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Phelinun, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2018. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 10c of Directive 2001/83/EC.

The applicant applied for the following indications: Melphalan alone or in combination with other cytotoxic drugs and/or total body irradiation, for the treatment of multiple myeloma, malignant lymphoma (Hodgkin, non-Hodgkin lymphoma), acute lymphoblastic and myeloblastic leukemia, childhood neuroblastoma, ovarian and mammary adenocarcinoma.

In the context of this hybrid marketing authorization application, the applicant is submitting also supportive data to include a new therapeutic indication concerning the use of melphalan as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (HSCT) in haematological diseases.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Alkeran, 50 mg/10 ml, powder and solvent for concentrate for solution for infusion
- Marketing authorisation holder: Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus - Dublin 24 Ireland
- Date of authorisation: 22 February 1996
  - Marketing authorisation granted by: Member State (EEA); France
    - National procedure
- Marketing authorisation number: 34009 559 526 88

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Alkeran, 50 mg/10 ml, powder and solvent for concentrate for solution for infusion
- Marketing authorisation holder: Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus - Dublin 24 Ireland

- Date of authorisation: 22 February 1996
- Marketing authorisation granted by: Member State (EEA); France
  - National procedure
- Marketing authorisation number: 34009 559 526 88

Information on paediatric requirements

Not applicable

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 submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Natalja Karpova

The application was received by the EMA on	11 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 July 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 January 2020
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	3 March 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 March 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 March 2020

The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	22 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	9 July 2020
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	19 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	3 September 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Phelinun on	17 September 2020
The CHMP adopted a report on similarity of Phelinun with Farydak (panobinostat), Ninlaro (ixazomib), Imnovid (pomalidomide), Kyprolis (carfilzomib), Mylotarg (gemtuzumab-ozogamicin), Besponsa (inotuzumab-ozogamicin), Vyxeos (cytarabin-daunorubicin), Iclusig (ponatinib), Blincyto (blinatumomab), Xaluprine (mercaptopurin), Dacogen (decitabine), Rydapt (midostaurin), Novartis Europharm Ltd, Xospata (gilteritinib), Qarziba (dinutuximab beta), Poteligeo (mogamulizumab), Kymriah (tisagenlecleucel), Yescarta (axicabtagen ciloleucel), Gazyvaro (obinutuzumab), Imbruvica (ibrutinib), Adcetris (brentuximab vedotin), Ledaga (chlormethine), Zejula (niraparib), Tepadina (thiotepa), Mozobil (plerixafor) - within the meaning of Article 3 of Commission Regulation (EC) No. 847/200 on	17 September 2020

2. Scientific discussion

2.1. Introduction

The current application concerns a hybrid application with reference to the European reference product Alkeran® 50 mg/10 ml, lyophilisat et solution pour usage parentéral (I.V.) from Aspen Pharma Trading Limited authorised in France. Together with the indications approved in France, the applicant seeks an additional new therapeutic indication for the use of Phelinun as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (allo-HSCT) on the basis of published literature.

The reference product Alkeran is also indicated in the treatment of childhood neuroblastoma, ovarian adenocarcinoma and mammary adenocarcinoma. Melphalan is part of a high dose consolidation regimen used in children with high-risk neuroblastoma with response to induction therapy (Ladenstein et al., 2017).

For ovarian adenocarcinoma, melphalan administered as oral tablets is used as a single-agent late-line treatment for patients with platinum-resistant disease or a contra-indication for continued treatment with carboplatin and/or paclitaxel. For mammary adenocarcinoma, the use of melphalan in clinical practice is currently very limited.

Melphalan, also known as L-phenylalanine mustard, is a phenylalanine derivative of nitrogen mustard and was first approved as a medicinal product in Canada on 26 September 1963. Since then, the drug product under the tradename Alkeran® has been approved worldwide in more than 100 countries. The European Union reference date (EURD) is September 26, 1963.

Alkeran is available in two formulations: 2 mg tablets for oral administration and 50 mg for regional arterial or intravenous (IV) injection. It is approved in a number of European countries through national and mutual recognition/decentralised procedures, sometimes with varying indications.

The specific European reference medicinal product identified for this MA Application is Alkeran® *50 mg/10 ml, lyophilisat et solution pour usage parentéral (I.V.)* from Aspen Pharma Trading Limited authorised in France (MA n: 559 526-8) through national procedure on February 22, 1996 (ANSM - Répertoire des Spécialités Pharmaceutiques). The indications for this product in the SmPC specify use at high dose alone or in combination with other cytotoxic agents and/or extended or total body irradiation (TBI) in the treatment of: multiple myeloma, malignant lymphoma (Hodgkin, non-Hodgkin lymphoma); acute lymphoblastic and myeloblastic leukaemia; childhood neuroblastoma; ovarian cancer, mammary adenocarcinoma.

2.1.1. Disease or condition

The proposed new indication of melphalan is in combination with other cytotoxic drugs, in adults and the paediatric population, as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (HSCT) in haematological diseases, for adults limited to malignant disease, for the paediatric population for both malignant and non-malignant conditions.

Haematopoietic stem cell transplantation (HSCT) involves the intravenous infusion of autologous or allogeneic haematopoietic stem cells collected from bone marrow, peripheral blood, or umbilical cord blood to re-establish haematopoietic function in patients with damaged or defective bone marrow or immune system. When the stem cells are collected from relatives (identical twins, HLA-matched related, mismatched related) or unrelated donors (matched unrelated, umbilical cord blood) it is called allogeneic transplant. In 2012, more transplants were obtained from unrelated donors than from related ones. The aim of allogeneic HSCT is cure of some forms of cancer (in particular leukaemia), bone marrow failure, hereditary metabolic disorders, and severe congenital immunodeficiencies, which would otherwise be fatal.

2.1.2. Epidemiology

According to the latest European Society for Blood and Marrow Transplant (EBMT) report, 45,418 transplants were reported in 41100 patients (4318 second or subsequent transplants) in Europe in the year 2017; of these, 18281 HSCTs (40%) were allogeneic and 27137 (60%) autologous. Compared with data from 2016, the total number of transplants increased by 4.1% (3.6% in the allo-HSCT and 4.4% in the auto-HSCT group). In 2015, there were 5,056 paediatric patients < 18 years of age receiving HSCT in Europe, 3,725 received an allogeneic and 1,331 an autologous HSCT.

The number of allo-HSCTs continues to increase by 10-20% annually, and reductions in organ damage, infection, and severe acute graft versus host disease (aGvHD) seem to be contributing to improved outcomes. Total mortality among patients who underwent allo-HSCT at the Fred Hutchinson Cancer Center in Seattle fell from 63% between 1993 and 1997 to 47% between 2003 and 2007. At the same time, non-relapse mortality fell from 41% to 26%. In a study by the Center for International Blood and Marrow Transplant Research (CIBMTR), the 10-year survival rate of 3788 patients who had survived at least two years after allo-HSCT without relapse of their underlying disease was 85%. Survival after

transplantation is comparable among patients receiving donor stem cells from HLA-identical sibling and matched unrelated donors for several diseases. Age when allogenic HSCT is undertaken depends of the haematological disease and varies from a paediatric population to a population over 65 years of age. In data obtained in the US for 2016, 30% of allogeneic transplant recipients were over 60 years of age and 4.6% of recipients were over 70 years of age (D'Souza et al, 2017).

2.1.3. Indications for allo-HSCT

Allogeneic HSCT is potentially curative for leukaemias, myelodysplastic syndromes (MDS), lymphomas and multiple myeloma (MM). It is also increasingly used in non-malignant diseases such as primary immunodeficiency, inborn errors of metabolism, haemoglobinopathies and bone marrow failure syndromes.

According to the latest EBMT report, the most common indication for an allo-HSCT is acute leukaemia (55%), especially AML (39%), followed by ALL (16%) and MDS/MPS (16%). The use in CML has declined rapidly since the introduction of highly potent tyrosine kinase inhibitors.

Main indications in children are acute lymphoblastic leukaemia (ALL; 26%), primary immunodeficiency (PID; 16%), AML (14%), bone marrow failure (12%), thalassaemia (9%), and MDS/MPS (8%).

Allo-HSCT is the treatment of choice in adult and paediatric patients with high-risk AML in their first complete remission (CR1). In patients with standard or good risk features, allo-HSCT is reserved for their second complete remission (CR2). Allo-HSCT is the only curative option for patients with primary refractory or relapsed AML.

In 2017, 7% of the total HSCTs performed in Europe were for non-malignant haematological diseases. Of these 2667 transplants, 81% were allogeneic HSCTs.

2.1.4. Conditioning regimens prior to allo-HSCT

Patients undergoing allo-HSCT are prepared with chemotherapy alone or chemotherapy combined with radiotherapy, the so-called conditioning regimen, with three aims: to reduce the tumour burden when the disease is neoplastic, to eliminate the self-renewing capacity of the patient's own haematopoiesis, and to suppress the recipient's immune system to allow engraftment of stem cells. Exceptions are infants with severe combined immune deficiency (SCID) and patients with severe aplastic anaemia with an identical twin donor who may be grafted without conditioning.

Transplant-related mortality (TRM) after myeloablative regimens increases with increasing age, and to reduce toxicity non-myeloablative (NMA) conditioning regimens were developed.

Myeloablative conditioning does not allow autologous recovery and require stem cell support whereas non-myeloablative regimens do not require stem cell support. Regimens that do not match these criteria have been classified as reduced-intensity conditioning (RIC), whereby the dose of total body irradiation (TBI) or the alkylating agent is usually reduced by at least 30% compared with an ablative regimen.

Myeloablative radiation-containing conditioning regimens

High dose total body irradiation (TBI), usually 12-16 Gray (Gy) has been widely used as part of the conditioning with other chemotherapeutic agents, most commonly cyclophosphamide (CY).

Higher doses of TBI reduce the relapse risk but result in increased toxicity. Other agents such as cytarabine (AraC), etoposide (ETO), melphalan (MEL), and busulfan (BU), have been combined with TBI as conditioning regimens.

Myeloablative conditioning regimens without radiation

These regimens have primarily been developed for autologous transplantation, but they have also been used in the allogeneic setting. The primary advantage is reduced toxicity. Additionally, the regimen is easier to administer, and radiation can still be given to sites of prior disease following transplantation. Alkylating agents remain the mainstay of such regimens.

Commonly used regimens are based on orally or intravenously administered BU and other cytotoxic agents. A regimen consisting of high-dose BU (16 mg/kg total dose) and CY (200 mg/kg total dose) was developed and modified (total CY dose was decreased to 120 mg/kg) and has been widely used.

Nonmyeloablative and reduced intensity conditioning regimens

For patients with haematologic malignancies, an important contributing factor is a graft-versus-tumour (GvT) effect mediated by the allogeneic donor cells. This effect depends on the permanent engraftment of donor-type immunocompetent cells, which does not necessarily require a myeloablative conditioning.

Due to its lowered toxicity, NMA transplants can be appropriate for patients older than 55 years, which is a common upper limit for standard myeloablative transplantation as well as for patients with co-morbidities that would exclude them from undergoing myeloablative transplantation.

Fludarabine (FLU) has been widely used because it is highly immunosuppressive, has anti-tumour activity in haematological malignancies and a low non-haematologic toxicity profile. Regimens that relied on FLU or lower doses of the conditioning agents are referred to as either NMA or RIC.

NMA regimens may result in minimal cytopaenias that do not require stem cell support whereas RIC regimens do require stem cell support.

Use of melphalan in conditioning for HSCT

There is no standard choice for conditioning regimens in allogeneic HSCT and clinical practice varies across countries and institutions. A decision regarding the use of a particular conditioning regimen takes into consideration a range of factors; recipient co-morbidities, underlying condition and disease status, donor, and graft source.

Melphalan is a widely used agent in conditioning regimens prior to auto-HSCT and it is the mainstay-conditioning drug for multiple myeloma (MM) and lymphomas. Melphalan is part of the BEAM regimen, one of the most commonly used conditioning regimen for HSCT for patients with lymphoma. BEAM consists of carmustine, etoposide, arabinoside and melphalan (the latter generally at 140 mg/m2). Although it is not specifically authorised, melphalan has been used as part of conditioning regimens before allo-SCT due to its myeloablative properties and broad antitumor effects as a DNA alkylating agent.

2.1.5. Complications of HSCT

Complications of HSCT pertain to:

- Prolonged and severe pancytopenia which necessitates the use of antibiotics and blood cell transfusions.
- Graft rejection where donor cells fail to regenerate within the recipient. Mechanisms include the failure of immunosuppressive agents to inactivate the host immune system, inadequate ratio of donor cells to facilitator cells infused, drug injury to marrow, or viral infections.

- Graft versus host disease (GvHD) when immunocompetent T and natural killer cells in the donor graft recognise host antigens as foreign targets and mediate a reaction. The disease may cause significant morbidity and mortality and has been divided into acute and chronic forms.
    - To avoid acute GVHD, patients are given potent immunosuppressives immediately before and for many months after transplantation.
    - Around 40-50% of patients develop chronic GVHD within five years of treatment (Carlens et al, Atkinson et al). It may develop as a continuation of active acute GvHD, after successful clearing of acute GvHD, or may appear without antecedent acute GvHD. The target organs are more widespread than in acute GvHD. Chronic GVHD is associated with fewer relapses, indicative of a GvT effect.
- Pulmonary complications like interstitial pneumonitis, often fatal and caused by viral infection, or lung injury due to TBI or pulmonary toxins (carmustine).
- Hepatic sinusoidal obstruction syndrome, previously known as veno-occlusive disease (VOD) manifests as jaundice, hepatomegaly, unexplained weight gain, or ascites. The condition usually develops by 30 days after HSCT, although it can occur later. Historically, its reported incidence ranges from approximately 5 to 60% (Coppell et al). Risk factors for this complication include a history of previous hepatocellular disease, certain conditioning regimens, advanced age, the presence of GvHD, the type of GvHD prophylaxis, poor performance status at transplantation, and the use of matched unrelated or mismatched donor grafts.
- Late-onset problems include an increased risk of malignancy (often many years after transplant), infections (like reactivation of dormant herpes viruses), and gonadal dysfunction in up to 92% of men and 99% of women. Further, the medications that transplant recipients need to take can impair liver function, and there is transfusion-associated haemosiderosis. Around 40% to 50% of patients suffer from lipid metabolic disturbances that increase the risk of myocardial infarction, peripheral arterial occlusive disease, and stroke. Life expectancy is shorter than that of the overall population.

About the product

Melphalan, also known as L-phenylalanine mustard (L-PAM), is a phenylalanine derivative of nitrogen mustard. It belongs to the pharmaco-therapeutic group of antineoplastic and immune-modulating agents, antineoplastic agents, alkylating agents, nitrogen mustard analogues (ATC code: L01AA03).

Melphalan is a DNA-alkylating agent with myeloablative properties and broad antitumor effects.

The current application is with reference to the European reference product Alkeran 50 mg/10 ml, lyophilisat et solution pour usage parentéral (I.V.) from Aspen Pharma Trading Limited authorised in France. Together with the indications of the reference product, the applicant seeks an additional new therapeutic indication for the use of Phelinun in HSCT and an additional strength of 200mg.

Melphalan, also known as L-phenylalanine mustard, is a phenylalanine derivative of nitrogen mustard and was first approved as a medicinal product in Canada on 26 September 1963. Since then, the drug product under the tradename Alkeran has been approved worldwide in more than 100 countries. The European Union reference date (EURD) is September 26, 1963.

Alkeran is available in two formulations: 2 mg tablets for oral administration and 50 mg for regional arterial or intravenous (IV) injection. It is approved in a number of European countries through national and mutual recognition/decentralised procedures, sometimes with varying indications.

The specific European reference medicinal product identified for this MA Application is Alkeran® *50 mg/10 ml, lyophilisat et solution pour usage parentéral (I.V.)* from Aspen Pharma Trading Limited authorised in France (MA n: 559 526-8) through national procedure on February 22, 1996 (ANSM - Répertoire des Spécialités Pharmaceutiques). The indications for this product in the SmPC specify use at high dose alone or in combination with other cytotoxic agents and/or extended or total body irradiation (TBI) in the treatment of: multiple myeloma, malignant lymphoma (Hodgkin, non-Hodgkin lymphoma), acute lymphoblastic and myeloblastic leukaemia, childhood neuroblastoma, ovarian cancer, mammary adenocarcinoma.

The dosage recommendations in the reference medicinal product SmPC are:

- Multiple myeloma, malignant lymphoma (Hodgkin, non-Hodgkin lymphoma), acute lymphoblastic and myeloblastic leukaemia, ovarian and mammary adenocarcinoma at high dose:

  the recommended dose is between 100 and 200 mg/m2 body surface area (approximatively 2.5 to 5.0 mg/kg body weight). The dose can be divided equally over 2 or 3 successive days.

  Autologous hematopoietic stem cell transplantation becomes essential following doses above of 140 mg/m2 body surface area.

- Childhood neuroblastoma:

  the recommended dose to consolidate a response obtained with a conventional treatment is one single dose between 100 and 240 mg/m2 body surface area (sometimes divided equally over 3 consecutive days) together with autologous haematopoietic stem cell transplantation; the infusion is used either alone or in combination with radiotherapy and/or other cytotoxic drugs.

The proposed additional indication for melphalan is:

"PHELINUN in combination with other cytotoxic drugsis indicated as reduced intensity conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (HSCT) in malignant haematological diseases in adults.

PHELINUN in combination with other cytotoxic drugs in paediatric population is indicated as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (HSCT) in haematological diseases."

Phelinun in combination with other cytotoxic medicinal products is indicated as conditioning regimen prior to allogeneic haematopoietic stem cell transplantation in haematological diseases in the paediatric population as:

- Myeloablative conditioning (MAC) treatment in case of malignant haematological diseases
- RIC treatment in case of non-malignant haematological diseases.

<u>The proposed posology for the new indication is:</u>

The recommended dose ranges before allogeneic haematopoietic stem cell transplantation in haematological diseases are as follows:

- Adults: the recommended dose is 140 mg/m2 as a single daily infusion or 70 mg/m2 once daily for two consecutive days.
- Paediatric: the recommended dose is as follows:
    - malignant haematological diseases: 140 mg/m^2 as a single daily infusion;
    - non-malignant haematological diseases: 140 mg/m^2 as a single daily infusion or 70 mg/m^2 once daily for two consecutive days.

Similarity with orphan medicinal products

It is considered that Phelinun is not similar to Farydak (panobinostat), Ninlaro (ixazomib), Imnovid (pomalidomide), Kyprolis (carfilzomib), Mylotarg (gemtuzumab-ozogamicin), Besponsa (inotuzumab-ozogamicin), Vyxeos (cytarabin-daunorubicin), Iclusig (ponatinib), Blincyto (blinatumomab), Xaluprine (mercaptopurin), Dacogen (decitabine), Rydapt (midostaurin), Novartis Europharm Ltd, Xospata (gilteritinib), Qarziba (dinutuximab beta), Poteligeo (mogamulizumab), Kymriah (tisagenlecleucel), Yescarta (axicabtagen ciloleucel), Gazyvaro (obinutuzumab), Imbruvica (ibrutinib), Adcetris (brentuximab vedotin), Ledaga (chlormethine), Zejula (niraparib), Tepadina (thiotepa), Mozobil (plerixafor) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder and solvent for concentrate for solution for infusion containing 50 mg or 200 mg of melphalan as the active substance. The product contains the hydrochloride salt.

Other ingredients of the powder are hydrochloric acid (for pH adjustment) and povidone. The solvent consists of water for injections, propylene glycol, ethanol and sodium citrate.

The product is available in type I glass vial closed with coated chlorobutyl rubber stopper and sealed with aluminium flip off cap as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of melphalan hydrochloride is 4-[bis(2-chloroethyl)amino]-L-phenylalanine hydrochloride corresponding to the molecular formula $C_{13}H_{18}N_2O_2.HCl$. It has a molecular weight of 341.367 g/mol and the following structure:

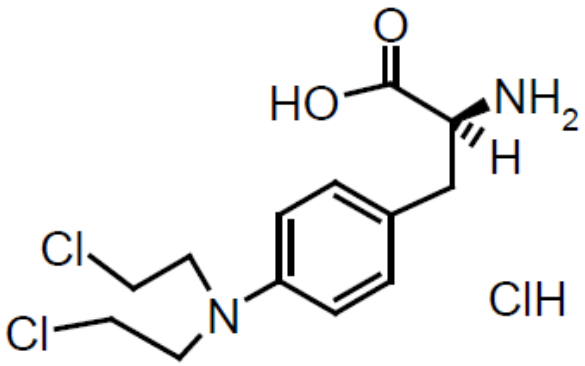


Figure 1: active substance structure

The chemical structure of melphalan hydrochloride was elucidated by a combination of infrared (IR) spectroscopy, ultraviolet (UV) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, mass spectroscopy and elemental analysis. The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and dynamic vapour sorption (DVS).

The active substance is a white to off white powder, soluble in ethanol, freely soluble in methanol and 1N HCl, practically insoluble in water and di-ethyl ether. Melphalan hydrochloride shows a significant water uptake. The observed water sorption process is reversible upon lowering of relative humidity during the desorption step and over multiple DVS cycles.

Melphalan exhibits stereoisomerism due to the presence of a chiral centre. The active substance is in the *S* (L) configuration. The origin of stereoisomerism is in the starting material (melphalan is an L-phenylalanine derivative of nitrogen mustard). Chiral purity of the active substance is controlled by chiral HPLC. Polymorphism has been observed for melphalan hydrochloride. It was demonstrated that the manufacturing process of the active substance consistently produces a single polymorphic form and the polymorphic form does not change during storage.

As there is a monograph of melphalan base in the European Pharmacopoeia (Ph. Eur.), however melphalan hydrochloride is a non-compendial active substance.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is sourced from a single manufacturer.

During the marketing authorisation application assessment procedure, at the request of CHMP, one of the starting materials was re-defined to a compound used in one synthesis step earlier. The originally proposed starting material is now considered an intermediate. This allows for a larger part of synthesis route to be conducted under GMP and increases control over the active substance quality.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in two tied low-density polyethylene (LDPE) bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. The bagged material is then inserted in an aluminium pouch, which is thermally sealed. The airtight packaging has been chosen to provide complete protection from moisture and light.

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), identity of chloride (Ph. Eur.), appearance of solution (Ph. Eur.), related substances (HPLC), D-enantiomer (chiral HPLC), water content (KF), ionizable chloride content (titration), assay (HPLC), residual solvents (GC), residue on ignition (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and microbiological limit test (Ph. Eur).

Impurity limits are within ranges of Ph. Eur. monograph for melphalan and appropriate specifications have been set. The Ph. Eur. monograph for melphalan free base foresees a limit of NMT 3.0% and NMT 1.0% for monohydroxy melphalan and melphalan dimer, respectively. Bacterial endotoxins content is determined according to Ph. Eur. which is set considering the administration of a high maximum daily dose (240 mg/m^2).

A risk assessment was carried out on elemental impurities potentially present in the active substance. The content of impurities identified as potentially present was tested and resulted to be lower than 30% of the ICH Q3D Option 1 limits. Based on this outcome, the test for elemental impurities has not been included in the specifications.

Melphalan hydrochloride is an anticancer drug that is known to be cytotoxic and genotoxic. The approach to control potentially genotoxic impurities by the purification steps included in the validated process is acceptable, as their content is not expected to impact the product safety.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 17 batches of commercial scale of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 7 commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (5 ºC ± 3 °C) and from 5 commercial scale batches for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed.

The following parameters were tested*:* appearance, related substances, D-enantiomer, assay, water content, bacterial endotoxin and microbiological purity. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. Impurity content increases slightly. No other trend can be observed. No out-of-specification result has been observed.

Forced degradation studies have revealed that melphalan hydrochloride degrades markedly in basic, oxidative and acidic media, less significant degradation is caused by heat and light.

One batch of the active substance was exposed in closed quartz dishes to light (in line with ICH Q1B Option 1) and under the same light conditions but kept in the unopened stability packaging (double

polyethylene bag + sealed aluminium bag). Photostability results collected on exposed and protected samples show that the active substance is light sensitive and that the primary packaging system adequately protect the product from light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months at 5 ºC ± 3 °C protected from light in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as powder and solvent for concentrate for solution for infusion containing 50 mg or 200 mg of melphalan (as hydrochloride). The finished product is formulated as sterile, non-pyrogenic freeze-dried powder in one single-dose clear glass vial and one clear glass vial of sterile solvent. The 50 mg strength of the finished product is reconstituted with 10 mL of solvent and the 200 mg strength with 40 mL of solvent. There are no overages contained in the target formulation of the solvent or the powder. Overfills for the solvent vials are applied to allow the withdrawal of labelled amount.

The finished product is prepared by reconstituting the freeze-dried powder with the solvent and immediately shaking vigorously until a clear solution, without visible particles, is obtained. Unless the concentrate is administered into a fast-running infusion solution via injection port, the reconstituted solution must be further diluted prior to administration with an appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection in order to obtain a final concentration between 0.45 and 4.0 mg/mL.

The aim of the pharmaceutical development was to develop a lyophilised formulation of the reference medicinal product Alkeran 50 mg/10 mL, lyophilisat et solution pour usage parentéral (I.V.) from Aspen Pharma Trading Limited authorised in France and a suitable aseptic manufacturing process as well as a suitable container closure system. Together with the indications approved in France, the applicant seeks an additional new therapeutic indication for the use of Phelinun. In addition, the applicant has developed a new strength (200 mg).

The key active substance physico-chemical characteristic that can influence the performance of the finished product, i.e. the manufacturability of the lyophilised dosage form, is the active substance solubility. The active substance is freely soluble in HCl diluted solutions and the formulated solution to be lyophilised contains HCl to match the reference product composition and to provide the required active substance solubility. Since the active substance is sensitive to light and heat, in order to minimise active substance degradation during compounding with excipients operation, compounding is performed at refrigerated conditions protected from direct light exposure.

The excipients used in the finished product have been chosen based on the excipients used in the reference product. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The suitability of the established formulation (API/excipients compatibility) and container closure system has been assessed and confirmed. The provided data demonstrated that the finished product is

not stable under light conditions unless a secondary packaging, such as a carton box, protects it. This is in line with the reference product SmPC that mentions: "Store protected from light."

Studies have been performed in order evaluate the compatibility between the active substance and components of the solvent in the reconstituted solution at 5 mg/mL of Phelinun for a time of 90 minutes at room temperature. All studies showed acceptable quality of the finished product when used in line with the SmPC.

No bioequivalence studies were provided to support the application. The proposed product 50 mg/10 ml has the same qualitative composition with same concentration of melphalan at the moment of infusion, same type of solution (i.e. aqueous intravenous solution), same method and means of administration for the current approved indications of Alkeran 50 mg/10 ml. The excipients used for the test product are qualitatively the same and quantitatively comparable to the reference product according to the information available to the CHMP. The composition and concentration of the other proposed formulation 200 mg/40 ml is identical to the 50 mg/10 ml formulation and has same final concentration after reconstitution and dilution corresponding to 5 mg/ml. The requirements stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) are fulfilled and the absence of a bioequivalence study can be accepted.

In addition to the acceptable biowaiver, on request of CHMP, the applicant generated supportive comparative physical and chemical characteristics of the test product and Alkeran sourced from the Dutch market. *In vitro* comparison of the reconstituted solution of the 50 mg/10 mL test product versus Alkeran 50 mg, and of the reconstituted solution of the 200 mg/40 mL test product versus 4 x Alkeran 50 mg/10 mL has been performed. It has been adequately demonstrated that both the compositions and the relevant physical-chemical parameters (appearance, pH, density, osmolality, assay, related substances, levels of ethanol and propylene glycol, reconstitution time, stability over reconstitution time) of the reconstituted products are equivalent.

Lyophilisation parameters have been studied by characterising the solution to be lyophilised in the frozen state by means of sub-ambient DSC studies (cooling and heating curves). Based upon the obtained experimental data, a number of trials were performed, and cycle parameters modified so as to obtain a lyophilised cake of suitable appearance and residual water content.

The choice of the sterilization method has been justified according to the relevant guideline (EMA/CHMP/CVMP/QWP/850374/2015). The aseptic processing of parenteral products is validated by performing media fill studies. This test is carried out to simulate the normal manufacturing conditions and all the critical subsequent manufacturing steps by replacing the pharmaceutical product with culture media. Microbial growth in the aseptically filled vials is monitored. The results of media fill studies are provided and considered acceptable.

The primary packaging is type I glass vial closed with coated chlorobutyl rubber stopper and sealed with aluminium flip off cap. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of the powder consists of 7 main steps: compounding, sterile filtration, filling and pre-stoppering, freeze drying and stoppering, sealing and packaging. The process is considered to be a non-standard manufacturing process due to the choice of sterile filtration and aseptic filling. The solvent is manufactured in 5 main steps: compounding, filtration, filling and stoppering, terminal sterilisation and packaging.

The processing/holding time were established and appropriately justified.

Major steps of the manufacturing process have been validated by a number of studies. Process validation has been carried out following a matrix approach in order to fully validate the manufacturing process for the presentation of 200 mg and to confirm the robustness and reproducibility of the manufacturing process for both strengths. This process validation addresses all critical process parameters and manufacturing steps. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications, include appropriate tests for this kind of dosage form: appearance, identity (HPLC, UV), identity of povidone (IR), assay (HPLC), organic impurities (HPLC), ionisable chlorine content (titration), uniformity of dosage units (Ph. Eur.), closure integrity (dye immersion test), water content (KF), residual solvents (GC), particulate contamination (Ph. Eur), bacterial endotoxins (Ph. Eur), sterility (Ph. Eur), reconstitution time, appearance of primary reconstituted solution, relative density of primary reconstituted solution (Ph. Eur), pH of primary reconstituted solution (Ph. Eur), clarity of primary reconstituted solution (Ph. Eur), colour of primary reconstituted solution (Ph. Eur) and particulate matter of primary reconstituted solution.

The specifications are in accordance with the general requirements of Ph. Eur., with the prescriptions of Ph. Eur. Parenteral preparations, with ICH Q3B and with ICH Q6A. The proposed impurity limits specifically, are either more strict or equal to the requirements set in the Ph. Eur. monograph for melphalan and in ICH Q3B, this is acceptable. All other limits are also acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The applicant has provided a risk evaluation concerning the presence of nitrosamine impurities in the product in question. The performed evaluation shows that for none of the components of this finished product there is real risk of contamination of nitrosamines, either from the components or from the process. Nevertheless, two batches of each component of each strength have been tested by a validated LC/MS method (description is provided). The calculation principle for the intake has been presented, it is in accordance with the prescriptions of Questions and answers on "Information on nitrosamines for marketing authorisation holders" EMA/CHMP/428592/2019. The results allow the exclusion of nitrosamine testing in the finished product specifications.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided on 3 commercial scale batches of each strength of the finished product confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

For the 50 mg strength, stability data from three commercial scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

For the 200 mg strength, stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, organic impurities, water content, particulate contamination, bacterial endotoxins, sterility and closure integrity (dye immersion test). The analytical procedures used are stability indicating.

All the stability results on the finished product met the specifications at all the storage conditions tested. No significant changes have been observed.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The data demonstrated that the finished product, is not stable under light conditions unless a secondary packaging, such as a carton box, protects it.

In-use stability study demonstrated that after reconstitution and dilution, chemical and physical stability has been demonstrated for 1 hour and 30 minutes at 25°C. Therefore, the total time from reconstitution and dilution to the completion of infusion should not exceed 1 hour and 30 minutes.

Based on available stability data, the proposed shelf-life of 36 months for the 50 mg strength and 30 months for 200 mg strength when the vials are kept in the outer carton in order to protect from light as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacodynamics have been sufficiently described for melphalan (as single agent or in combination with other chemotherapeutics) for most of the different malignancy indications. The applicant has not submitted non-clinical primary pharmacodynamics data in relation to the indication childhood neuroblastoma and the new therapeutic indication concerning the use of melphalan as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (HSCT) in haematological diseases.

The applicant was asked to explain why non-clinical primary pharmacodynamics data in relation to the indication childhood neuroblastoma and HSCT in haematological diseases were not submitted. Furthermore, the applicant was asked to support the non-clinical primary pharmacology regarding these indications by (literature) data without asking for new animal data. The applicant submitted revised module 2.4 including non-clinical primary pharmacodynamics data from literature in relation to the above-mentioned indications. In Module 2.4, assessment for these indications is cross-referenced to the clinical data in Module 2.5. Additional literature references are provided in Module 4. Non-clinical studies data in rodents have shown evidence of the activity of melphalan against neuroblastoma xenografts. The immunosuppressive effect of melphalan is known and this active substance has been used for promotion of bone marrow suppression in rat studies. Although non-clinical data in these indications are limited, melphalan is a well-known substance and clinical studies data in above-mentioned indications should supersede limited non-clinical data. Therefore, additional non-clinical studies data to support these indications are not deemed necessary.

Secondary pharmacodynamic studies

No information on the secondary pharmacodynamics of melphalan has been included. No new studies on the secondary pharmacodynamics of melphalan were performed by the applicant. Off target effects can be predicted from clinical data and conducted toxicology studies.

Safety pharmacology programme

No standard safety pharmacology studies are available. Since melphalan has since long been used in clinical practice, where the undesirable effects and risk potential are well known, conventional non-clinical safety pharmacology studies are considered not necessary.

Pharmacodynamic drug interactions

In vitro or *in vivo* enhanced anti-tumour effects of melphalan were found with vasoactive agents (a.o. hydralazine, nifedipine, verapamil) and the glutathione synthesis inhibitor buthionine sulfoximine. These interactions do not have a negative impact on the activity of melphalan and therefore, these do not need to be described in section 4.5 of the SmPC.

2.3.3. Pharmacokinetics

All individual components of the pharmacokinetics of melphalan have been sufficiently addressed by the applicant. However, the data appear to be derived from studies with adult animals only; the applicant has not submitted specific non-clinical data to support use of melphalan in the paediatric population. Standard non-clinical studies using adult animals, or safety information from adult humans, cannot always adequately predict differences in safety profiles for all paediatric age groups. Especially effects on the immature immune system and the organs or tissues which play a role in the pharmacokinetics of a medicinal product may be difficult to predict. Nevertheless, additional non-clinical data (e.g. in juvenile animals) or evaluation of the relevance of available non-clinical pharmacokinetic data for the paediatric population are not considered of added value. It is more appropriate to evaluate pharmacokinetic data in the intended patient population clinically, using relevant exposure levels (see clinical assessment). Therefore, no supportive non-clinical pharmacokinetic data will be required.

According to the applicant, there are no non-clinical PK interaction studies available in literature. However, busulfan is known to reduce melphalan clearance. This interaction is considered clinically relevant, because melphalan is also used in combination with e.g. busulfan for myeloablation. Therefore, description of this interaction in section 4.5 of the SmPC will be required (see clinical assessment/SmPC document).

2.3.4. Toxicology

Melphalan is associated with significant toxicity. Bone marrow suppression (myelosuppression) and gastro-intestinal toxicity are the most significant toxicities observed after melphalan administration. Melphalan is mutagenic, carcinogenic and can cause reproductive and developmental toxicity.

The applicant did provide reprotoxicity data on fertility and pre- and post-natal development. Taken into account the proposed human target populations, the safety profile of melphalan in the paediatric patient population should be clear. However, it is considered most relevant to obtain this safety

information from clinical studies instead of non-clinical studies (see clinical assessment). Therefore, no additional non-clinical juvenile safety data will need to be presented.

Local tolerance

Melphalan is mildly irritating to skin, when topically applied. However, evaluation of local tolerance by the intended intravenous route was not made and no local tolerance data for intravenous route is provided or discussed. However, melphalan has been used (intravenously) in clinical practice for a long time also at the proposed high dose. Recommendations regarding method of administration are provided (e.g. slow injection via a central venous line) in section 4.2 of the SmPC to diminish local tolerability issues.

Other toxicity studies

The applicant has provided data related to tissue-specific toxicity, e.g. effects on the liver and kidney. It was noted that no data on immunotoxicity are discussed. Because melphalan is indicated and intended for myelosuppression (while the scope of ICH S8 for immunoxicity data is focused on unintended immunosuppression) and because the applicant has already provided sufficient data with respect to myelosuppression and haematologic toxicity, no additional toxicity data are required.

Safety of the different excipients and diluent components is sufficiently described and can be endorsed. In addition, no unexpected toxic effects are anticipated for the (structure-related) impurities present in the drug product.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant has calculated the Log Kow, which value is well below 4.5. The study appears to be conducted correctly. Based on the value of the PECsw, Phase II is indeed required. The applicant was asked to perform the Phase II studies and provide the results in an updated ERA. In their response to the D120 list of questions, the applicant stated that 6 Phase II studies had been started and that the results will be submitted in an updated ERA. The studies as indicated by the applicant were in line with the guidance. Depending on the outcome of these studies additional studies might be required. Considering that the dossier was still incomplete and the ERA could not be finalised, the Phase II study reports were awaited. In their response to the Day 180 list of outstanding issues, the applicant had provided additional Phase II studies. However, the proposed adaptations to study requirements of performing an OECD 121 study (instead of the OECD 106 study) and waiving the OECD 308 study were not accepted. Therefore, references for the Fpen/PEC_{sw} refinement and additional studies were to be provided, including an updated ERA. Moreover, the endpoints for all toxicity studies were to be expressed on melphalan and not melphalan.HCl as the calculations of the PEC were also based on melphalan. In addition, the calculations of the endpoints of the algae study were to be adapted.

At the current stage of the procedure the applicant has provided a new ERA in which the endpoints of the toxicity studies are expressed on melphalan, and further calculations on the algea study. The studies on toxicity to daphnia and fish will be submitted later together with an update ERA as a post approval commitment. Although the applicant does not refer to the requested OECD 106 study, in their ERA, they have further elaborated their request to replace this study with the OECD 121 and tested the stability of the substance under test conditions comparable to the OECD 106 study. For the requested OECD 308 transformation study, the applicant has provided justification of the absence of data from aerobic and anaerobic transformation in aquatic sediment systems (OECD 308). The applicant agrees that depending on the outcome of the required studies, additional studies might be required.

The CHMP agree with the adapted PECws calculation and accept the post approval commitment for the delayed studies with completion in the last quarter of 2020 and completion of further potential studies in the third quarter of 2021. The replacement of the OECD 106 test by the OECD 121 test has been sufficiently underpinned and is accepted. It is presumed that this test will be completed within the timeline of the committed toxicity studies. However, the OECD 308 study is still required. The toxicity observed in the ecotoxicity test is most likely caused by the hydrolysis products. Therefore, studies on the fate of the substance are of importance for the risk assessment. Also, the submission of generated endpoints for toxicity of the hydrolysis products is not accepted as replacement of the 308 study. Since the applicant is recommended to perform their ERA on the basis of the degradation products, the full set of required studies on the degradation products should be performed.

The proposed product information (SmPC, PL) contains information aimed at minimizing of unused medicine into the environment in line with draft *Guideline on the environmental risk assessment of medicinal products for human use*, 15 November 2018 (EMEA/CHMP/SWP/4447/00 Rev. 1).

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends points for further investigation (see discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

The applicant has provided information in the non-clinical overview to support the malignancy and myeloablation (for HSCT) indications proposed for melphalan. Because of its alkylating properties, this drug product leads to considerable cytotoxicity, primarily in highly proliferative tissue such as tumours, bone marrow and the GI tract. Melphalan is genotoxic and carcinogenic *in vitro* and *in vivo*. Moreover, melphalan is associated with reproductive and developmental toxicity. Degradation products and excipients are not expected to lead to additional safety issues.

In their integrated overview and conclusions, the applicant has discussed the applicability of melphalan studies conducted i.p. instead of i.v., the anticipated toxic effects and the safety margin (or dose-limiting toxicity) of the doses used in the non-clinical studies compared to the anticipated human doses. Risks associated with melphalan use are well described.

All individual components of the pharmacokinetics of melphalan have been sufficiently addressed by the applicant. However, the data appear to be derived from studies with adult animals only; the applicant has not submitted specific non-clinical data to support use of melphalan in the paediatric population. Standard non-clinical studies using adult animals, or safety information from adult humans, cannot always adequately predict differences in safety profiles for all paediatric age groups. Especially effects on the immature immune system and the organs or tissues which play a role in the pharmacokinetics of a medicinal product may be difficult to predict. Nevertheless, additional non-clinical data (e.g. in juvenile animals) or evaluation of the relevance of available non-clinical pharmacokinetic data for the paediatric population are not considered of added value (see also discussion on Clinical efficacy) with regard to the additional indication in allo-HSCT. It is more appropriate to evaluate pharmacokinetic data in the intended patient population clinically, using relevant exposure levels (see clinical assessment). Therefore, no further non-clinical pharmacokinetic data will be required.

Busulfan is known to reduce melphalan clearance. This interaction is considered clinically relevant, because melphalan is also used in combination with e.g. busulfan for myeloablation. Therefore, description of this interaction in section 4.5 of the SmPC is included.

The text in section 4.3, 4.6 and 5.3 of the SmPC was submitted in line with the French originator /English translated SmPC of the reference product and is updated so that these sections are now also

in line with the guideline on reproduction and lactation and have been revised according to the information on the new indications.

Data as regards the ERA are still lacking. The applicant has agreed to the recommendations of the CHMP to submit the following studies (including reports) and the results will be used in an updated ERA:

-Adsorption-desorption using the HPLC method (OECD 121) for melphalan and its significant transformation products;

-Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308);

-Daphnia sp. reproduction test (OECD 211, use version 2012);

-Fish, early life stage (E.L.S.) toxicity test (OECD 210, use version 2013);

Out of all requested chronic toxicity studies and the OECD 209 test, a NOEC and/or EC10 is needed for the risk assessment. In case a limit test is performed, the OECD guidelines should be followed: if the limit test results in a statistically significant effect, a new test to determine a dose-response relationship should be performed, from which a NOEC and/or EC10 should be reported.

Depending on the outcome of these studies, the following additional studies might be required:

-Aerobic and anaerobic transformation in soil (OECD 307);

-Soil Micro-organisms: Nitrogen Transformation Test (OECD216);

-Terrestrial Plants, Growth Test (OECD 208);

-Earthworm, Acute Toxicity Test (OECD 207);

-Collembola, Reproduction Test (ISO 11267)

-effects on a sediment dwelling organism: Hyalella sp; Lumbriculus sp. (OECD 225) or Chironomus sp. (OECD 218 or 219).

Nevertheless, the procedures for the safe handling and disposal of antineoplastic agents must be followed by healthcare professionals or medical personnel and should comply with the current recommendations for cytotoxic medicinal products (see SmPC section 4.2 and 6.6). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

2.3.7. Conclusion on the non-clinical aspects

The applicant has provided sufficient non-clinical data to support the current application, however the ERA is incomplete; further studies will be provided post-approval (see above) as per the CHMP's recommendations to the applicant.

2.4. Clinical aspects

2.4.1. Introduction

The current application concerns an abridged application with reference to the European reference product ALKERAN® 50 mg/10 ml, lyophilisat et solution pour usage parentéral (I.V.) from Aspen

Pharma Trading Limited authorised in France. Together with the indications approved in France, the applicant seeks an additional new therapeutic indication for the use of Phelinun as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (allo-HSCT).

No bioequivalence studies were submitted to support the application and the following justification is provided by the applicant:

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), bioequivalence studies are generally not required if the proposed product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product, both products contain the same excipients in similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.

The drug product melphalan 50 and 200 mg powder and solvent for concentrate for solution for infusion has the same active moiety, qualitative excipient composition as the reference product Alkeran, and both medicinal products are administered i.v. as aqueous solution. In terms of excipients, none is expected to interact with the active substance or affect its disposition. The additional 200 mg strength of melphalan is proportional in quantitative composition to the other presentation of 50 mg (authorised for the reference medicinal product) and both presentations (i.e. 50 and 200 mg) have the same final concentration after reconstitution and dilution corresponding to 5 mg/ml. The requirements stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) are fulfilled and the absence of a bioequivalence study can be accepted.

Clinical studies

A summary of the publications in support of the newly proposed indication is presented in the table below.

Table 1 List of relevant initially submitted literature used for efficacy and safety – Adult studies

Reference	Region	Study design (control type)	Dose of melphalan	No exposed melphalan; Age Range (years)	Target Population	Efficacy endpoints	Safety
(Eom et al., 2013)	Korea	Prospective controlled (TBI/Cy)	Single dose Mel 140 mg/m2 i.v. (combined with Flu cumulative dose 150 mg/m^2 as RIC)	N=60 Mean 46; Range 15-63	Allo-SCT for the treatment of high risk ALL	OS, DFS, NRM, relapse	Acute and chronic GvHD Causes of death not related to leukemic relapse
(Kirschbaum et al., 2012)	USA	Prospective phase 1 dose response	Dose level 1: Mel i.v. 100 mg/m2 + clofarabine 30 mg/m2 (n=3) Dose level 2: Mel i.v. 100 mg/m2 + clofarabine 40 mg/m2 (n=12) Dose level 3: Mel i.v. 140 mg/m2 + clofarabine 40 mg/m2 (n=1)	N=16 Median 63; Range 30-66	Allo-SCT for the treatment of AML	Engraftment immune reconstitution, immune reconstitution, and treatment outcome including relapse, OS, EFS	Graft failure or rejection Dose-limiting toxicities
(van Besien et al., 2005)	USA	Prospective phase II	Single dose Mel 140 mg/m2 i.v (combined with Flu 30 mg/m2 and alemtuzumab 20 mg/day for 5 days)	N=52 Median 52; Range 17-71	Allo-SCT for the treatment of AML and MDS	Engraftment relapse rate, PFS, OS	Acute and chronic GvHD Treatment related mortality
(Kawamura et al., 2017)	Japan	Retrospective, comparative (Flu + intermediate or high dose Bu)	Single dose of Mel 140 mg/m2 i.v. (combined with Flu)	N=432 Median 59; Range 50-71	Allo-SCT for the treatment of AML, ALL and MDS	Primary: OS Secondary: NRM, DFS, relapse rates	Acute and chronic GvHD
(Damlaj et al., 2016)	USA	Retrospective, comparative (Flu/Bu)	Two daily doses of Mel at 70 mg/m2 i.v. (combined with Flu 25 mg/m^2 per 5 days)	N=87 Median 61; Range 33-72	Allo-SCT for the treatment of AML and MDS	Engraftment rate, NRM, relapse rate, PFS, OS	Acute and chronic GvHD Causes of death not related to leukemic relapse
(Dhere et al., 2017)	USA	Retrospective, comparative (Bu/Cy)	Two daily doses of Mel at 70 mg/m2 i.v. (combined with Flu 25 per 4 days)	N=83 Median 59; Range 33-72	Allo-SCT for the treatment of AML	Relapse rates, RFS/DFS, OS, NRM	Acute and chronic GvDH Hospitalization Veno-occlusive disease
(Baron et al., 2015)	EU	Retrospective, comparative (Flu/Bu)	Single dose Mel 130-150 mg/m2 i.v. (combined with Flu)	N=176 Median 54; Range 21-71	Allo-SCT for the treatment of AML	Relapse incidence, NRM, LFS rate, OS	Acute and chronic GvHD
(Yamamoto et al., 2016)	Japan	Retrospective, comparative (Flu/Bu +/- TBI)	Single dose Mel i.v.: 80 mg/m2 (n=3), 120 mg/m2 (n=1), 140 mg/m2 (n=27) or 180 mg/m2 (n=1) (combined with Flu ± TBI)	N=32 Median 57; Range 32-64	Allo-SCT for the treatment of various haematological malignancies	Relapse rates, OS, NRM	Treatment-related mortality

ALL: Acute lymphoblastic leukaemia lymphoma; allo-SCT: allogenic stem cell transplantation; AML: Acute myeloid leukemia; Bu: Busulfan; Cy: Cyclophosphamide; Disease free survival; EFS: Event free survival; Flu: fludarabine; GvHD: Graft versus host disease; i.v. intravenous; Mel: Melphalan; MDS: myelodysplastic syndromes; ; NRM: Non-relapse mortality; OS; Overall survival; RIC: reduced intensity conditioning; TBI: total body irradiation.

continued - List of relevant initially submitted literature used for efficacy and safety – Adult studies

Reference	Region	Study design (control type)	Dose of melphalan	No exposed melphalan; Age Range (years)	Target Population	Efficacy endpoints	Safety
(Imataki et al., 2009)	Japan	Retrospective, comparative (TBI/Cy or Bu/Cy)	Two daily doses of Mel at 70 mg/m2 i.v. (combined with Flu 25 mg/m2 per 4 days)	N=40 Median 51; Range 19-71	Allo-SCT for the treatment of various haematological diseases (n=75) and non-haematological diseases (n=5) and solid tumours (n=2)	Primary OS Secondary: TRM or NRM	AEs leading to death Acute and chronic GvHD Mucosal toxicity
(Gomez E et al., 2014)	France	Retrospective, comparative (TBI/Flu or Bu/Flu)	Single dose Mel 100 mg/m2 i.v.(combined with Flu 30 mg/m^2 per 3 days and TBI 200 cGY)	N=71 Median 51; Range 19-71	Allo-SCT for the treatment of various haematological malignancies	Primary: GvHD Secondary: OS, engraftment, chimerism, relapse, EFS, NRM	Infection Acute and chronic GvHD
(Jain T et al., 2019)	USA	Retrospective, comparative (Bu/Flu)	FluMel group: single dose of Mel 140 mg/m2 i.v. (combined with Flu 150 mg/m2) FBM group: single dose of Mel 140 mg/m2 i.v. (combined with Flu 150 mg/m2 and carmustine 200 mg/m2)	FluMel N=22 Median 58; Range 43-69 FBM N=22 Median 59; Range 45-69	Allo-SCT for the treatment of myelofibrosis	Engraftment, relapse rate, DFS, OS	Causes of death Acute and chronic GvHD
(de Lima et al., 2004)	USA	Retrospective, comparative (Flu/cytarabine /idarubicine)	Single dose Mel 140 or 180 mg/m2 i.v. (combined with Flu 120 mg/m^2 or 150 mg/m^2)	N=62 Median 54; Range 22-75	Allo-SCT for the treatment of AML and MDS	Major: PFS, NRM, relapse mortality Secondary: engraftment, chimerism, OS	Acute and chronic GvHD Adverse events leading to death Various toxicities, including amongst others gastrointestinal toxicities, laboratory parameters, pulmonary haemorrhage
(Ciurea SO et al., 2018)	USA	Retrospective	Single dose Mel 100 or 140 mg/m2 i.v. (combined with Flu 160 mg/m2, thiotepa 5 mg/kg or 2 Gy TBIand TBI or TT)	N=43 Median 61 Range 55-69	Allo-SCT for the treatment of AML and MDS	OS, PFS, NRM, relapse rate	Acute and chronic GvHD Causes of death

allo-SCT: allogenic stem cell transplantation; AML: Acute myeloid leukemia; Bu: Busulfan; Cy: Cyclophosphamide; Disease free survival; EFS: Event free survival; FBM: fludarabine- bis-chlorethyl-nitroso-urea/ carmustine –melphalan; Flu: fludarabine; GvHD: Graft versus host disease i.v. intravenous; Mel: Melphalan; MDS: myelodysplastic syndromes; ; NRM: Non-relapse mortality; OS; Overall survival; PFS: Progression free survival; TBI: total body irradiation; TRM: Transplant related mortality

Table 2: List of relevant initially submitted literature used for efficacy and safety – Paediatric studies

Reference	Region	Study design (control type)	Dose of melphalan	No exposed melphalan; Age Range (years)	Target Population	Efficacy endpoints	Safety
(Shenoy et al., 2018)	USA	Prospective phase II multicentre	Single dose of Mel 140 mg/m2 i.v. (combined with Flu 150 mg/m2, thiotepa 8 mg/kg, alemtuzumab 50 or 75 or 100 mg)	N=33 Median 10 Range: 1-17 in patients receiving a BM Median 3.5 Range 1-15 in patients receiving a UBC	Allo-SCT for the treatment of thalassemia	Primary: TFS Secondary: graft rejection, OS	Acute and chronic GvHD Causes of death Hepatic sinusoidal obstruction syndrome and CMV reactivation, viremia
(Ngwube et al., 2015)	USA	Prospective phase II multicentre	Single dose of Mel 140 i.v. mg/m2 (combined with Flu 150 mg/m2 and alemtuzumab 30 or 45 or 60 mg)	N=17 Median 12.5; Range 3–17	Allo-SCT for the treatment of Severe Aplastic Anemia	Primary: EFS Secondary: engraftment, OS	Acute and chronic GvHD Fatal adverse events
(Lucchini et al., 2017)	EU	Retrospective, comparative (Bu/Cy or TBI/Cy)	Single dose of Mel 140 mg/m2 i.v. (combined with Bu 16 mg/kg and Cy 120 mg/kg)	N=133 Median 9; Range 2.1-17.9	Allo-SCT for the treatment of AML	Primary: 5 year LFS and OS Secondary: NRM, relapse rate	Acute and chronic GvHD Fatal adverse events
(Kato et al., 2015)	Japan	Retrospective, comparative (TBI/Cy, TBI/Cy/etoposide, TBI/Cy/cytarabine, others)	Total dose of Mel 180-200 mg/m2 i.v.	N=139 Median 9	Allo-SCT for the treatment of ALL	EFS, OS, relapse rate, NRM	None
(Kudo et al., 2015)	Japan	Retrospective, comparative (Flu/Cy +/- TBI or others)	Single dose of Mel 80 mg/m2 i.v.(n=6) or 120 mg/m2 i.v. (n=2) or 140 mg/m2 i.v. (n=2) or 180 mg/m2 i.v. (n=2) (combined with Flu +/- TBI)	N=12 Median 9; Range 1-15 (for all 55 patients)	Allo-SCT for the treatment of Severe Aplastic Anemia	OS, GF, FFS	None
(Yabe et al., 2015)	Japan	Retrospective	Mel 90 mg/m2 i.v. once daily for 2 days, total dose 180 mg/m2, or 70 mg/m2 i.v. once daily for 3 days (combined with Flu 120 mg/m2)	N=30 Median 2.2 Range 0.6-6.8	Allo-SCT for the treatment of juvenile myelomonocytic leukemia	OS, EFS	Causes of death Regimen-related toxicity Acute and chronic GvHD
(Marsh et al., 2015)	USA	Retrospective	Single dose Mel 140 mg/m2 i.v. (combined with Flu 150 mg/m2 and alemtuzumab 3, 10, 15, 0r 20 mg)	N=210 Median 4.1; Range 0.24-27.2	Allo-SCT for the treatment of non-malignant diseases	OS, EFS	Hepatotoxicity Causes of death Mucosal inflammation

Table 3. ALL: Acute lymphoblastic leukaemia lymphoma; allo-SCT: allogenic stem cell transplantation; AML: Acute myeloid leukemia; BM: Bone marrow; Bu: Busulfan; Cy: Cyclophosphamide; EFS: Event free survival; FFS: Failure free survival; Flu: fludarabine; GF: Graft failure; GvHD: Graft versus host disease; i.v. intravenous; LFS: Leukemia free survival; Mel: Melphalan; NRM: Non-relapse mortality; OS; Overall survival; RIC: reduced intensity conditioning; TBI: total body irradiation; TFS: Thalassemia free survival; UBC: Umbilical cord blood

In addition to the above articles, the applicant has included three additional recent large prospective cohort studies (Oran et al., 2007, Popat et al., 2012, van Besien et al., 2012) in the dossier in support of the adult indication in maligne haematological diseases as requested.

For the paediatric population with malignant haematological diseases the applicant added the retrospective study by Strahm et al. 2011, to support the indication of melphalan as part of BuCyMel conditioning in paediatric MDS.

Additional data on melphalan-based RIC before allo-HSCT in patients with diverse non-malignant haematological diseases were submitted (Shenoy et al., 2005, Matthes-Martin et al., 2013, Oshrine et al., 2014, King et al., 2015, Kothari et al., 2015, Madden et al., 2016, Allen et al., 2018, and Parikh et al., 2014). Incidence rates for graft failure, GvHD, TRM, OS and EFS were presented for melphalan-based RIC and MAC regimens in MAC in paediatric patients with non-malignant haematological diseases.

2.4.2. Pharmacokinetics

Clinical pharmacokinetics of melphalan are summarised as follows:

Absorption

The absorption of oral melphalan is highly variable with respect to both the time to first appearance of the medicinal product in plasma and peak plasma concentration.
In studies of the absolute bioavailability of melphalan, the mean absolute bioavailability ranged from 56 to 85%.
Intravenous administration can be used to avoid variability in absorption associated with myeloablative treatment.

Distribution

Melphalan is distributed in most tissues of the body. It is moderately bound to plasma proteins with reported binding ranging from 69% to 78%. There is evidence that the protein binding is linear in the range of plasma concentrations usually achieved in standard dose therapy, but that the binding may become concentration-dependent at the concentrations observed in high-dose therapy. Serum albumin is the major binding protein, accounting for about 55 to 60% the binding, and 20% is bound to α1-acid glycoprotein. In addition, melphalan binding studies have revealed the existence of an irreversible component attributable to the alkylation reaction with plasma proteins.

In 28 patients with various malignancies who were given doses between 70 and 200 mg/m^2 body surface area as a 2 to 20 min infusion, the mean volumes of distribution at steady state and central compartment were, respectively, 40.2 ± 18.3 litres and 18.2 ± 11.7 litres.

Melphalan displays limited penetration of the blood-brain barrier. Several investigators have sampled cerebrospinal fluid and found no measurable medicinal product. Low cerebrospinal fluid concentrations (~10% of that in plasma) were observed in a single high-dose study in children.

Biotrasformation

The chemical hydrolysis of melphalan to monohydroxymelphalan and dihydroxy melphalan is the most important metabolic route in humans. These metabolites are inactive.

In vivo and *in vitro* data suggest that spontaneous degradation rather than enzymatic metabolism is the major determinant of the medicinal product's half-life in man.

Elimination

In 15 children and 11 adults given high-dose intravenous melphalan (140 mg/m^2 body surface area) with forced diuresis, the mean initial and terminal half-lives were found to be 6.5 ± 3.6 min and 41.4 ± 16.5 min, respectively. Mean initial and terminal half-lives of 8.8 ± 6.6 min and 73.1 ± 45.9 min, respectively, were recorded in 28 patients with various malignancies who were given doses of between 70 and 200 mg/m^2 body surface area as a 2 to 20 min infusion. The mean clearance was 564.6 ± 159.1 ml/min.

No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life (see section 4.2).

The recommended doses for the approved indications of melphalan are the same as in the reference product. For the proposed additional indication (i.e. as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation in haematological diseases), the recommended dose is 140 mg/m^2 or 70 mg/m^2 once daily for two consecutive days in adults and 140 mg/m^2 or a maximum cumulative dose of 210 mg/m^2 as result of 70 mg/m^2 once daily infusion for three consecutive days in the paediatric population. According to the applicant, these doses are proposed as they appeared to be the most widely used in the preparative regimen for transplantation in the literature provided for efficacy and safety. It is agreed that the dose of 140 mg/m^2 is the most commonly used dose reported in the literature, for adult as well as paediatric patients. However, the addition of the total maximum cumulative dose of 210 mg/m^2, as a result of 70 mg/m^2 administered for three consecutive days in children, was not sufficiently justified considering that the pharmacokinetics of melphalan in the paediatric population and adults is similar. In this current round, the applicant modified the originally proposed dosing recommendation for haematological diseases in the paediatric population. The addition of "Total maximum cumulative dose of 210 mg/m2 as a result of 70 mg/m2 administered for three consecutive days." is deleted for malignant haematological diseases. This is agreed as melphalan was given as a single dose of 140 mg/m2 in the studies from the literature supporting the paediatric indication in haematological diseases. In addition, the applicant is now proposing to add "… or 70 mg/m2 once daily for two consecutive days" for the non-malignant haematological diseases. This is also agreed as this is supported by the studies of King et al., 2015 and Parikh et al., 2014.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

Discussion on clinical pharmacology

Following intravenous administration of melphalan, drug plasma declined rapidly in a bi-exponential manner over the time. The initial and terminal elimination half-lives of melphalan are approximately 8 minutes and 90 minutes, respectively. Melphalan is actively metabolised and probably undergoes to spontaneous degradation rather than enzymatic metabolism.

Degradation products (monohydroxy-melphalan and dihydroxy-melphalan) have been detected in patients' plasma; peak plasma levels are approximately 60 and 105 minutes after injection, respectively.

Melphalan is distributed in most tissues of the body. Plasma protein binding ranges from 30 to 60%.

Renal excretion is a major route of elimination for melphalan.

No bioequivalence studies were provided to support the application. The proposed product 50 mg/10 ml has the same qualitative and comparable quantitative composition (according to the information available), same type of solution (i.e. aqueous), same method and means of administration for the current approved indications of the reference product Alkeran® 50 mg/10 ml approved nationally in France in 1996. The composition and concentration of the other proposed formulation 200 mg/40 ml is identical to the 50 mg/10 ml formulation and has the same final concentration after reconstitution and dilution corresponding to 5 mg/ml. Moreover, information concerning bridging between the product(s) used in the studies included in the dossier to support the proposed additional indication in the proposed medicinal product were also now provided and showed that Alkeran or melphalan generics with the same pharmaceutical formulation and qualitative and quantitative composition as that of the reference product had been used in the majority of the studies. Hence, in line with the requirements stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) on parenteral aqueous solution, the absence of a bioequivalence study can be accepted.

Melphalan displays limited penetration of the blood-brain barrier. Several investigators have sampled cerebrospinal fluid and found no measurable medicinal product. Low cerebrospinal fluid concentrations (~10% of that in plasma) were observed in a single high-dose study in children.

The chemical hydrolysis of melphalan to monohydroxymelphalan and dihydroxy melphalan is the most important metabolic route in humans. These metabolites are inactive.

In 15 children and 11 adults given high-dose intravenous melphalan (140 mg/m^2 body surface area) with forced diuresis, the mean initial and terminal half-lives were found to be 6.5 ± 3.6 min and 41.4 ± 16.5 min, respectively. Mean initial and terminal half-lives of 8.8 ± 6.6 min and 73.1 ± 45.9 min, respectively, were recorded in 28 patients with various malignancies who were given doses of between 70 and 200 mg/m^2 body surface area as a 2 to 20 min infusion. The mean clearance was 564.6 ± 159.1 ml/min.

Melphalan clearance may be decreased in renal impairment (see SmPC sections 4.2 4.4 and 5.2).

No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life (see SmPC section 4.2).

The recommended doses for the approved indications of melphalan are the same as in the reference product. For the proposed additional indication (i.e. as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation in haematological diseases), the recommended dose is 140 mg/m^2 or 70 mg/m^2 once daily for two consecutive days in adults and 140 mg/m^2 or a maximum cumulative dose of 210 mg/m^2 as result of 70 mg/m^2 once daily infusion for three consecutive days in the paediatric population. These doses are proposed as they appeared to be the most widely used in the preparative regimen for transplantation in the literature provided for efficacy and safety. It is agreed that the dose of 140 mg/m^2 is the most commonly used dose reported in the literature, for adult as well as paediatric patients. However, the addition of the total maximum cumulative dose of 210 mg/m^2, as a result of 70 mg/m^2 administered for three consecutive days in children, was not sufficiently justified considering that the pharmacokinetics of melphalan in the paediatric population and adults is similar. The applicant modified the originally proposed dosing recommendation for haematological diseases in the paediatric population. The addition of "Total maximum cumulative dose

of 210 mg/m2 as a result of 70 mg/m2 administered for three consecutive days." is deleted for malignant haematological diseases. This is agreed as melphalan was given as a single dose of 140 mg/m2 in the studies from the literature supporting the paediatric indication in haematological diseases. In addition, the applicant added "… or 70 mg/m2 once daily for two consecutive days" for the non-malignant haematological diseases. This is also agreed as this is supported by the studies of King et al., 2015 and Parikh et al., 2014.

Conclusion on clinical Pharmacology

The pharmacokinetic properties in section 5.2 of the SmPC have been revised according to available information in the literature as required.

2.4.4. Clinical efficacy

Clinical efficacy is based on literature data. No randomised controlled trials have been performed comparing a RIC regimen containing melphalan to other conditioning regimes prior to allogeneic HSCT in haematological diseases. The applicant submitted a dossier of twenty publications, no main or pivotal studies were defined. As the studies were only described by the applicant at a very high level, and as a selection of results was presented in the dossier, most of the tables and summaries of outcome data were taken by the assessor from the provided publications.

In the adult population, from thirteen publications, the study by **Baron et al., 2015** is the only large study performed in European patients and as such considered important for evaluation of the benefit/risk of melphalan in the EU and assessed as the main study. The study performed by **Kawamura et al., 2017** is a very large retrospective study including not only ALL patients but also patients with AML or MDS, therefore this study is also considered important in view of the applied broad indication. **Eom et al., 2013** is the only prospective comparative study included in the dossier.

The applicant has initially included seven trials performed in the paediatric population in the dossier, five studies in malignant and two studies in non-malignant haematological diseases. Two large retrospective registry studies compared conditioning regimens in AML (**Lucchini et al., 2017**) and ALL (**Kato et al., 2015**). These are assessed as the main studies. In these regimens, addition of melphalan is considered an intensification of the myeloablative conditioning regimen. In paediatric non-malignant haematological diseases, melphalan-conditioning regimen is considered a RIC (**Marsh et al., 2015** and **Shenoy et al., 2018**).

Additional studies submitted during the procedure were considered as main or supportive studies dependent on the body of evidence.

Dose response study

Kirschbaum et al., 2012 was a phase I dose-escalation study, the primary objective was to establish the recommended phase II dose for the combination of clofarabine and melphalan as RIC for allo-HSCT. Only the dose of clofarabine was escalated from level 1 to level 2, whilst the dose of melphalan that was administered remained the same at 100 mg/m2. No conclusions on the dose-response relationship of melphalan can be drawn from this study. It is therefore assessed as a supportive study.

Main studies

Baron et al., 2015: Reduced-intensity conditioning with fludarabine and busulfan versus fludarabine and melphalan for patients with acute myeloid leukemia: a report from the acute leukemia working party of the European group for blood and marrow transplantation.

Methods

This retrospective study, performed by the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT), compared the outcomes for a cohort of 394 acute AML patients receiving a sibling HSCT after fludarabine-busulfan (n=218) or fludarabine- melphalan (n=176) between 2000 and 2012.

Study Participants

The population selection criteria included primary or secondary AML, first allo-SCT from an HLA-identical sibling between 2000 and 2012, bone marrow or granulocyte colony-stimulating factor–mobilised peripheral blood stem cells as a stem cell source, and FB (with a total busulfan dose ranging from 7.1 to 8.9 mg/kg [oral] or from 6.0 to 6.9 mg/kg [intravenous]) or FM (with a total melphalan dose ranging from 130 to 150 mg/m2). The population exclusion criteria included another chemotherapy drug or total body irradiation in the conditioning regimen and in vivo (ATG or alemtuzumab) or in vitro T-cell depletion. Matched unrelated donor allo-SCT recipients were excluded to avoid confounding factors for analyses comparing RI, NRM, and graft-versus-host disease (GVHD) between the 2 groups and because the vast majority of unrelated recipients received in vivo T-cell depletion with ATG or alemtuzumab.

Treatments

Both treatment regimens are considered reduced intensity conditioning.

FB: fludarabine with a total busulfan dose ranging from 7.1 to 8.9 mg/kg [oral] or from 6.0 to 6.9 mg/kg [intravenous]

FM: fludarabine with a total melphalan dose ranging from 130 to 150 mg/m2

Outcomes/endpoints

2-year relapse incidence (RI), non-relapse mortality (NRM) rate, leukaemia-free survival (LFS) rate, and overall survival (OS) rate are mentioned in the publication by Baron et al, but no primary endpoint is formulated.

Randomisation and blinding (masking)

No randomisation was performed, blinding of participants and study physicians was not possible given the design of the study.

Statistical methods

Data from all patients meeting the inclusion/exclusion criteria were included in the analyses. The start time was the date of transplantation for all endpoints. To evaluate RI, patients dying either from direct toxicity of the procedure or from any other cause not related to leukaemia were censored. NRM was defined as death in CR. Patients were censored at the time of relapse or last follow-up. Cumulative incidence functions were used for RI and NRM in a competing risk setting because death and relapse were competing together. For estimating the cumulative incidence of chronic GVHD, death was considered a competing event. OS and LFS rates were calculated with Kaplan-Meier estimates. Univariate analyses were performed with Gray's test for cumulative incidence functions and with the log-rank test for OS and LFS. Associations of patient and graft characteristics with transplantation outcomes (chronic GVHD, RI, NRM, LFS, and OS) were evaluated in multivariate analyses with Cox proportional hazards. The factors included in the Cox models were FM versus FB, CR versus no CR at transplantation, female donor to male.

Results

Baseline data

Table 3 below shows the baseline characteristics of the patients. Median age was 56 years (range 21-76), and subjects receiving FM were younger (54 vs 58 years, $p<0.001$) but with more advanced disease phase than patients treated with FB (20% vs 11%, P=0.05) and significantly more frequently CMV-seronegative and given grafts from CMV-seronegative donors (18% vs 9%, P=.009). No statistical difference was detected in term of sex, cytogenetic risk, source of stem cells and interval from diagnosis to transplantation.

Table 3: Baseline characteristics Baron et al.

	Flu-Bu (n = 218)[a]	Flu-Mel (n = 176)	P[b]
Patient age, median (range), y	58 (23-76)	54 (21-71)	<.001
Year of SCT, median (range)	2009 (2000-2012)	2007 (2000-2012)	.001
Recipient sex: male, n (%)	124 (57)	83 (47)	.06
Donor sex: male, n (%)	111 (51)	95 (54)	.6
Female donor/male recipient, n (%)	59 (27)	36 (20)	.05
Time from diagnosis to SCT, median, d	178	157	.12
Secondary AML, n (%)	23 (11)	8 (5)	.03
Status at transplantation, n (%)			
CR1	155 (71)	111 (63)	.05
CR2+	39 (18)	30 (17)	
Advanced	24 (11)	35 (20)	
Cytogenetics, n (%)			
Good risk[c]	9 (7)	9 (8)	.87
Intermediate risk[d]	99 (76)	82 (76)	
High risk*	23 (18)	17 (16)	
Not reported/failed	87	68	
CMV D−/R−, n (%)	19 (9)	32 (18)	.009
Stem cell source, n (%)			
G-CSF–mobilized peripheral blood stem cells	194 (89)	158 (90)	.8
Bone marrow	24 (11)	18 (10)	
Postgrafting immunosuppression, n (%)			
CSA alone	18 (8)	37 (21)	.001
CSA + MTX	134 (61)	83 (47)	
Other	66 (30)	56 (32)	
CSA+ MMF	42	53	
Tacrolimus + MMF	12	2	
Other	12	1	

Abbreviations: AML, acute myeloid leukemia; CMV, cytomegalovirus; CR1, first complete remission; CR2+, second or later complete remission; CSA, cyclosporine A; D−/R−, donor-seronegative/recipient-seronegative; Flu-Bu, fludarabine and busulfan reduced-intensity conditioning; Flu-Mel, fludarabine and melphalan conditioning; G-CSF, granulocyte colony-stimulating factor; MMF, mycophenolate mofetil; MTX, methotrexate; SCT, stem cell transplantation.

[a]This group included 137 patients given oral busulfan (with the total busulfan dose ranging from 7.1 to 8.9 mg/kg) and 81 patients given intravenous busulfan (with the total busulfan dose ranging from 6.0 to 6.9 mg/kg). The 81 patients included 59 patients in CR1, 15 patients in CR2+, and 7 patients with advanced disease at the time of transplantation.

[b]*P* values were calculated with χ^2 statistics for categorical variables and with the Mann-Whitney test for continuous variables.

[c]*Good risk* was defined as t(8;21), t(15;17), inv or del(16), or acute promyelocytic leukemia (these abnormalities only or combined with others).

[d]*Intermediate risk* was defined as all cytogenetics not belonging to the good- or high-risk categories (including trisomies).

[*]*High risk* was defined as 11q23 abnormalities, a complex karyotype, and abnormalities of chromosomes 5 and 7.

Numbers analysed

394 patients were included in the analysis, 218 in the FB group and 176 in the FM group.

Outcomes and estimation

Two-year RI, NRM, LFS, and OS rates for FB and FM patients were as follows (univariate analysis):

	FB	FM	p-value
2y-RI	31%±3%	20%±3%	(P=0.007)
2y-NRM	18%±3%	20%±3%	(P=0.4)
2y-LFS	51%±4%	60%±4%	(P=0.08)
2y-OS	54%±4%	62%±4%	(P=0.2)

In univariate analyses, secondary AML versus primary AML was associated with higher NRM (P=0.02), whereas advanced disease at transplantation was associated with higher RI (P<0.001), which translated into lower LFS (P=0.003) and OS (P=0.01). Furthermore, CMV-seronegative patients given grafts from CMV-seronegative donors had lower NRM (P=0.01). These associations are as expected.

After adjustments for variables having different distributions between FB and FM and associated with P<0.05 in univariate analyses, RI remained significantly lower for FM patients versus FB patients (HR, 0.5; 95% CI, 0.3-0.8; P=0.01), whereas there was a suggestion of higher NRM for FM patients versus FB patients (HR, 1.6; 95% CI, 0.9-2.7; P=0.1). This translated into similar progression-free survival (HR, 0.8; 95% CI, 0.6-1.2; P=0.2) and OS (HR, 0.9; 95% CI, 0.6-1.3; P=0.6) for FM and FB patients.

In conclusion, FM appears to give a lower relapse risk than FB, but PFS and OS are similar between these two regimens, but the difference in NRM between groups was not statistically significant. Information on post-relapse treatments is not provided.

Kawamura et al., 2017: Comparison of conditioning with Fludarabine/Busulfan and Fludarabine/Melphalan in allogeneic transplantation recipients 50 Years or older.

Methods

This is a nationwide, retrospective study performed in Japan, to compare the transplant outcomes of three conditioning regimens in patients aged 50 years or older with AML, ALL or MDS, treated between 2007 and 2014.

Study Participants

Patients were selected according to the following criteria: 50 years of age or older; diagnosis of AML, ALL, or MDS; matched or 1 allele/antigen mismatched unrelated donor, matched or 1 antigen mismatched related donor; and undergoing the condition regimens of Fludarabine with melphalan (140 mg/m2 i.v.; FM140), Fludarabine with intermediate doses of Busulfan (6.4 mg/kg i.v.; FB2) or Fludarabine with higher doses of Busulfan (12.8 mg/kg i.v.; FB4).

Treatments

Treatment regimens were as follows:

- Fludarabine with melphalan (140 mg/m2 i.v.); FM140
- Fludarabine with intermediate doses of Busulfan (6.4 mg/kg i.v.); FB2
- Fludarabine with higher doses of Busulfan (12.8 mg/kg i.v.) FB4

FM140 and FB2 are considered RIC-regimens, and FB4 is considered a MAC regimen.

Outcomes/endpoints

The primary endpoint was OS. Secondary endpoints were DFS, the cumulative incidences of acute and chronic GVHD, relapse, and NRM.

Randomisation and blinding (masking)

No randomisation was performed, blinding of participants and study physicians was not possible given the design of the study.

Statistical methods

Categorical variables were compared among groups with the chi-square test or Fisher's exact test, and continuous variables were compared with the Kruskal-Wallis test. The probabilities of OS and DFS were estimated according to the Kaplan-Meier method and compared among groups with the log-rank test. The probabilities of acute and chronic GVHD, relapse, and NRM were estimated on the basis of cumulative incidence methods and compared among groups with the Gray test. Multivariate analyses for OS and DFS were performed using the Cox proportional hazards model, whereas multivariate analyses for acute and chronic GVHD, relapse, and NRM were performed using the Fine and Gray regression model. The considered variables were: patient age at transplantation (50 to 59 years or ≥60 years), patient sex, disease type (AML, ALL, or MDS), disease risk (standard or high risk), Eastern Cooperative Oncology Group Performance Status (0 to 1 or 2 to 4), hematopoietic cell transplantation–specific comorbidity index, donor type, conditioning regimen, use of low-dose TBI, use of in vivo T cell depletion, GVHD prophylaxis, and year of transplantation.

Results

Participant flow

1607 patients were enrolled. 423 patients were treated with Flu-Mel (FM140), 463 with Flu and intermediate doses of Bu (FB2) and 721 with Flu and higher doses of Bu (FB4).

Baseline data

Table 4 is taken from the publication by Kawamura et al, and shows the baseline characteristics of the included patients.

Table 4: baseline characteristics Kawamura et al

Patient Characteristics

Characteristic	FB2 (n = 463)	FB4 (n = 721)	FM140 (n = 423)	P
Median age, yr (range)	61 (50-74)	60 (50-75)	59 (50-71)	.002
Recipient sex				
Female	180 (38.9)	274 (38.0)	156 (36.9)	.83
Male	283 (61.1)	447 (62.0)	267 (63.1)	
Disease				
AML	277 (59.8)	483 (67.0)	220 (52.0)	<.001
ALL	46 (9.9)	26 (3.6)	92 (21.7)	
MDS	140 (30.2)	212 (29.4)	111 (26.2)	
Disease risk				
Standard risk	264 (57.0)	377 (52.3)	237 (56.0)	.20
High risk	197 (42.5)	343 (47.6)	185 (43.7)	
Unknown	2 (.4)	1 (.1)	1 (.2)	
ECOG PS				
0-1	420 (90.7)	665 (92.2)	373 (88.2)	.091
2-4	41 (8.9)	56 (7.8)	49 (11.6)	
Unknown	2 (.4)	0 (.0)	1 (.2)	
HCT-CI				
0	229 (49.5)	407 (56.4)	215 (50.8)	.24
1-2	114 (24.6)	185 (25.7)	119 (28.1)	
≥3	93 (20.1)	128 (17.8)	66 (15.6)	
Unknown	27 (5.8)	1 (.1)	23 (5.4)	
Donor type				
Matched related*	142 (30.7)	218 (30.2)	157 (37.1)	<.001
One antigen mismatched related*	33 (7.1)	37 (5.1)	8 (1.9)	
Matched unrelated†	161 (34.8)	306 (42.4)	165 (39.0)	
One locus mismatched unrelated†	127 (27.4)	160 (22.2)	93 (22.0)	
GVHD prophylaxis				
CSA-based	144 (31.1)	241 (33.4)	139 (32.9)	.70
TAC-based	312 (67.4)	469 (65.0)	280 (66.2)	
Others/unknown	7 (1.5)	11 (1.5)	4 (.9)	
Use of low-dose TBI				
No	131 (28.3)	437 (60.6)	268 (63.4)	<.001
Yes	332 (71.7)	284 (39.4)	155 (36.6)	
Use of in vivo T cell depletion				
No	415 (89.6)	667 (92.5)	400 (94.6)	.022
Yes	48 (10.4)	54 (7.5)	23 (5.4)	
Year of transplant				
2007-2010	207 (44.7)	169 (23.4)	170 (40.2)	<.001
2011-2014	256 (55.3)	552 (76.6)	253 (59.8)	

Values are n (%), unless otherwise defined. ECOG PS indicates Eastern Cooperative Oncology Group Performance Status; HCT-CI, hematopoietic cell transplantation–specific comorbidity index; CSA, cyclosporine; TAC, tacrolimus.

* HLA compatibility was defined according to HLA-A, HLA-B, and HLA-DR loci.

† HLA compatibility was defined according to HLA-A, HLA-B, HLA-C, and HLA-DRB1 loci.

There is a statistically significant but small difference of the median age.

The treatment regimen of fludarabine with a higher dose of busulfan (FB4) was used mainly in the more recent years of the study period.

Acute leukemia in the first or second remission and MDS excluding refractory anemia with excess blasts or leukemic transformation were defined as standard-risk diseases, whereas others were defined

as high-risk diseases. There is no information provided regarding cytogenetic alterations in the different diseases.

Numbers analysed

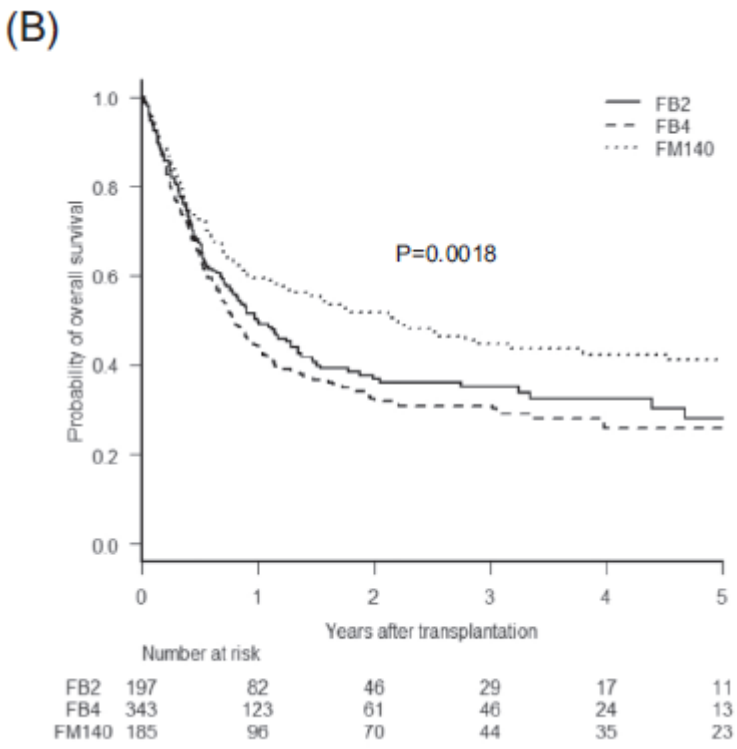
423 patients were treated with Flu-Mel (FM140), 463 with Flu and intermediate doses of Bu (FB2) and 721 with Flu and higher doses of Bu (FB4).

Outcomes and estimation

Analysis in the total study population (AML+ALL+MDS patients)

The 3-year OS rates in patients with high-risk disease were 34.8% (95% CI, 27.4% to 42.3%) in the FB2 group, 30.7% (95% CI, 25.3% to 36.6%) in the FB4 group, and 44.6% (95% CI, 36.5% to 52.3%) in the FM140 group (P = .0018**, Figure 2**(B)). However, in multivariate analysis there was no statistically significant difference in OS between the three treatment groups, as shown in Table 5.

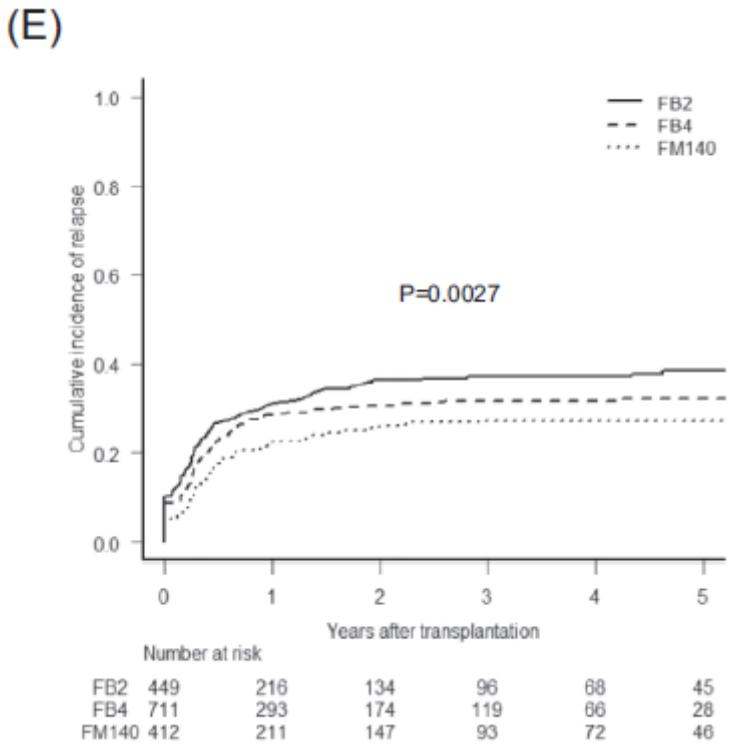
Figure 2: Kaplan Meier estimates of overall survival



DFS was not significantly different between treatment groups in multivariate analysis.

The cumulative incidences of relapse at 3 years in the FB2, FB4, and FM140 groups were 37.2% (95% CI, 32.5% to 42.0%), 31.7% (95% CI, 28.1% to 35.3%), and 27.4% (95% CI, 23.0% to 32.0%), respectively (P = 0.0027, Figure 3 (E) below). Multivariate analysis confirmed that the risks of relapse in the FB4 group (HR, 0.73; 95% CI, 0.58 to 0.93; P = 0.011) and in the FM140 group (HR, 0.56; 95% CI, 0.42 to 0.74; P = 0.000042) were lower than that in the FB2 group (Table 5).

Figure 3: Kaplan Meier estimates of relapse



The cumulative incidences of NRM at 3 years in the FB2, FB4, and FM140 groups were 19.4% (95% CI, 15.5% to 23.6%), 27.1% (95% CI, 23.6% to 30.7%), and 28.0% (95% CI, 23.4% to 32.7%), respectively (P = .0010), and the incidence of NRM in the FB2 group was significantly lower than those in the FB4 (HR, 1.63; 95% CI, 1.23 to 2.16; P = .00065) and FM140 groups (HR, 1.71; 95% CI, 1.25 to 2.32; P = 0.00067) (Table 5).

Table 5: Multivariate analysis of outcomes in all patients

Results of a Multivariate Analysis of Outcomes in all Patients

	HR (95% CI)	*P*
OS*		
FB2	1.00	Reference
FB4	1.19 (.98-1.44)	.072
FM140	.91 (.73-1.13)	.38
DFS†		
FB2	1.00	Reference
FB4	1.07 (.89-1.27)	.49
FM140	.85 (.69-1.04)	.12
NRM‡		
FB2	1.00	Reference
FB4	1.63 (1.23-2.16)	.00065
FM140	1.71 (1.25-2.32)	.00067
Relapse§		
FB2	1.00	Reference
FB4	.73 (.58-.93)	.011
FM140	.56 (.42-.74)	.000042
Grades II-IV acute GVHD¶		
FB2	1.00	Reference
FB4	1.42 (1.14-1.77)	.0020
FM140	1.58 (1.24-2.03)	.00027
Grades III-IV acute GVHD**		
FB2	1.00	Reference
FB4	1.59 (1.07-2.38)	.023
FM140	2.08 (1.36-3.20)	.00082
Chronic GVHD††		
FB2	1.00	Reference
FB4	1.02 (.81-1.27)	.90
FM140	1.05 (.82-1.33)	.72
Extensive chronic GVHD‡‡		
FB2	1.00	Reference
FB4	1.09 (.82-1.46)	.54
FM140	1.32 (.95-1.81)	.095

* Adjusted for the other significant variables including disease, disease risk, ECOG PS, and HCT-CI.

† Adjusted for the other significant variables including disease, disease risk, and ECOG PS.

‡ Adjusted for the other significant variables including recipient sex, ECOG PS, HCT-CI, and donor type.

§ Adjusted for the other significant variables including disease, disease risk, ECOG PS, donor type, and use of low-dose TBI.

¶ Adjusted for the other significant variables including ECOG PS, donor type, use of low-dose TBI, GVHD prophylaxis, and use of in vivo T cell depletion.

** Adjusted for the other significant variables including recipient sex, donor type, use of low-dose TBI, and GVHD prophylaxis.

†† Adjusted for the other significant variables including recipient sex and use of low-dose TBI.

‡‡ Adjusted for the other significant variable including disease.

Analysis per disease group

Table 6: multivariate analysis of OS, NRM and relapse per disease

Table 3
Results of a Multivariate Analysis of OS, NRM, and Relapse for Each Disease

	AML		ALL		MDS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
OS*						
FB2	1.00	Reference	1.00	Reference	1.00	Reference
FB4	1.07 (.85-1.36)	.56	2.08 (.88-4.94)	.097	1.34 (.94-1.93)	.11
FM140	.81 (.61-1.06)	.13	1.92 (.91-4.03)	.085	1.06 (.69-1.62)	.80
NRM†						
FB2	1.00	Reference	1.00	Reference	1.00	Reference
FB4	1.42 (1.00-2.00)	.049	3.54 (1.04-12.10)	.044	2.03 (1.16-3.58)	.014
FM140	1.35 (.90-2.02)	.15	3.71 (1.17-11.81)	.026	2.65 (1.44-4.90)	.0018
Relapse‡						
FB2	1.00	Reference	1.00	Reference	1.00	Reference
FB4	.70 (.52-.94)	.018	.58 (.17-2.03)	.39	.85 (.54-1.33)	.48
FM140	.64 (.46-.90)	.011	.61 (.24-1.58)	.31	.38 (.20-.72)	.0032

* Adjusted for the other significant variables including disease risk and ECOG PS for AML; disease risk only for ALL; and recipient sex, ECOG PS, use of low-dose TBI, use of in vivo T cell depletion, and year of transplantation for MDS.
† Adjusted for the other significant variables including recipient sex, GVHD prophylaxis, and use of low-dose TBI for AML; no other significant variables for ALL; and donor type only for MDS.
‡ Adjusted for the other significant variables including disease risk, ECOG PS, donor type, and use of low-dose TBI for AML; disease risk only for ALL; and ECOG PS only for MDS.

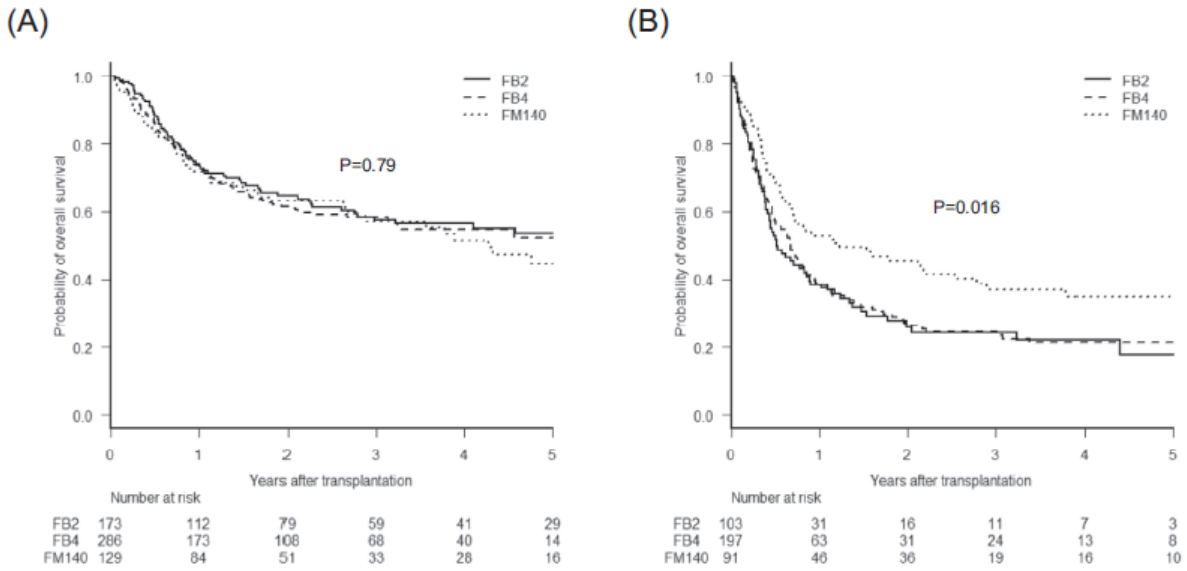
Figure 3. OS (A, standard-risk AML; B, high-risk AML; C, standard-risk ALL; D, high-risk ALL; E, standard-risk MDS; F, high-risk MDS) in the FB2, FB4, and FM140 groups, classified according to the background disease.

AML

OS in patients with standard-risk AML did not differ among the 3 groups (P = .79, Figure 4 (A)). The 3-year OS rate in patients with high-risk AML in the FM140 group (37.0% [95% CI, 26.6% to 47.4%] was higher than that in the FB2 group (24.4% [95% CI, 15.6% to 34.2%] and FB4 group (24.6% [95% CI, 18.2% to 31.6%] (P = .016, Figure 4 (B)), however in multivariate analysis there was no significant difference in OS between groups (Table 6).

In multivariate analysis adjusted for disease risk and other covariates, the risks of relapse in the FB4 group (HR, 0.70; 95% CI, 0.52 to 0.94; P = 0.018) and FM140 group (HR, 0.64; 95% CI, 0.46 to 0.90; P = 0.011) were lower than that in the FB2 group. The risk of NRM in the FB4 group (HR, 1.42; 95% CI, 1.00 to 2.00; P = .049) was higher than that in the FB2 group. The difference in NRM between the FM140 and FB2 group was not statistically significant (p=0.15).

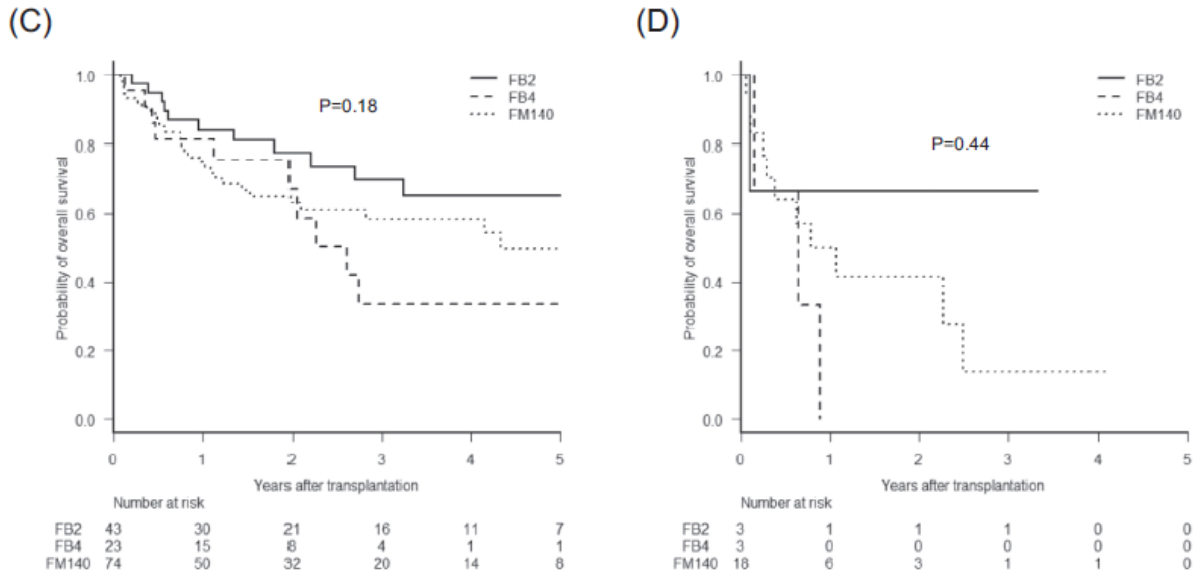
Figure 4: OS in standard and high-risk AML



ALL

No statistically significant differences were found in OS in patients with either standard- or high-risk ALL in the FB2, FB4, and FM140 groups (P = 0.18 and P = 0.44**, Figure 5** C and D below). In a multivariate analysis adjusting for disease risk and other covariates, although there were no significant differences in the risks of relapse for ALL patients among the 3 groups, the risks of NRM in the FB4 and FM140 groups were higher than that in the FB2 group (HR, 3.54; 95% CI, 1.04 to 12.10; P = .044, and HR, 3.71; 95% CI, 1.17 to 11.81; P = .026) (**Table 6** above). The subgroup of ALL patients was however very small and this hampers interpretation of results in this subgroup.

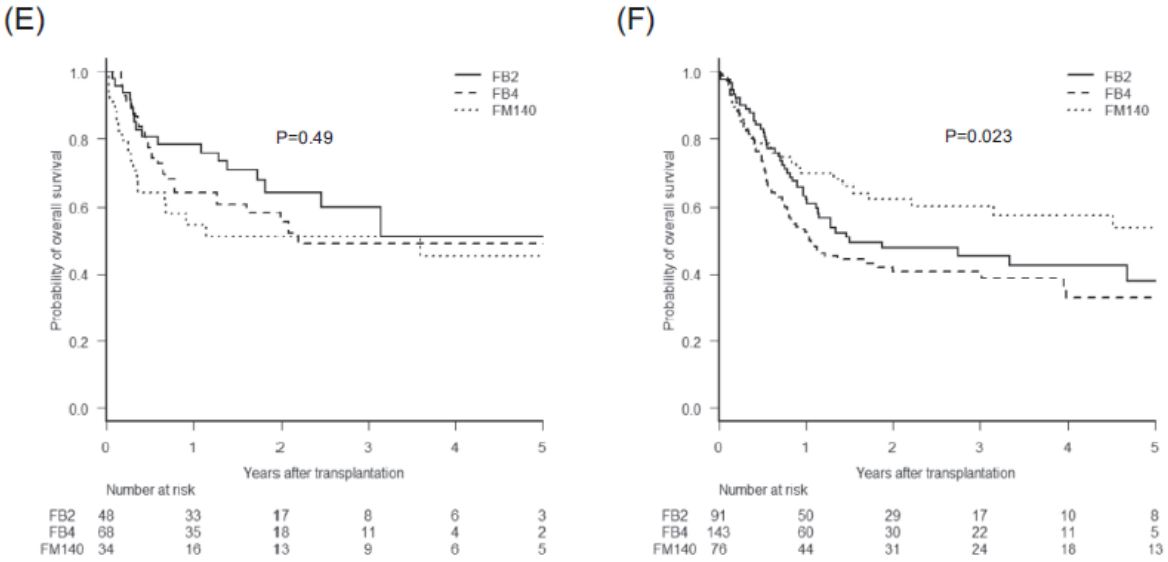
Figure 5: OS in standard or high-risk ALL



MDS

OS in patients with standard-risk MDS did not differ among the 3 groups (P = .49, **Figure 6** E below).The 3-year OS rates in patients with high-risk MDS in the FM140 group (60.2% [95% CI, 47.0% to 71.0%]) were superior to those in the FB2 group (45.5% [95% CI, 33.7% to 56.6%]) and FB4 group (40.6% [95% CI, 31.7% to 49.4%]) (P = .023, **Figure 6** F below), however in multivariate analysis adjusting for disease risk and other covariates there was no significant difference in OS between groups (**Table 6** above). The risk of relapse for MDS patients in the FM140 group was significantly lower than that in the FB2 group (HR, 0.38; 95% CI, 0.20 to 0.72; P = 0.0032), but the risks of NRM in the FB4 and FM140 groups were higher than that in the FB2 group (HR, 2.03; 95% CI, 1.16 to 3.58; P = 0.014, and HR, 2.65; 95% CI, 1.44 to 4.90; P = 0.0018) (**Table 6** above).

Figure 6: OS in standard and high-risk MDS



In conclusion there was no statistically significant difference in OS or DFS between treatment regimens FB2, FB4 and FM140 in the total study population or any of the disease subgroups.

Relapse risk was lower in the FM140 group compared to the FB2 group in the total study population, and non-relapse mortality was higher.

Regarding subgroups, interpretation of analyses in the ALL patients is hampered by the low patient number.

In AML patients, the risk of relapse was lower in the FM140 treatment group compared to the FB2 group, but non-relapse mortality was not significantly different.

In MDS patients, the risk of relapse was lower in the FM140 treatment group compared to the FB2 group, but non-relapse mortality was also significantly higher.

Ancillary analyses

The analyses of outcomes in the subgroups of patients with AML, ALL and MDS are discussed above.

Eom et al., 2013: Comparable long-term outcomes after reduced-intensity conditioning versus myeloablative conditioning allogeneic stem cell transplantation for adult high-risk acute lymphoblastic leukaemia in complete remission.

Methods

This is a case-control study performed in a single university hospital in South Korea. 60 patients receiving a reduced intensity conditioning (RIC) allogeneic stem cell transplantation (SCT) were included from July 2000 to February 2010. During the same period, a total of 482 patients received a myeloablative conditioning (MAC)-SCT under the same pre- and post-transplantation treatment protocol. Of these, 120 patients were matched to the 60 patients receiving a RIC-SCT.

Study Participants

High-risk ALL patients in first or second complete remission.

Patients were classified as high-risk ALL if they met one of the following criteria at diagnosis: (1) older age (≥35 years); (2) high leukocyte count (≥30 x 10^9/L for B-lineage ALL, ≥100 x 10^9/L for T-lineage ALL); (3) adverse cytogenetics (Ph, t(4;11), t(8;14), complex karyotype, or low hypodiploidy-near triploidy) or (4) delayed CR1 (>28 days of induction therapy).

To be eligible for MAC-SCT, patients had to be <50 years of age without any signs of organ dysfunction or active infections. RIC-SCT was offered to high-risk patients not eligible for MAC-SCT.

All RIC transplants had at least one of the following high risk factors: ≥ 35 years; high leukocyte count (45%); adverse cytogenetics (63.3%) and delayed CR1.

RIC transplants were matched in a 1:2 ratio with 120 MAC transplants using a computer-based individual matching method with the following four criteria: disease status at transplantation (CR1 or CR2), cytogenetic risk, proportions of high leukocyte count, and donor type. Because the cut-off age for making a choice of MAC vs. RIC was 50 years, matching was done without accounting for age in this study.

Treatments

The conditioning treatments given were as follows:

- RIC: melphalan 140 mg/m2 and fludarabine 150mg/m2 administered intravenously.
    - Fludarabine 30mg/m2/d, days -8, -7, -6, -5 and -4
    - Melphalan 70mg/m2/d, days -3 and -2
- MAC: total body irradiation (TBI) 13,2 Gy + cyclophosphamide 120mg/kg

Pre- and post-transplantation treatment protocol was the same for patients in both treatment groups. Induction therapy was started with hyper-fractionated cyclophosphamide (300 mg/m2, every 12 hr, days 1–3), vincristine (1.4 mg/m2, maximum dose 2 mg, days 4 and 11), idarubicin (12 mg/m2, days 4 and 11), and dexamethasone (40 mg, days 1–4 and days 11–14). Subsequently, patients in CR received consolidation courses consisting of high-dose cytarabine (2 g/m2, every 12 hr, days 1–5) and mitoxantrone (12 mg/m2, days 1–2) therapy (at each odd cycle of consolidation) alternating with the above induction regimens (at each even cycle of consolidation), which were dependent on donor availability and the time of transplantation. Central nervous system prophylaxis was performed by intrathecal administration of triple agents (methotrexate, cytarabine, and methylprednisolone; 6 times

in total). Patients with Philadelphia chromosome (Ph)-positive ALL received imatinib-based chemotherapy before transplantation.

GVHD prophylaxis was attempted by administering calcineurin inhibitors (cyclosporine for RD transplants, tacrolimus for URD transplants) plus methotrexate. If residual leukemia was detected in the absence of GVHD at 3 months after transplantation, calcineurin inhibitors were rapidly discontinued.

Outcomes/endpoints

No primary outcome was described for this study. The main end points of this study included overall survival (OS), disease-free survival (DFS), non-relapse mortality (NRM) and relapse.

Randomisation and blinding (masking)

No randomisation was performed, blinding of participants and study physicians was not possible given the design of the study.

Statistical methods

Survival curves were plotted using the Kaplan–Meier method and compared by the log-rank test. Relapse and NRM were calculated using cumulative incidence estimates to accommodate the following competing events: death for relapse and relapse for NRM; the groups were compared with the Gray test.

The prognostic significances of covariates affecting OS and DFS were determined using the Cox proportional hazards model, including variables with a P-value< 0.10 in earlier univariate testing. Factors were considered significant if they had an associated P-value of <0.05 as determined by the likelihood ratio test, using two-tailed significance testing. The prognostic significances of covariates affecting relapse and NRM were determined using the proportional hazards model for subdistribution of a competing risk. In these models, acute and chronic GVHD were considered as time-dependent covariates. Because conditioning intensity was the main interest of this study, it was included in all steps of model building. Other variables considered were patient age (<30 years vs. 30–39 years vs. >40 years), sex (male vs. female), leukocyte count (low vs. high), adverse cytogenetics (positive vs. negative), extramedullary involvement (positive vs. negative), delayed CR1 (positive vs. negative), disease status at SCT (CR1 vs. CR2), MRD status at SCT (Ph-positive ALL; MMR vs. CMR4.5 vs. <3 to 2-log reduction vs. <2-log reduction), Karnofsky performance score (>80% vs. <80%), donor type (8/8-matched RD vs. 8/8-matched URD vs. 7/8-matched URD vs. 6/8-matched URD), graft source (BM vs. peripheral blood), donor-recipient sex match (female– male vs. others), time-to-transplantation (<150 days vs. >150 days), acute GVHD (positive vs. negative), and chronic GVHD (positive vs. negative).

Results

Participant flow

60 patients receiving a reduced intensity conditioning (RIC) allogeneic stem cell transplantation (SCT) were included from July 2000 to February 2010. During the same period, a total of 482 patients received a myeloablative conditioning (MAC)-SCT under the same pre- and post-transplantation treatment protocol. Of these, 120 patients were matched to the 60 patients receiving a RIC-SCT.

Baseline data

Compared to the TBI/CY group, the melphalan group had a significant older age (46 years vs. 33 years, P<0.001) and a statistically significant higher proportion of transplantation using peripheral blood (93.3% vs. 13.3%; P<0.001). Other characteristics were comparable between the two groups.

Table 7 shows the baseline characteristics of the included patients.

Table 7: Baseline characteristics Eom et al.

TABLE I. Characteristics of Patients

Characteristic	RIC ($n=60$)	MAC ($n=120$)	P
Indication for RIC, *n* (%)			
Age (≥50 years)	26 (43.3)	–	
Comorbidities (<50 years)	34 (56.7)	–	
Median age, years (range)	46 (15–63)	33 (15–48)	<0.001
<30 years	8 (13.3)	49 (40.8)	
30–39 years	11 (18.4)	47 (39.2)	
40–49 years	15 (25.0)	24 (20.0)	
≥50 years	26 (43.3)	0 (0)	
Older age (≥35 years), n (%)	46 (76.7)	51 (42.5)	<0.001
Male sex, n (%)	32 (53.3)	69 (57.5)	0.595
B-lineage, n (%)	55 (91.7)	101 (84.2)	0.163
Median leukocyte count, × 10^9/L (range)	23.6 (1.5–1428.0)	25.4 (0.5–392.5)	0.941
High leukocyte count, n (%)	27 (45.0)	54 (45.0)	1.000
Adverse cytogenetics, n (%)	38 (63.3)	76 (63.3)	1.000
Ph	29 (48.3)	52 (43.3)	
t(4;11)/t(8;14)/complex/Ho-Tr	9 (15.0)	24 (20.0)	
Extramedullary involvement, n (%)	28 (46.7)	58 (48.3)	0.833
Delayed CR1 (>28 days), n (%)	19 (31.7)	38 (31.7)	1.000
Disease status at SCT, n (%)			1.000
CR1	52 (86.7)	104 (86.7)	
CR2	8 (13.3)	16 (13.3)	
MRD status at SCT in Ph-positive ALL, n (%)			0.876
MMR	11/29 (37.9)	24/52 (46.2)	
$CMR^{4.5}$	10/29 (34.5)	15/52 (28.8)	
<3~2-log reduction	3/29 (10.4)	6/52 (11.5)	
<2-log reduction	5/29 (17.2)	7/52 (13.5)	
KPS at SCT, *n* (%)			0.335
≥80%	47 (78.3)	101 (84.2)	
<80%	13 (21.7)	19 (15.8)	
Donor type, *n* (%)			1.000
8/8-matched related donor	42 (70.0)	84 (70.0)	
8/8-matched unrelated donor	5 (8.3)	10 (8.3)	
7/8-matched unrelated donor	7 (11.7)	14 (11.7)	
6/8-matched unrelated donor	6 (10.0)	12 (10.0)	
Graft source, *n* (%)			<0.001
Bone marrow	4 (6.7)	104 (86.7)	
Peripheral blood	56 (93.3)	16 (13.3)	
Donor-recipient sex match, *n* (%)			0.102
Female–male	7 (11.7)	26 (21.7)	
Others	53 (88.3)	94 (78.3)	
Median time-to-SCT, days (range)	153 (111–370)	142 (114–341)	0.430
Median follow-up, months (range)	67 (32–148)	79 (32–148)	0.136

RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; Ph, Philadelphia chromosome; CR, complete remission; SCT, stem cell transplantation; MRD, minimal residual disease; ALL, acute lymphoblastic leukemia; MMR, major molecular response; $CMR^{4.5}$, complete molecular response (4.5 log sensitivity); KPS, Karnofsky performance score.

Outcomes and estimation

Figure 7 below shows the Kaplan-Meier curves of relapse (A), non-relapse mortality (B), disease-free survival rate (C) and overall survival (D) according to conditioning intensity (RIC-SCT=red, MAC-SCT=blue). Table 8 shows the multivariate analysis of factors possibly affecting outcomes.

Figure 7: Kaplan Meier estimates of relapse (A), non-relapse mortality (B), disease-free survival rate (C) and overall survival (D) according to conditioning intensity

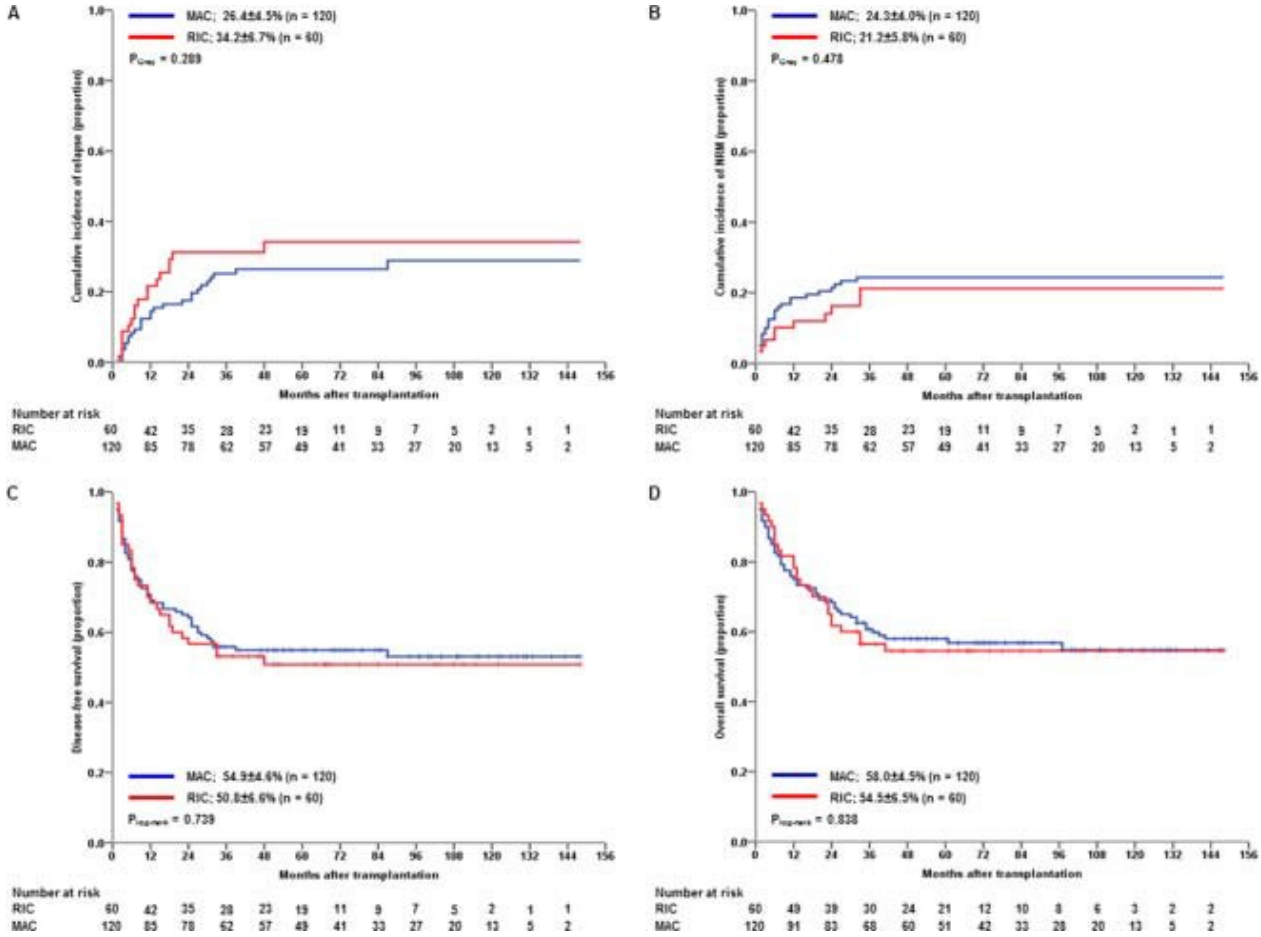


Table 8: Multivariate analysis of outcomes

TABLE III. Multivariate Analysis of Independent Variables Affecting Transplantation Outcomes

	All transplants ($n = 180$)		Ph-negative ALL transplants ($n = 99$)		Ph-positive ALL transplants ($n = 81$)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Relapse						
Conditioning intensity						
MAC	1		1		1	
RIC	2.07 (1.13–3.81)	0.019	1.39 (0.62–3.11)	0.429	3.46 (1.22–9.85)	0.020
Disease status at SCT						
CR1	1		1		–	–
CR2	3.28 (1.70–6.35)	< 0.001	2.70 (1.23–5.92)	0.013	–	–
MRD status at SCT						
MMR	–	–	–	–	1	
CMR$^{4.5}$	–	–	–	–	0.81 (0.13–4.92)	0.822
<3~2-log reduction	–	–	–	–	6.54 (1.44–29.74)	0.015
<2-log reduction	–	–	–	–	14.27 (2.79–72.90)	0.001
Chronic GVHD						
Positive	1		1		1	
Negative	9.98 (4.39–22.70)	< 0.001	6.93 (2.60–18.45)	< 0.001	9.89 (1.90–51.49)	0.006
NRM						
Conditioning intensity						
MAC	1		1		1	
RIC	0.68 (0.30–1.52)	0.345	0.62 (0.20–1.89)	0.401	0.69 (0.21–2.25)	0.540
Acute GVHD						
Negative	1		–	–	1	
Positive	3.30 (1.42–7.66)	0.005	–	–	9.55 (1.24–73.48)	0.030
DFS						
Conditioning intensity						
MAC	1		1		1	
RIC	1.53 (0.92–2.53)	0.100	1.04 (0.50–2.14)	0.923	2.07 (0.93–4.60)	0.073
Disease status at SCT						
CR1	1		1		–	–
CR2	2.59 (1.47–4.58)	0.001	2.33 (1.20–4.55)	0.013	–	–
MRD status at SCT						
MMR	–	–	–	–	1	
CMR$^{4.5}$	–	–	–	–	1.33 (0.49–3.60)	0.572
<3~2-log reduction	–	–	–	–	2.51 (0.75–8.37)	0.135
<2-log reduction	–	–	–	–	6.12 (2.06–18.13)	0.001
Chronic GVHD						
Positive	1		1		–	–
Negative	3.18 (1.92–5.28)	< 0.001	3.14 (1.60–6.17)	0.001	–	–
Overall survival						
Conditioning intensity						
MAC	1		1		1	
RIC	1.38 (0.82–2.32)	0.227	0.98 (0.46–2.08)	0.948	1.76 (0.77–4.04)	0.184
Disease status at SCT						
CR1	1		1		–	–
CR2	2.65 (1.49–4.71)	0.001	2.51 (1.28–4.95)	0.008	–	–
MRD status at SCT						
MMR	–	–	–	–	1	
CMR$^{4.5}$	–	–	–	–	1.60 (0.56–4.61)	0.381
<3~2-log reduction	–	–	–	–	2.83 (0.83–9.68)	0.097
<2-log reduction	–	–	–	–	7.19 (2.56–20.24)	< 0.001
Chronic GVHD						
Positive	1		1		–	–
Negative	2.82 (1.67–4.77)	< 0.001	2.85 (1.42–5.71)	0.003	–	–

Ph, Philadelphia chromosome; ALL, acute lymphoblastic leukemia; HR, hazard ratio; CI, confidence interval; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; SCT, stem cell transplantation; CR, complete remission; MRD, minimal residual disease; MMR, major molecular response; CMR$^{4.5}$, complete molecular response (4.5 log sensitivity); GVHD, graft-versus-host disease; NRM, nonrelapse mortality; DFS, disease-free survival.

Ph, Philadelphia chromosome; ALL, acute lymphoblastic leukemia; HR, hazard ratio; CI, confidence interval; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; SCT, stem cell transplantation; CR, complete remission; MRD, minimal residual disease; MMR, major molecular response; CMR$^{4.5}$, complete molecular response (4.5 log sensitivity); GVHD, graft-versus-host disease; NRM, nonrelapse mortality; DFS, disease-free survival.

Relapse

The non-adjusted cumulative incidence of relapse at 5 years was 34.2%±6.7% for RIC and 26.4%±4.5% for MAC (P=0.289). The potential factors predicting higher relapse risk were high leukocyte count (P=0.050), transplantation in CR2 (P<0.001), and the absence of acute (P=0.034) or chronic (P<0.001) GVHD in univariate analysis. In multivariate analysis, relapse risk was significantly higher for RIC transplants than for MAC transplants (hazard ratio [HR] 2.07; 95% confidence interval [CI], 1.13–3.81; P=0.019). Regardless of conditioning intensity, factors independently associated with a higher relapse risk included the absence of chronic GVHD (HR, 9.98; 95% CI: 4.39–22.70; P<0.001) and transplantation in CR2 (HR, 3.28; 95% CI: 1.70–6.35; P<0.001).

Non-relapse mortality

The non-adjusted cumulative incidence of NRM at 5 years was 21.2%±5.8% for RIC and 24.3%±4.0% for MAC (P=0.478), irrespective of age category. The potential factors predicting higher NRM were

transplantation from mismatched URD (P=0.018) and the presence of acute GVHD (P=0.003) in univariate analysis. In multivariate analysis, conditioning intensity had no impact on NRM (RIC vs. MAC; HR, 0.68; 95% CI: 0.30–1.52; P=0.345).

The primary causes of NRM were as follows: infections (n=12; 3 RIC, 9 MAC), chronic GVHD (n=10; 4 RIC, 6 MAC), acute GVHD (n=8; 3 RIC, 5 MAC), organ failure (n=6; 1 RIC, 5 MAC), and haemorrhage (n=3; 0 RIC, 3 MAC).

Disease-free survival

Non-adjusted DFS-rate at 5 years was not significantly different between RIC (50.8%±6.6%) and MAC (54.9%±4.6%) (p=0.739). In multivariate analysis, conditioning intensity had no significant impact on DFS. Regardless of conditioning intensity, factors independently associated with poorer DFS were the absence of chronic GVHD (HR, 3.18; 95% CI: 1.92–5.28; P<0.001) and transplantation in CR2 (HR, 2.59; 95% CI, 1.47–4.58; P=0.001).

Overall survival

No statistically significant difference was found in OS-rate at 5 years between RIC and MAC (54.5%±6.5% vs. 58.0%±4.5%; p=0.838; HR 1.38 (95% CI, 0.82–2.32; P=0.227)).

In conclusion, RIC transplants showed comparable long-term survival to MAC transplants, despite older age and the presence of co-morbidities. There was a higher relapse risk for RIC transplants.

Ancillary analyses

The subgroup analysis that was performed in this study (results in Philadelphia chromosome positive vs negative patients) is considered not relevant for the current application, and is therefore not assessed further.

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

Not applicable.

Clinical studies in special populations

Paediatric population – malignant haematological diseases

Lucchini et al., 2017: Impact of conditioning regimen on outcomes for children with acute myeloid leukaemia undergoing transplantation in first complete remission. An analysis on behalf of the paediatric disease working party of the European group for blood and marrow transplantation.

Methods

In this retrospective European registry study, patients treated in 204 European Group for Blood and Marrow Transplantation centers between 2000 and 2010 were analysed.

Study participants

Patients aged >2 to <18 years undergoing a first allogeneic HSCT from a matched sibling or unrelated donor for AML in CR1.

Patients below the age of 2 were excluded from the study as they were mostly conditioned without TBI. Patients receiving HSCT from umbilical cord blood were excluded from the study. Patients with AML French-American-British subtype acute promyelocytic leukaemia (M3) subtype and juvenile myelomonocytic leukaemia were excluded from the study.

CR was defined by the absence of physical signs of leukaemia or detectable leukaemia cells on blood smears, bone marrow with normal hematopoiesis, and <5% leukaemia blasts cells (morphologically identified).

Treatments

Patients received 1 of the following conditioning regimens:

- Cyclophosphamide 120 mg/kg with TBI with a hyperfractionated regimen (7 to 14.4 Gy, median dose 12) (TBICy)
- Busulfan, median dose of 16 mg/kg (range, 8 mg/kg to 23 mg/kg) with 120 or 200 mg/kg Cyclophosphamide (BuCy)
- Busulfan, median dose of 16 mg/kg (range, 10 mg/kg to 20 mg/kg) with 120 mg/kg Cyclophosphamide and 140 mg/m2 Melphalan (BuCyMel)

Outcomes/endpoints

The primary endpoint of the study was 5-year LFS and overall survival (OS) after HSCT in children with AML in CR1 at HSCT. LFS was defined as the time from the date of transplantation to the date of relapse or death from any cause, whichever comes first. OS was defined as the time from HSCT to death, regardless of the cause.

Secondary endpoints included the incidences of acute and chronic graft-versus-host disease (GVHD), relapse, and NRM. GVHD was diagnosed and graded according to internationally accepted criteria. NRM was defined as any death occurring in complete remission.

Randomisation/blinding (masking)

No randomisation was performed. Participants, study physicians and response-assessors were not blinded or masked for treatment.

Statistical methods

Kaplan- Meier estimators and confidence intervals were used to estimate LFS and OS and the log-rank test was used for the comparison. The cumulative incidences of relapse and NRM were estimated for competing risks by the Fine-Grey method and the Cox proportional hazard regression models to evaluate the impact on relapse, LFS, and OS of the following variables: age at transplantation, conditioning regimen, donor type, time from diagnosis to transplantation, stem cell source, presence of GVHD, and year of transplantation.

Results

Baseline data

Patient and transplantation characteristics according to the conditioning regimen are summarised in Table 9. Patients who received TBI were significantly older and underwent transplantation earlier in time than patients receiving Bu-based conditioning.

Data about the route of Bu administration were available for 66% of the reported patients. Oral administration was significantly more frequent in patients receiving BuCyMel than in those receiving BuCy conditioning (85.5% versus 44.5%, P < .001).

There were no significant differences among the 3 groups of patients in terms of transplantation characteristics.

Table 9: Baseline characteristics Lucchini et al., 2017

Table 1
Patient and Transplantation Characteristics according to the Myeloablative Conditioning Regimen

Characteristic	TBICy (n = 109)	BuCy (n = 389)	BuCyMel (n = 133)	Total (n = 631)	*P* Value (95% CI)
Age at HSCT, median (range), yr	14.8 (2.1-17.9)	11.7 (2-18)	9.8 (2.1-17.9)	11.9 (2-18)	.0001
Year of HSCT, median	2005	2007	2007	2007	.0001
Diagnosis to HSCT median, range	4.7 (2-20.5)	4.8 (.8-66.6)	5.3 (1.8-50.1)	4.9 (.8-66.6)	.0345
Patient sex: male	64 (58.7%)	206 (53%)	79 (59.4%)	349 (55.3%)	1.00
Donor sex: male	68 (63.6%)	212 (55.5%)	69 (52.3%)	349 (56.2%)	1.00
Female donor to male recipient	22 (20.6%)	87 (22.8%)	33 (25%)	142 (22.9%)	1.00
Donor type					
MSD	74 (67.9%)	302 (77.6%)	82 (61.7%)	458 (72.6%)	.148
MUD	35 (32.1%)	87 (22.4%)	51 (38.3%)	173 (27.4%)	
In vivo T cell depletion: yes	29 (26.6%)	67 (17.2%)	42 (31.6%)	138 (21.9%)	.127
Stem cell source					.127
BM	82 (75.2%)	250 (64.3%)	108 (81.2%)	440 (69.7%)	
PB	27 (24.8%)	139 (35.7%)	25 (18.8%)	191 (30.3%)	
Busulfan					<.0001
Missing		153	23		
Oral	NA	105 (44.5%)	94 (85.5%)		
Intravenous	NA	131 (55.5%)	16 (14.5%)		

MSD indicates matched sibling donor; MUD, matched unrelated donor; BM, bone marrow; PB, peripheral blood.

Outcomes and estimation

Relapse was the primary cause of death in the entire cohort. Overall, relapse incidence was 27.3% (95% CI, 23.7% to 31.1%). Patients conditioned with BuCyMel had a statistically significant lower chance of developing disease relapse than both TBICy and BuCy conditioned patients (14.7% versus 30% versus 31.5%, P < .01) (**Table 10** below). This difference remained statistically significant after correction for covariates in multivariate analysis (**Table 11** below). 5-year LFS was also significantly higher in patients conditioned with BuCyMel than in both TBICy- and BuCy-conditioned patients (**Figure 8** A). Overall survival rate at 5 years was also higher in the BuCyMel group compared to the other two treatment groups (**Figure 8** B), but in multivariate analysis this difference did not remain statistically significant with a p-value of 0.07. Non-relapse mortality rate at 5 years was not different between the three groups.

Figure 8: LFS (A) and OS (B) estimation according to conditioning regimen

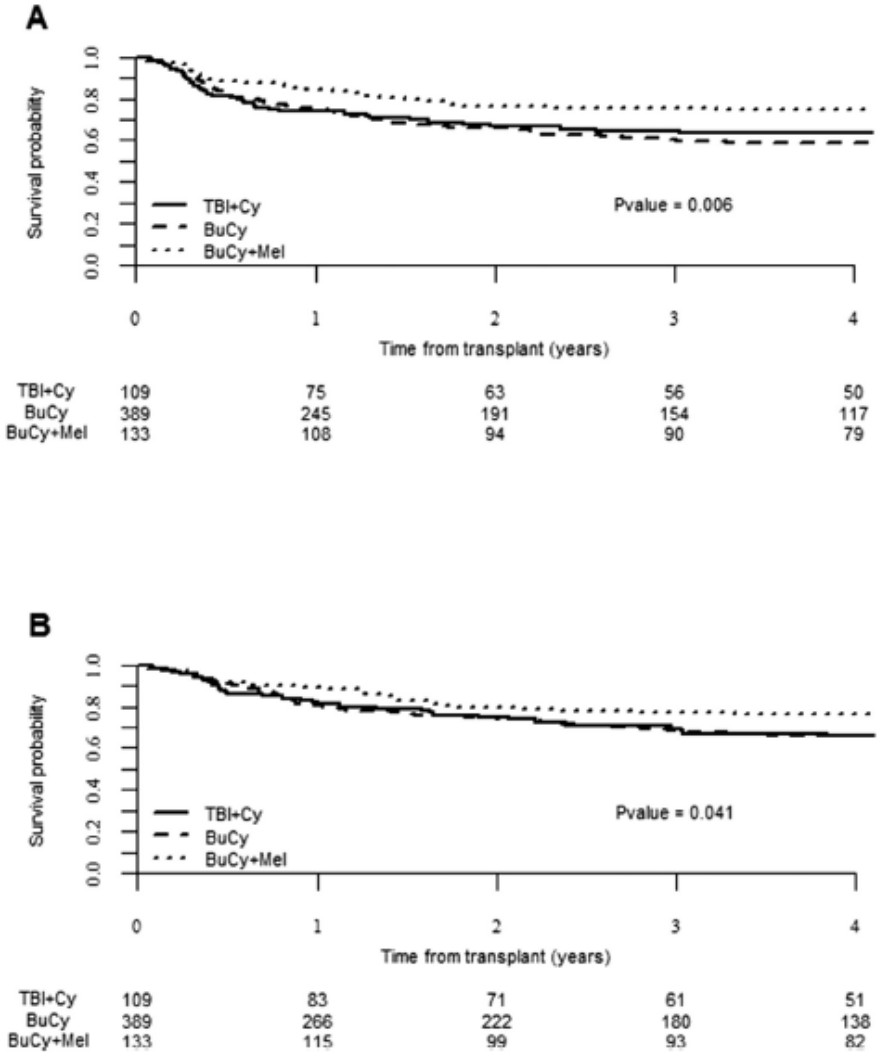


Table 10: Outcomes according to conditioning regimen

Table 2
Patient Outcome according to Conditioning Regimen

Outcome	TBICy (n = 109)	BuCy (n = 389)	BuCyMel (n = 133)	Total (n = 631)	*P* Value (95% CI)
Engraftment	100 (95.6-100)	97.9 (95.7-99)	98.4 (93-99.7)	98.4 (96.9-99.1)	.065
aGVHD grade ≥ II	31.1 (22.5-41.1)	29.3 (24.8-34.3)	42.7 (34.2-51.7)	32.5 (28.8-36.4)	.233
aGVHD grade ≥ III	6.8 (3.0-14.0)	9.6 (6.9-13.2)	17.6 (11.7-25.4)	10.8 (8.5-13.6)	.052
cGVHD	27.8 (18.6-37.9)	25.8 (20.7-31.1)	35.2 (26-44.5)	27.5 (23.7-31.7)	1.00
Five-year NRM	8.1 (3.7-14.7)	10.5 (7.4-14.1)	10.8 (6.2-16.8)	10.1 (7.7-12.8)	.79
Five-year relapse	30 (21.4-39)	31.5 (26.5-36.7)	14.7 (9.2-21.5)	27.3 (23.7-31.1)	<.001
Five-year LFS	61.9 (53.1-72.2)	58 (52.8-63.7)	74.5 (67.3-82.4)	62.6 (58.7-66.8)	.005
Five-year OS	64.5 (55.6-74.9)	64 (58.7-69.7)	76.6 (69.6-84.4)	67.2 (63.3-71.3)	.041

Data presented are % (95% CI) unless otherwise indicated.
aGVHD indicates acute graft-versus-host disease; cGVHD, chronic GVHD.

Table 11: Multivariate analysis of outcomes

Table 5
Multivariate Analysis according to Cox Regression Model

Risk Factor	OR (95% CI) and *P* value			
	Relapse	NRM	LFS	OS
BuCy versus TBICy	.96 (.63-1.46) .84	1.63 (.69-3.83) .27	1.07 (.73-1.56) .72	1.04 (.69-1.58) .84
BuCyMel versus other conditioning	**.44 (.25-0.8)** **<.01**	1.22 (.45-3.32) .70	**.57 (.35-0.94)** **.03**	.61 (.36-1.03) .07
Age at HSCT >10 yr	1.00 (.97-1.04) .82	**1.11 (1.04-1.19)** **<.01**	1.03 (1-1.06) .08	1.03 (1-1.06) .09
MUD versus MSD	1.44 (.96-2.13) .07	1.61 (.85-3.06) .15	**1.46 (1.05-2.03)** **.03**	**1.56 (1.09-2.22)** **.02**
Time from dx to HSCT (>1 yr)	.81 (.5-1.3) .38	**1.66 (1.15-2.41)** **<.01**	1.1 (.81-1.49) .55	1.14 (.84-1.55) .39
aGVHD	.44 (.18-1.09) .08	**4.17 (2.01-8.68)** **<.01**	1.11 (.65-1.89) .70	1.52 (.88-2.61) .13
Stem cell source PB versus BM	1.24 (.86-1.78) .25	**2.07 (1.13-3.8)** **.02**	**1.40 (1.03-1.9)** **.03**	**1.83 (1.32-2.54)** **<.01**
Year of HSCT before 2007	1 (.95-1.06) .97	.99 (.9-1.1) .91	1 (.95-1.05) .99	1.01 (.96-1.06) .72

Bold typeface indicates statistical significance.
Dx indicates diagnosis.

Kato et al., 2015: Comparison of chemotherapeutic agents as a myeloablative conditioning with total body irradiation for pediatric acute lymphoblastic leukemia: a study from the pediatric ALL working group of the Japan Society for Hematopoietic Cell Transplantation.

Methods

In this retrospective Japanese registry study, patients treated between 2000 and 2012 were analysed.

Study participants

Inclusion criteria were as follows: patients diagnosed with ALL; aged 15 years or younger when receiving HSCT; allogeneic HSCT performed in first or second complete remission (CR1 or CR2); 12 Gy of TBI-based myelo-ablative conditioning and no prior HSCT.

Treatments

Patients were divided into five treatment groups, based on the chemotherapeutic agent that was added to TBI:

- Cyclophosphamide (CY)
- Melphalan (L-PAM)
- Cyclophosphamide + etoposide (Cy+VP16)
- Cyclophosphamide + AraC (Cy+AraC)
- Others: melphalan + etoposide, Cyclophosphamide + fludarabine, Fludarabine

Most cases of HSCT with Cyclophosphamide used a dose of 120 mg/kg (or 3600 mg/m2).

For etoposide, 60 mg/kg (or 1800 mg/m2) was the dose most frequently used. For melphalan, 180 mg/m2 of was given in 73 cases (52.5%) of HSCT, whereas 200 mg/m2 or more was used in 45 cases (32.4%) of HSCT.

Outcomes/endpoints

EFS was the primary endpoint of the study. OS, NRM and relapse rate were analysed as secondary endpoints. The duration of event-free survival (EFS) was defined as the time from HSCT to either treatment failure (relapse, death, or the diagnosis of secondary cancer) or the last day of observation when confirmed to be alive.

Randomisation/blinding (masking)

No randomisation was performed. Participants, study physicians and response-assessors were not blinded or masked for treatment.

Statistical methods

The overall survival (OS) probability was calculated using Kaplan–Meier estimates. Cumulative incidence curves were used in a competing risk setting to calculate the probability of engraftment, graft-versus host disease (GVHD), and non-relapse mortality (NRM). Univariate analyses of EFS were performed using the log-rank test, and Gray's test was used for group comparisons of cumulative incidences. Multivariate analysis was performed using the Cox proportional-hazard regression model, and the factors with $P<0.2$ by the univariate analysis were entered into the multivariate analysis. A two-sided P-value of less than 0.05 was considered to be significant.

Results

Baseline data

Table 12: Baseline characteristics Kato et al., 2015

TABLE I. Patient and Transplantation Characteristics

		Chemotherapeutic agents					
Characteristics	All (%)	CY (%)	L-PAM (%)	CY+VP16 (%)	CY + AraC (%)	Other (%)	*P*
All patients	767 (100)	74 (100)	139 (100)	408 (100)	73 (100)	73 (100)	
Age at HSCT							0.06
<10	427 (55.7)	32 (43.2)	72 (51.8)	242 (59.3)	44 (60.3)	37 (50.7)	
≥10	340 (44.3)	42 (56.8)	67 (48.2)	166 (40.7)	29 (39.7)	36 (49.3)	
Immunophenotype							0.40
Non-T lineage	597 (77.8)	60 (81.1)	109 (78.4)	307 (75.2)	62 (84.9)	59 (80.8)	
T-lineage	158 (20.6)	14 (18.9)	28 (20.1)	93 (22.8)	10 (13.7)	13 (17.8)	
Unknown	12 (1.6)	0 (0.0)	2 (1.4)	8 (2.0)	1 (1.4)	1 (1.4)	
Cytogenetics							<0.01
Low risk	47 (6.1)	6 (8.1)	10 (7.2)	24 (5.9)	2 (2.7)	5 (6.8)	
Hyperdiploid	32	5	6	16	1	4	
t(12;21)	15	1	4	8	1	1	
Intermediate risk	531 (69.2)	62 (83.8)	113 (81.3)	254 (62.3)	61 (83.6)	41 (56.2)	
t(1;19)	16	1	2	9	3	1	
Normal	324	41	71	140	48	24	
Other abnormality	191	20	40	105	10	16	
High risk	189 (24.6)	6 (8.1)	16 (11.5)	130 (31.9)	10 (13.7)	27 (37.0)	
t(9;22)	129	4	9	90	7	19	
MLL rearrangement	49	0	4	37	3	5	
Hypodiploid	11	2	3	3	0	3	
Disease status at HSCT							<0.01
CR1	435 (56.7)	41 (55.4)	58 (41.7)	270 (66.2)	24 (32.9)	41 (56.2)	
CR2	332 (43.3)	33 (44.6)	81 (58.3)	138 (33.8)	49 (67.1)	32 (43.8)	
Stem cell source							<0.01
Matched related donor	208 (27.1)	22 (29.7)	50 (36.0)	101 (26.5)	20 (27.4)	15 (20.5)	
Mismatched related donor	87 (11.3)	8 (10.8)	14 (10.1)	39 (9.6)	11 (15.1)	15 (20.5)	
Unrelated donor	291 (37.9)	32 (43.2)	52 (37.4)	168 (41.2)	21 (28.8)	18 (24.7)	
Cord blood	181 (23.6)	12 (16.2)	23 (16.5)	100 (24.5)	21 (28.8)	25 (34.2)	

P-value calculated by Fisher's exact test for independence of each categorical data. CR, complete remission; HSCT, hematopoietic stem cell transplantation; CY, cyclophosphamide; L-PAM, melphalan; VP16, etoposide.

There are statistically significant differences between the treatment groups with regards to cytogenetic risk (more high risk patients in the cyclophosphamide+etoposide group), disease status at HSCT (more patients transplanted in CR2 in the melphalan and cyclophospohamide + AraC group) and stem cell source (more patients in the melphalan group had a matched related donor).

Outcomes and estimation

Figure 9 A (EFS), B (relapse) and C (NRM) below show the Kaplan-Meier curves for the main study endpoints according to treatment group. The curve for the melphalan treatment group is depicted in blue.

Table 13 shows the uncorrected results of HSCT.

In Table 14 the result of multivariate analysis of the primary endpoint is shown. After correction for transplantation in CR1 or CR2 and stem cell source, no statistically significant difference in EFS was found between treatment groups.

Relapse rate at 5 years was lower in the melphalan and 'other' treatment groups, the differences in NRM between groups were not statistically significant. No multivariate analysis of relapse or NRM between groups was reported.

No point estimate or comparison of OS per treatment group is reported.

Figure 9: Kaplan-Meier estimates of EFS, relapse and NRM

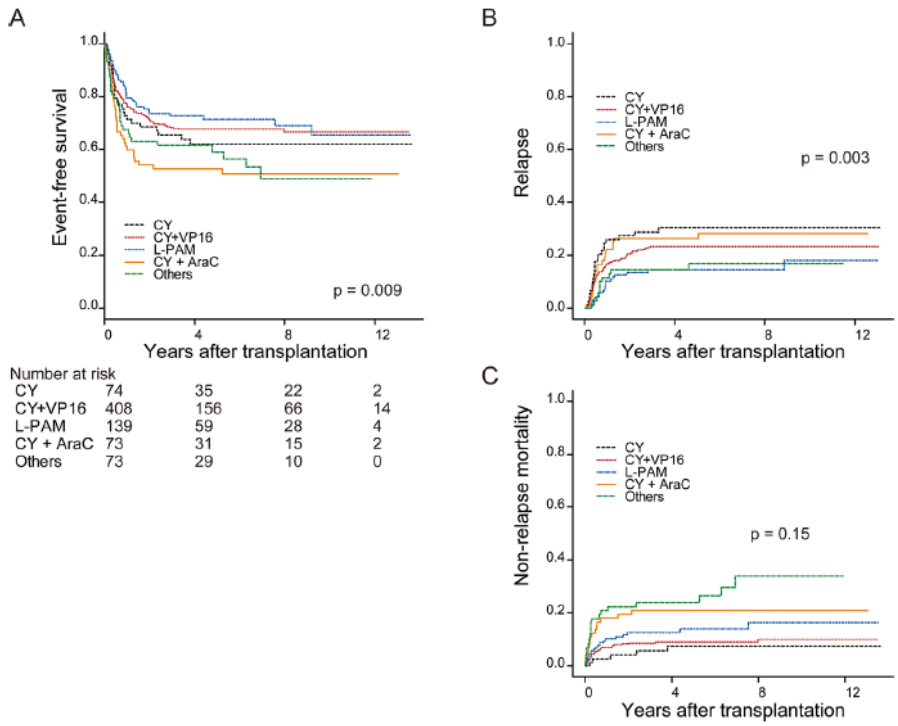


Fig. 1. Outcome of TBI-based HSCT of all patients. Outcome is shown according to chemotherapeutic agent group. (**A**) Overall survival, (**B**) relapse incidence, and (**C**) non-relapse mortality. CY, cyclophosphamide; L-PAM, melphalan; VP16, etoposide; AraC, cytarabine.

Table 13: Outcomes of HSCT

TABLE II. Outcome of HSCT

Characteristics	n	CI of relapse (at 5 years)	*P*	CI of NRM (at 5 years)	*P*	EFS (at 5 years)	*P*
All patients	767	22.2±1.6		11.9±1.2		65.5±1.8	
Age at HSCT			0.16		0.03		0.77
<10	427	23.9±2.1		9.9±1.5		66.2±2.3	
≥10	340	20.2±2.4		15.5±2.1		64.3±2.8	
Immunophenotype			0.16		0.42		0.56
non-T	597	23.5±1.8		11.6±1.3		64.9±2.0	
T	158	16.7±3.1		15.1±3.0		68.2±3.9	
Disease status at HSCT			<0.001		0.02		<0.001
CR1	435	16.6±1.8		10.0±1.5		73.4±2.2	
CR2	332	29.3±2.6		15.4±2.0		55.2±2.9	
Cytogenetic risk[1]			0.91		0.10		0.51
Low	47	26.9±6.8		10.9±4.7		62.1±7.3	
Intermediate	531	21.1±1.8		13.9±1.6		65.0±2.2	
High	189	24.1±3.4		8.1±2.0		67.8±3.6	
Stem cell source			0.33		0.003		0.13
Matched related donor	208	26.4±3.2		6.9±1.9		66.8±3.5	
Mismatched related donor	87	20.2±4.4		14.0±3.8		65.8±5.1	
Unrelated donor	291	17.8±2.3		14.5±2.1		67.8±2.9	
Cord blood	181	25.2±3.4		14.5±2.6		60.3±3.8	
Chemotherapeutic agents			0.003		0.15		0.009
CY	74	30.5±5.5		7.3±3.2		62.2±5.8	
L-PAM	139	14.6±3.1		14.0±3.1		71.4±4.1	
CY+VP16	408	23.4±2.2		9. ±3.2		67.6±2.4	
CY + AraC	73	26.4±5.2		21.0±4.9		52.6±5.9	
Other	73	17.0±4.9		23.9±5.1		59.1±6.1	

[1]Low risk includes hyperdiploid and t(12;21); high risk includes hypodiploid, MLL rearrangement, and t(9;22). Other cytogenetic statuses are categorized as intermediate risk. *P*-values were calculated for the null hypothesis of equal hazard ratio or survival curves using Gray's test for CI of relapse and NRM, and log-rank test for EFS. CI, cumulative incidence; NRM, non-relapse mortality; OS, overall survival; CR, complete remission.

Table 14: Multivariate analysis of EFS

TABLE III. Multivariate Analysis of the Risk Factors for EFS

Characteristics	Hazard ratio (95%CI)	*P*-value
Disease status at HSCT		
CR1	1	
CR2	1.92 (1.49–2.48)	<0.001
Stem cell source		
Matched-related donor	1	
Mismatched-related donor	1.09 (0.72–1.67)	0.68
Unrelated donor	0.99 (0.72–1.36)	0.93
Cord blood	1.24 (0.88–1.74)	0.22
Chemotherapeutic agents		
CY	1	
L-PAM	0.69 (0.42–1.13)	0.14
CY+VP16	0.94 (0.62–1.43)	0.77
CY+AraC	1.26 (0.76–2.09)	0.37
Others	1.29 (0.76–2.09)	0.34

The factors with $P < 0.2$ by the univariate analysis were entered into the multivariate analysis. CI, confidence interval; HSCT, hematopoietic stem cell transplantation; CR, complete remission; CY, cyclophosphamide; L-PAM, melphalan; VP16, etoposide.

Ancillary analyses

Based on the highest 5-year cumulative incidences of EFS in the L-PAM (melphalan) and Cy+VP16 (cyclophosphamide + etoposide) treatment groups, further subgroup analyses were performed comparing these two regimens in patients receiving transplants from matched related versus alternative donors. These subgroup analyses were not pre-specified and are considered exploratory.

In HSCT from a matched-related donor, the EFS of L-PAM was 83.2±6.7%, while that of CY+VP16 was 66.7± 4.9%, a statistically significant difference (P=0.02). The relapse incidence of L-PAM (7.1±4.0%) was significantly lower than that of CY+VP16 (29.0±4.8%) (P=0.008). The NRM incidences of L-PAM and CY+VP16 were 9.6±5.8% and 4.3±2.1%, respectively (P=0.73).

In HSCT from an alternative donor, no statistically significant differences were found between L-PAM and Cy+VP16 regarding, 5-year rates of EFS, RR or NRM.

Paediatric population – non-malignant haematological diseases

An overview of literature studies on allo-HSCT after a melphalan-containing RIC regimen and after a myelo-ablative regimen in paediatric non-malignant haematological diseases was provided (Table 15). In total, 21 studies were analysed: 11 studies for MAC (965 patients) and 10 studies for melphalan-based RIC (504 patients). Paediatric patients aged 2 months to 18 years with diverse non-malignant haematological diseases were treated with RIC regimen in the different studies, including sickle cell anaemia, thalassaemia, immune deficiencies, congenital anaemia and haemophagocytic lymphohistiocytosis.

Table 15 Summary table of clinical studies on allo-HSCT after a melphalan-containing RIC regimen and after a myelo-ablative regimen (MAC) in paediatric non-malignant haematological diseases

MAC (N=965)			RIC (N=504)		
Study	**n**	**Indication**	**Study**	**n**	**Indication**
(Lucarelli *et al.*, 1990)	99	Thalassemia	(Shenoy *et al.*, 2005)	11	Non-malignant diseases including sickle cell anaemia, thalassemia and congenital dyserythropietic anaemia
(Walters *et al.*, 1996)	22	Sickle cell anaemia and thalassemia	(Matthes-Martin *et al.*, 2013)	8	Sickle cell disease
(Vermylen *et al.*, 1998)	50	Sickle cell anaemia	(Parikh *et al.*, 2014)	22	Inherited non-maligant disease including haemoglobinopathies
(Locatelli *et al.*, 2003)	44	Sickle cell disease and thalassemia	(King *et al.*, 2015)	52	Sickle cell disease and thalassemia
(Panepinto *et al.*, 2007)	67	Sickle cell disease	(Marsh *et al.*, 2015)	206	Inherent non-malignant diseases
(Gaziev *et al.*, 2010)	71	Sickle cell disease and thalassemia	(Madden *et al.*, 2016)	84	Non-malignant diseases including haemoglobinopathies
(Sabloff *et al.*, 2011)	179	Thalassemia	(Kothari *et al.*, 2015)	11	Marrow failure of genetic origin
(McPherson *et al.*, 2011)	27	Sickle cell disease	(Allen *et al.*, 2018)	46	Hemophagocyic lymphohistiocytosis, and other primary immunodeficiencies,
(Hussein *et al.*, 2013)	31	Thalassemia	(Oshrine *et al.*, 2014)	31	Hemophagocyic lymphohistiocytosis, other primary immune deficiencies, haemoglobinopathies, and bone marrow failure
(Mathews *et al.*, 2013)	139	Thalassemia	(Shenoy *et al.*, 2018)	33	Thalassemia
(Bernaudin *et al.*, 2020)	234	Sickle cell disease			

The largest study on a RIC regimen for allo-HSCT in non-malignant haematological diseases included in the dossier was published by **Marsh et al., 2015**. A total of 210 children received a RIC regimen of Alemtuzumab, Fludarabine, and melphalan 140mg/m2. Aim of the study was to assess survival and chimerism in this schedule in which alemtuzumab was added to the previously used FM. The hypothesis was that the majority of patients would survive a RIC allo-HSCT without graft loss. Included diseases were HLH and X-linked lymphoproliferative disease (n=91), combined immune deficiency and common variable immunodeficiency (n=23), severe combined immune deficiency (SCID) (n=24), non-Fanconi anaemia marrow failure disorders (n=25) and metabolic disorders (n=22). 1-year and 3-year probability of overall survival was 78% and 69%. Three-year EFS was 84% for patients who underwent transplantation with an HLA-matched related donor compared with 64%, 57% and 14% for patients who underwent transplantation with a matched unrelated donor, 1 allele mismatched donor, or 2 allele mismatched donor, respectively ($P < .001$). For all patients, the cumulative incidence of mixed

chimerism was 46%. 5% of patients required re-transplantation, and over 75% of patients possessed greater than 90% whole blood donor chimerism at the time of last follow-up.

Shenoy et al., 2018, performed a prospective single-arm trial in 33 children with transfusion-dependent thalassemia, investigating thalassemia-free survival (TFS) at 2 years after allo-HSCT with conditioning by hydroxyurea, alemtuzumab, fludarabine, thiotepa and melphalan (140 mg/m2 i.v.).

A threshold for efficacy was pre-specified at and incidence of TFS ≥75%, stopping rules included graft rejection, treatment-related mortality, or grade IV acute GVHD > 20%. The efficacy threshold was met, but incidence of acute GVHD grade III and IV was >20%. It is not clear from the dossier or the publication what the incidence of grade IV acute GVHD was and if the trial was stopped.

Shenoy et al., 2005, Matthes-Martin et al., 2013, Oshrine et al., 2014, King et al., 2015, Kothari et al., 2015, Madden et al., 2016, Allen et al., 2018, are other trials on the use of melphalan in combination with alemtuzumab and fludarabine as RIC before allo-HSCT in which patients aged 2 months to 18 years with diverse non-malignant haematological diseases were treated, including sickle cell anemia, thalassemia, immune deficiencies, congenital anemia and haemophagocytic lymphohistiocytosis. Parikh et al., 2014, added hydroxyurea and thiotepa to this regimen.

Rates of graft failure, GVHD, transplant-related mortality, event-free and overall survival were provided (mean: sum of percentage specific event divided by the number of publications and range percentages across studies) for the studies using melphalan-containing RIC and for those using MAC (Table 16).

Table 16: Outcomes after MAC and melphalan-based RIC regimens for paediatric non-malignant haematological diseases

Outcome	MAC (N = 965)	RIC (N = 504)
Incidence of graft rejection/failure (mean ± SD) Range	9.5 ± 6% 0-20%	11 ± 11% 0-37%
Incidence of acute GVHD Range	22 ± 12% 9-44%	22.5 ± 9% 0-33%
Incidence of chronic GVHD Range	13 ± 6.5% 4.5-20%	19 ± 13% 0-41%
Transplant-related mortality Range	6 ± 9% 0-28%	10 ± 8% 0-25%
Overall survival Range	91 ± 11% 60-100%	82 ± 10% 69-100%
Event-free survival Range	82 ± 12% 57-96%	79 ± 14% 64-100%

Supportive studies

Adult population

Two prospective uncontrolled studies **(Van Besien et al., 2005, Kirschbaum et al.,2012)** and seven retrospective controlled studies (**Damlaj et al., 2016, Dhere et al., 2017, Yamamoto et al., 2016, Imataki et al., 2009, Gomez et al., 2014, Jain et al., 2019, De Lima et al., 2004)** are considered supportive and briefly addressed here based on the summaries provided by the applicant.

In the single-arm study by **van Besien et al., 2005**, 52 consecutive patients with AML and MDS received a combination of fludarabine, melphalan and alemtuzumab prior to allo-SCT. The patient

population had mainly high-risk disease, had co-morbidities and poor performance status. With a median follow-up for survivors of 18 months, 1-year survival was 48%, progression-free survival 38% and cumulative incidence of relapse 32%. The authors conclude the observed outcomes to be valuable given the poor risk population.

Kirschbaum et al., 2012, performed a prospective, phase I dose-response without placebo study to determine the recommended phase II dose of clofarabine plus melphalan as a conditioning regimen for allo-HSCT. Patients treated were 16 adults with AML, receiving clofarabine (dose level 1 30mg/m2, dose levels 2 and 3 40mg/m2) plus melphalan (dose levels 1 and 2, 100 mg/ m2; dose level 3, 140 mg/m2). One patient at dose level 2 and the first patient at dose level 3 died of multi-organ failure before engraftment. The decision was made to not enrol any more patients on dose level 3, but rather to further expand dose level 2 to 12 patients. Twelve patients received clofarabine 40 mg/ m2 and melphalan 100 mg/ m2 conditioning regimen. Two patients relapsed. OS point estimates at six months were 92% (range 54%-99%) at six months and 73% (range 38%-91%) at one year. Estimated EFS was 83% (range 46%-95%) at six months and 61% (range 26%-84%) at one year. The authors concluded that the combination of clofarabine and melphalan at 40 mg/m2 and 100 mg/m2 should be further investigated in a randomised trial compared to fludarabine plus melphalan.

Damlaj et al., 2016, performed a retrospective study to compare HSCT outcomes in 134 patients with AML and MDS receiving RIC-HSCT with fludarabine busulfan (FB) or fludarabine melphalan (FM). In multivariate analysis, relapse risk at 2 years was higher with the FB regimen. **Yamamoto et al., 2016,** retrospectively compared the same two regimens in 41 patients with different haematological malignancies (e.g. AML, ALL, MDS, myelofibrosis, lymphoma), only 9 patients received FB. The 3-year cumulative incidence of relapse was significantly lower with FM compared to FB in multivariate analysis. **Jain et al., 2019,** compared clinical outcomes of 61 myelofibrosis patients who underwent allogeneic HSCT with RIC using either FB, FM or fludarabine + carmustine + melphalan (FBM). No statistically significant differences in OS, DFS or relapse were found.

Dhere et al., 2017, report a retrospective study to compare outcomes of busulfan cyclophosphamide (Bu-Cy) versus fludarabine-melphalan (Flu-Mel) before allo-HSCT in 156 patients with AML. No difference in OS or relapse rate was found, but non-relapse mortality was lower in the Flu-Mel group despite these patients being older than those in the Bu-Cy group.

Imataki et al., 2009, reviewed the clinical data of 82 consecutive patients who underwent allo-SCT for various haematological malignancies (e.g. AML, MDS, ALL, CML, lymphoma) or benign haematological diseases (n=5). The conventional regimen of cyclophosphamide and TBI or cyclophosphamide and busulfan was compared to fludarabine + melphalan. Patients receiving fludarabine + melphalan were significantly older. OS, NRM and relapse rate were not significantly different between groups.

Gomez et al., 2014, retrospectively compared the incidence of GVHD (primary endpoint) in 175 patients with various haematological malignancies (e.g. ALL, MDS, MM, MF, CLL, NKL) either receiving fludarabine/melphalan/TBI or fludarabine/busulfan. There was no difference between the two groups in terms of the secondary endpoints OS and EFS, acute GVHD, relapse and non-relapse mortality incidence.

De Lima et al., 2004, compared clinical outcomes of a non-myeloablative regimen of fludarabine, cytarabine and idarubicin (FAI) to FM prior to allo-HSCT in 94 patients with AML or MDS**.** PFS was longer for patients treated with FM, but treatment-related mortality was higher. Because relapse-related mortality was higher in the FAI group, the overall survival was not different between FM or FAI.

The studies by **Oran et al., 2007**, and **Popat et al., 2012**, studied the outcomes of Flu-Mel RIC and allo-HSCT in adult patients with high-risk AML or MDS. **Besien et al., 2012**, studied the outcome of a

RIC of alemtuzumab-clofarabine-melphalan in adults with different haematological malignancies, also mainly AML or MDS.

Paediatric population – malignant haematological diseases

Kudo et al., 2015, used the registration data of the Japanese Society for Hematopoietic Cell Transplantation to assess the outcome of 55 children with severe aplastic anaemia (SAA) receiving a second hematopoietic stem cell transplantation. 12 patients received fludarabine, melphalan with or without TBI conditioning regimen, 14 fludarabine, cyclophosphamide with or without TBI and 29 patients received various conditioning regimens. All patients who received the fludarabine/melphalan regimen were alive and without graft failure at the end of follow-up, but as incidence rates of graft failure and OS are not reported for the other treatment groups, these results are difficult to interpret.

Ngwube et al., 2015, performed a prospective single-arm trial in the same patient population of SAA**.** Seventeen children received an allo-HSCT after alemtuzumab, fludarabine and melphalan 140 mg/m2. At a median follow up of 61 months, the 5 year EFS (primary endpoint) and OS for the entire cohort was 88%.

Yabe et al., 2015, describe the outcome of 30 paediatric patients with juvenile myelomonocytic leukemia (JMML) receiving an allo-HSCT with busulfan, fludarabine, and melphalan as conditioning. The 5-year OS and EFS rates for the entire cohort were 72.4 and 53.1 %, respectively.

Strahm et al., 2011, report an analysis of the European Working Group of MDS in Childhood (EWOG-MDS) 98 study. In this study, 97 children with MDS were treated with an allo-HSCT following induction by BuCyMel (melphalan 140mg/m2 single dose). OS-rate was 63%, EFS-rate was 59% and relapse rate was 21% at 5 years.

To discuss the efficacy and safety of melphalan in children below the age of 2 with AML, the applicant provided a summary of two additional studies from literature.

Locatelli et al., 2015, studied 243 high risk paediatric AML patients who were given either auto- or allo-HSCT after achievement of CR1 with induction therapy. Of these, 143 were given an allo-HSCT after BuCyMel induction with a dose of melphalan 140mg/m2, including 39 patients between 0-1 years of age and 17 between 1-2 years. Regarding efficacy, the 8-year probability of OS was 74.7% for the 143 patients given an allo-HSCT, the 8-year DFS was 73.3%. Cumulative incidence (CI) of relapse was 17.4% after allo-HSCT. Regarding safety, the transplant-related mortality was 7.4%. CI of grade II–IV and grade III–IV acute GVHD was 38.1% and 13.7%, respectively. The overall CI of cGVHD was 25.3% while that of extensive cGVHD was 8.6%.

In a subgroup analysis of different age categories (<1 year, 1-2 year, 2-10 year, >10 year) there was no statistically significant difference in disease-free survival at 8 years. Analysis of the association of age and the endpoints OS and TRM was not reported in the submitted publication.

Beier et al., 2013, performed a retrospective study to evaluate the efficacy of a Matched Related Donor and a Matched Unrelated Donor allo-SCT in patients with AML in second complete remission. Sixty patients were included from 31 German centers, all patients received the same conditioning regimen containing BU, CY and melphalan (140mg/m2 as a single dose). The median age at allo-HSCT was 12.2 years, ranging from 0.9-18.7 years. Regarding efficacy, OS-rate was 62±6% at 5 years, and EFS-rate at 5 years was 55±7%. The cumulative incidence of relapse was 33±4% at 5 years.

In multivariate analysis age at diagnosis of relapse (<12 years vs >12 years) and age at HSCT (<12 years vs >12 years) had no significant impact on OS, EFS and TRM. The number of patients below the age of 2 years included in this trial were not reported.

Discussion on clinical efficacy

In line with the requirements stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) on parenteral aqueous solution, bioequivalence studies are generally not required if the product is be administered as an aqueous intravenous solution containing the same active substance as the currently approved product, as in this case.

The European reference product chosen is Alkeran® 50 mg/10 ml, lyophilisat et solution pour usage parentéral (I.V.) authorised in France through a national procedure in 1996. The recommended doses for the approved indications of melphalan are the same as in the reference product. For the proposed additional indication (i.e. as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation in haematological diseases), the recommended dose is 140 mg/m^2 or 70 mg/m^2 once daily for two consecutive days in adults and 140 mg/m2 or a maximum cumulative dose of 210 mg/m^2 as result of 70 mg/m^2 once daily infusion for three consecutive days in the paediatric population. These doses are proposed as they appeared to be the most widely used in the preparative regimen for transplantation in the literature provided for efficacy and safety. It is agreed that the dose of 140 mg/m^2 is the most commonly used dose reported in the literature, for adult as well as paediatric patients. However, the addition of the total maximum cumulative dose of 210 mg/m^2, as a result of 70 mg/m^2 administered for three consecutive days in children, is considered not sufficiently discussed or justified.

Design and conduct of clinical studies

Clinical efficacy in the new proposed indication as conditioning treatment is based on literature data. No randomised controlled trials have been performed comparing a reduced intensity conditioning (RIC) regimen containing melphalan to other conditioning regimes prior to allogeneic HSCT in haematological diseases. The provided literature includes the largest published studies on the use of melphalan containing regimens prior to allo-HSCT.

The absence of a bioequivalence study has been justified in line with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The applicant confirmed that the reference product was used in the provided studies from the literature.

The applicant submitted a dossier of twenty-eight publications of studies ranging from one relatively large prospective comparative study to small retrospective single-institution case series. Overall the studies have several methodological shortcomings related to the retrospective nature, being lack of randomisation, blinding, standardisation of treatment regimens and pre-defined timing of outcome assessments. Prognostic factors could differ between treatment groups despite correction in multivariate analysis, biasing the observed effect size. No power calculation appears to be performed for any of the submitted studies. The methodology of the studies is only described at a very high level by the applicant, and most of the referred publications do not provide all the details necessary for a rigorous assessment. All of these issues bias outcome analyses and make interpretation of the study results difficult.

The endpoints of the main studies are overall survival (OS), disease-free survival (DFS), non-relapse mortality (NRM) and relapse rate (RR). These endpoints are considered clinically relevant. It is not clear whether statistical analysis plans for the main studies were developed beforehand, and if the schedule of assessments was pre-specified and comparable between treatment groups for each study. OS and NRM are considered the most robust endpoints, as difference in the timing of assessment could have impact on DFS and RR.

The two largest studies in adults (**Baron et al., 2017, Kawumura et al., 2015**) are retrospective studies using data obtained from a registry, and study procedures were not defined beforehand. Because inclusion took over ten years for both studies, treatment protocols might have changed during this time. Although this concerns highly protocollised therapies, differences between patient groups and hospitals cannot be excluded. Regarding **Kawamura et al., 2015**, patients were stratified as being high risk or standard risk. How patients were stratified is not clear. The study by **Eom et al., 2013,** is presented as the only prospective comparative study. Data collection for the patient group treated with melphalan in this study was performed prospectively, but whether this was also the case for the comparator-arm treated with a myelo-ablative conditioning is not clear.

For the paediatric population, two large retrospective registry studies compared conditioning regimens in AML (**Lucchini et al., 2017**) and ALL (**Kato et al., 2015**). These were assessed as the main studies. In these regimens, addition of melphalan is considered an intensification of the myeloablative conditioning regimen. All of the abovementioned uncertainties pertaining to retrospective analyses apply. The largest study performed in non-malignant haematological diseases is a retrospective non-comparative analysis in 210 patients by **Marsh et al., 2015**. Survival and chimerism were evaluated in 210 children and adolescents receiving a RIC regimen of Alemtuzumab, Fludarabine, and melphalan 140mg/m2. Nine other small prospective or retrospective single-arm trials investigated reduced intensity conditioning in patients with thalassemia, sickle cell anaemia, immune deficiencies and other rare non-malignant haematological diseases.

For the proposed additional indication (i.e. as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation in haematological diseases), the recommended dose is 140 mg/m2 or 70 mg/m2 once daily for two consecutive days in adults as well as paediatric patients. No phase I dose-finding studies are provided, but these doses are proposed as they appeared to be the most widely used in the preparative regimen for transplantation in the literature provided for efficacy and safety. It is agreed that the dose of 140mg/m2 is the most commonly used dose reported in literature, for adult as well as paediatric patients. The proposed posology is in the range of the recommended dose for the currently authorised indications.

The literature provided includes data on HSCT where the graft source is bone marrow or peripheral stem cells and donor being matched related or - unrelated. Additional submitted publications included patients treated with umbilical cord blood as a graft or haploidentical donors, the latter being increasingly used especially in the paediatric patients. These developments show the dynamics of the HSCT field and would support the notion that the choice of conditioning regimen for different clinical settings will be up to the treating physician.

In all the studies in adults melphalan was given as part of a RIC regimen, in combination with fludarabine. In the paediatric population with malignant haematological diseases, melphalan was given in different myelo-ablative regimens. In children with non-malignant haematological diseases, melphalan was given as part of a RIC regimen. This information is reflected in the therapeutic indication and the SmPC.

Adult population

In most of the studies in the dossier, only older patients or patients with co-morbidities were included in the RIC treatment group receiving a melphalan containing regimen. These patients are in clinical practice deemed ineligible for a myeloablative conditioning regimen. As described in literature RIC or non-myeloablative (NMA) conditioning provides these patients with the option of an allogeneic HSCT nevertheless. The population included in the studies is representative for the target population for RIC.

The patient population reflected in the main studies includes adult patients with ALL, AML and MDS. In the supportive studies patients with myelofibrosis and small patient groups of other malignant

haematological diseases were also included, but only 5 patients with non-malignant haematological diseases were reported. For non-malignant diseases, the risk of graft failure after allo-HSCT is considered higher after reduced intensity conditioning, due to the more competent immune-system of these patients compared to patients with malignant haematological diseases. Furthermore, in benign disease there is no need for a graft-versus-malignancy effect, and graft-versus-host-disease should be avoided (EBMT-handbook). The applicant has now proposed a restricted indication for use in adults as RIC in malignant haematological diseases only and this is agreed.

One main study and one supportive study in adults were performed in the EU; a retrospective comparison of survival outcomes of two RIC regimens from European registry data including 394 patients with AML (**Baron et al., 2015**, n=176 treated with melphalan) and a retrospective comparison of two RIC regimens in 124 patients with different haematological malignancies mainly focusing on GVHD as an endpoint (**Gomez et al., 2014**, n=51 treated with melphalan). The other included studies were performed in the US and Asia. Extrapolation of study outcomes to the European population is acceptable, as treatment protocols for haematological diseases are considered sufficiently comparable. Treatment regimens used as comparator in the controlled studies performed outside the EU contained cytostatics that are also licensed and used in Europe.

In the ESMO guidelines on ALL, AML and MDS, it is stated that RIC could be considered for older patients (age>50-55) and patients unfit for MAC because of co-morbidities. Guidance on the choice of RIC regimen is not provided in the guidelines.

The studies by **Baron et al., 2015,** and **Kawamura et al., 2017,** compare two different RIC regimens, which is considered the most appropriate comparator to assess the benefit of melphalan in the intended indication. **Eom et al., 2013,** used a MAC-regime as comparator and more importantly, MAC was used in a younger and fitter group of patients. As the other patient and disease characteristics and treatments were comparable between groups, this study is informative regarding the feasibility of RIC and outcomes in a patient group that would normally not qualify for an allo-HSCT.

Paediatric population – malignant haematological diseases

In the European trial by **Lucchini et al., 2017,** selection bias cannot be excluded, with the fittest patients receiving the most intense regimen. On the other hand, these 'real world data' show that better results can be achieved by intensifying the conditioning regimen for those patients that can tolerate this. For the trial by **Kato et al., 2015**, in which five different conditioning regimens were retrospectively compared, has several methodological shortcomings making interpretation of study outcomes and its relevance for the EU difficult.

The two main paediatric studies did not include patients from all age categories, as **Lucchini et al., 2017,** excluded patients <2 years and **Kato et al., 2015,** excluded patients >15 years. Furthermore, it is not clear how many patients were included from the different age categories and outcomes were not described separately. The applicant provided an additional literature study by **Locatelli et al., 2015,** supporting the efficacy of the BuCyMel regimen followed by allo-HSCT in children below the age of 2 years, including 39 patients between 0-1 years of age and 17 between 1-2 years.

Paediatric population – non-malignant haematological diseases

In total, 21 studies were analysed: 11 studies for MAC (965 patients) and 10 studies for melphalan-based RIC (504 patients). Paediatric patients aged 2 months to 18 years with diverse non-malignant haematological diseases were treated with melphalan-containing RIC in the different studies, including sickle cell anemia, thalassemia, immune deficiencies, congenital anemia and haemophagocytic lymphohistiocytosis. Results of graft failure, GVHD, transplant-related mortality, event-free and overall survival (mean and range of percentage event reported) were provided for the studies on melphalan-containing RIC and those on MAC.

Efficacy data and additional analyses

Adult population

All the methodological issues taken into account, the main studies in malignant haematological diseases support a clinically relevant effect of fludarabine-melphalan as RIC before allo-HSCT and there are no signs of detrimental effects that would oppose the use as RIC in allo-HSCT. In a patient group not eligible for a 'conventional' myeloablative conditioning followed by allo-HSCT, similar OS can be achieved using a melphalan containing RIC regimen (**Eom et al., 2013)**. It is recognised that a randomised controlled trial to assess outcomes of reduced intensity conditioning versus myeloablative conditioning is not feasible in the population of older patients with co-morbidities, as these patients are deemed ineligible for a MAC-HSCT.

Compared to fludarabine-busulfan, a melphalan containing RIC regimen leads to similar OS, with a lower risk of relapse (**Kawamura et al., 2017**). This could be due to a higher non-relapse mortality of fludarabine-melphalan, suggesting that fludarabine-melphalan could be more toxic than fludarabine-busulfan. On the other hand, the difference in NRM between the two RIC schedules in **Baron et al., 2015,** was not statistically significant.

It remains unclear when a melphalan containing regimen should be preferred over another reduced intensity conditioning regimen such as fludarabine-busulfan. In the main studies, outcomes of a melphalan containing RIC-regimen appear comparable to fludarabine-busulfan, taking into account that patient and doctor preferences influenced treatment choice. A randomised trial comparing a melphalan-containing RIC regimen to another RIC regimen would provide a more robust estimate of the efficacy and safety of melphalan in the intended indication. It is however acknowledged that melphalan has been used in clinical practise as part of conditioning treatment for allo-HSCT in malignant haematological diseases for at least two decades, as described in the provided literature. Therefore, the lack of a randomised study comparing both RIC regimens is considered acceptable, and the place of melphalan in the treatment landscape of reduced intensity conditioning prior to allogeneic HSCT is expected to be further established in clinical practice.

A broad indication in malignant haematological diseases is agreed upon, taking into account that the indication for allogeneic HSCT is a clinical decision based on guidelines for the separate disease entities, and in line with the broad label of Busulfan as a conditioning agent. A RIC regimen could provide older patients and patients with co-morbidity the opportunity for an allo-HSCT, and this is not considered to be different between AML and other malignant haematological diseases in adults. Therefore, extrapolation from efficacy results among these patient populations is considered acceptable.

Description of the main studies in section 5.1 has been included and is acceptable.

Paediatric population

AML-patients conditioned with BuCyMel had a lower chance of relapse than both TBICy and BuCy conditioned patients, with a relapse rate of 15% in the melphalan-containing regimen being half that of the other two regimens (Lucchini et al., 2017). OS-rate at 5 years was numerically higher in the BuCyMel group, but in multivariate analysis this difference was not statistically significant. Non-relapse mortality rate at 5 years was not different between the three groups, which is considered reassuring as intensification of the conditioning regimen has a higher risk of toxicity. The lower relapse rate and a trend towards better OS are clinically relevant effects. In European treatment protocols, the BuCyMel-regimen is considered the standard induction regimen prior to allo-HSCT. However, the study by Lucchini et al., 2017, did not include children below the age of two, and the study by Locatelli et al., 2015, did not report OS, safety data and TRM separately for this age category. Furthermore, in the

study by Sauer et al., 2019, assessing the BuCyMel regimen in children with AML, TRM correlated with age with a rate of 9% in children younger than 12 years and 31% in older children and adolescents. The applicant has proposed warnings in section 4.4 of the SmPC, which are now acceptable after minor revisions.

For ALL-patients, EFS was similar for TBI+melphalan compared to the other induction regimens (Kato et al., 2015). The reported lower relapse rate for melphalan cannot be confirmed, as no multivariate analysis was performed. No OS-data were reported. The EU reference regimen, TBI+etoposide, was not included as a comparator. This makes interpretation of study outcomes difficult and its relevance unclear.

Based on the data from literature provided by the applicant, the role of melphalan in the conditioning regimen prior to allo-HSCT in paediatric malignant haematological diseases such as MDS and JMML is recognised. Other malignant haematological diseases besides the beforementioned, are very rare and robust data is not expected. However, it can be argued that the main effect of the conditioning regimen before allo-HSCT is immunosuppression by eradication of the patient's bone marrow, to allow for successful engraftment. This effect is unlikely to be dependent on the underlying disease. Because of the rarity of these diseases the use of allo-HSCT and choice of conditioning regimen is regarded a clinical decision. Furthermore, there are other factors influencing treatment outcomes after allo-HSCT in malignant diseases, such as graft source and use of immunosuppressants after HSCT. Finally, conditioning regimens for allo-HSCT in paediatric malignant haematological diseases vary between treatment centres, and European consensus-based guidelines are updated once new data emerges.

Overall, the literature data are considered to support a broad indication in paediatric patients with malignant diseases despite their methodological limitations. Data from randomised controlled trials is not available, because of the rarity of these diseases and difficulties in performing RCTs when preferences for treatment regimens vary between centres. The limitations in terms of available data should be reflected in section 5.1 of the SmPC. Concerns remain on use in ALL and AML in children below the age of two and in children >12 years of age based on the available literature, which are addressed in section 4.4 of the SmPC.

For children with non-malignant haematological diseases, the study by Marsh et al., 2015, shows an OS at 3 years of 69% after RIC allo-HSCT (alemtuzumab/fludarabine/melphalan). Furthermore, re-transplantation due to graft loss was performed in 5% of patients, which is considered low by the authors. The majority of patients had >90% whole blood donor chimerism. However, theoretically there could be a higher risk of graft failure and occurrence of GvHD with RIC compared to MAC. The applicant has now provided data on these events for the melphalan-based RIC and for MAC in children with non-malignant haematological diseases. The incidence rates for graft failure and GvHD reported in literature are roughly in the same order of magnitude between melphalan-based RIC regimen and MAC, though this indirect comparison is associated with the same uncertainties that prevent a direct comparative study. Nevertheless, the data support the use of melphalan-based RIC in paediatric patients with non-malignant haematological diseases. It is understood that a reduced intensity conditioning regimen might make an allo-HSCT possible for paediatric patients with comorbidities and residual toxicities from earlier treatment, who would not be able to tolerate a MAC allo-HSCT. The choice for a conditioning regimen in these rare diseases is made based on doctor and patient's preference, and treatment guidelines and protocols are continuously adapted across European academic treatment centers. It is understood that a melphalan-containing RIC regimen is one of the treatment options already used for paediatric non-malignant haematological diseases in current clinical practice.

Overall, the submitted data provided support a broad indication of melphalan as part of conditioning treatment for allo-HSCT in paediatric patients with haematological diseases. As the type of conditioning regimen is different for malignant diseases (MAC) and for non-malignant diseases (RIC), this is reflected in the amended wording of the indication.

Conclusions on clinical efficacy

In adult patients with haematological malignancies not eligible for myeloablative conditioning followed by allo-HSCT, similar OS can be achieved using a melphalan containing RIC regimen. In the main studies a melphalan containing regimen appears comparable to fludarabine-busulfan as a RIC regimen. Efficacy can be considered demonstrated in this setting.

Regarding the paediatric population, AML-patients conditioned with BuCyMel had a lower chance of relapse than both TBICy and BuCy conditioned patients, with a relapse rate of 15% in the melphalan-containing regimen being half that of the other two regimens. Efficacy has been shown in this population. For other paediatric malignant haematological diseases, such as ALL and non-malignant haematological diseases, the data to support the indication in paediatric patients with malignant diseases is limited. However, based on extrapolation, a broad indication for melphalan in paediatric patients with malignant diseases, could be agreed. The limitations in terms of available data are reflected in section 5.1 of the SmPC. Furthermore, the use in children with AML below the age of 2 and above the age of 12 is described in section 4.4 of the SmPC.

For children with non-malignant diseases, it is understood that a RIC might make an allo-HSCT possible for paediatric patients with comorbidities and residual toxicities from earlier treatment, who would not be able to tolerate a MAC allo-HSCT. This is supported by data.

Overall, submitted data provided support a broad indication of melphalan as part of conditioning treatment for allo-HSCT in paediatric patients with haematological diseases. As the type of conditioning regimen is different for malignant diseases (MAC) and for non-malignant diseases (RIC), this is reflected in the amended wording of the indication.

2.4.5. Clinical safety

Patient exposure

Safety data in support of the additional indication (conditioning treatment prior to allo-SCT) is based on the literature studies submitted to support efficacy in the new indication (see Table 1). Of the 20 studies submitted, two (Kato et al., 2015 and Kudo et al. 2015) did not report data on toxicities. Therefore, safety data from 18 publications are included. Because the publications usually did not specifically report or define adverse drug reactions (ADRs), a conservative approach was taken concerning the definition of suspect ADR and any adverse events (AEs), not specifically identified with aetiologies other than melphalan, were defined as suspect ADRs to melphalan.

In addition, a search in EudraVigilance database covering the period between 2004 and 2018 was performed. A check was made to ensure that there was no duplication of cases before analyses of the data obtained from this source were undertaken. Because patient exposures are not available from a database such as EudraVigilance, the identified ADR data were analysed only by computing the proportion of all ADRs which an individual ADR represented. None of these literature cases in EudraVigilance were from the 18 studies providing safety results described above.

Patient exposure

Overall, results for 1536 patients of whom 213 were from studies reporting results only in the paediatric population (under the age of 18 years) were available. The underlying diseases for which allogeneic SCT was being undertaken were diverse and included mainly malignant haematological diseases whereas exposure in non-malignant diseases is limited. From these publications a total of 1589 suspect ADRs were reported. In the paediatric patients 275 individual ADRs were reported. About 60% of patients in adult and paediatric studies were male. For 3 studies gender was not reported. Melphalan was administered as a single dose of 100-180 mg/m^2 i.v. (mostly 140 mg/m^2) or two daily doses of 70 mg/m^2 i.v. Within the pediatric studies, most patients received a single dose of 140 mg/m^2 i.v.. In all cases, melphalan was used in combination with other cytotoxic agents. The melphalan based RIC in adults always included fludarabine. In some studies, Mel/Flu was combined with another agent and/or TBI. The conditioning regimen in paediatric studies was diverse.

In total 421 individual cases were identified in EudraVigilance which included 1702 suspect ADRs. Of these 170 cases (736 suspect ADRs) were reported from the adult population (age between 18 years and 65 years) and 153 cases (629 suspect ADRs) from the paediatric population (under the age of 18 years) and 30 cases (144 suspect ADRs) were from the elderly population (older than 65 years). Age was unspecified in 68 cases (193 suspect ADRs).

Adverse events / Serious adverse events

Safety data are presented separately for the main studies used to support efficacy and for those studies with a more extensive reporting of adverse events. Overall, predominantly serious ADRs were reported in the publications with most studies only reporting GvHD and fatal events.

Separate safety data for the paediatric population is presented in the section special populations below.

Safety data from main efficacy studies - adults

Baron et al., 2015. This retrospective EU study compared transplantation outcomes for a cohort of 394 acute AML patients given bone marrow (BM) or peripheral blood stem cell (PBSC) from human

leukocyte antigen–identical siblings after Flu-Bu (n=218) or Flu-melphalan (n=176). Melphalan dose was ranged between 130 to 150 mg/m^2. The follow up was 42 months in Flu-Mel group and 18 months in Flu-Bu group. Three graft failures happened in the Flu-Bu group and none in the Flu-Mel patients. Acute and chronic GvHD was reported for 70 (39.8%) and 84 (47.7%) patients respectively.

Kawamura et al., 2017. This retrospective study was aimed at comparing three different conditioning regimens before allo-SCT in 1,607 patients (997 males, 610 females) aged 50 years or older with AML, ALL, or MDS. Treatment regimens were as follows: Flu with melphalan (140 mg/m^2 i.v.; Flu-Mel; n=423), Flu with intermediate doses of Bu (6.4 mg/kg i.v.; Flu-Bu, n=463) or Flu with higher doses of Bu (12.8 mg/kg i.v.; Flu-Bu, n=721). Acute and chronic GvHD was reported for 167 (39.5%) and 191 (54.2%) patients respectively.

Eom et al., 2013. A prospective study was conducted to compare long-term outcomes of 60 consecutive RIC transplants (fludarabine plus melphalan) with 120 MAC transplants (total body irradiation plus cyclophosphamide) for adult high-risk ALL in first or second complete remission. RIC consisted of melphalan (140 mg/m2) and fludarabine (Flu), n=60; 32M, 28F), both administered i.v., whereas MAC conditioning consisted of TBI + cyclophosphamide (n=120; 69M, 51F). Median follow-up was 67 months.

In RIC transplants, 29 patients (48.3%) developed acute GvHD. The cumulative incidence of acute GvHD at 100 days was not different between the two groups. Of the 56 RIC transplants who survived for at least 100 days with sustained engraftment after transplantation, 34 developed chronic GvHD (56.7%). The cumulative incidence of chronic GvHD at 5 years was not different between the two groups. Eleven patients receiving RIC regimen died of causes other than leukemic relapse. The primary causes of NRM in this group were as follows: infections (n=3; 5.0%), chronic GvHD (n=4; 6.7%), acute GvHD (n=3; 5.0%), and organ failure (n=1; 1.7%).

Studies reporting most extensive safety data adult and paediatric population

The main efficacy studies limited the safety information to GvHD and causes of death. The following studies presented most extensive information on additional toxicities or reported ADRs at a relatively high rate.

De Lima et al., 2004. This retrospective study was performed to determine in adult patients with AML and MDS a reduced-intensity conditioning regimen would result in lower relapse rates than non-ablative regimen. The non-ablative regimen consisted of fludarabine, cytarabine (araC), and idarubicin (FAI) while the reduced intensity conditioning regimen included fludarabine in combination with melphalan 140 or 180 mg/m^2 (FM140 or FM180). Ninety-four patients with AML or MDS underwent an allogeneic progenitor cell transplantation from an HLA-compatible donor were enrolled: 32 in FAI group vs 62 in FM group.

The following toxicities have been reported for the FM group: diarrhoea (N=29; 46.8%), nausea (N=47; 75.8%), pancreatitis (N=1; 1.6%), vomiting (N=47; 75.8%), mucosal inflammation (N=28; 45.2%), blood bilirubin increased (N=11; 17.7%), blood creatinine increased (N=32; 51.6%), ejection fraction decreased (N=6; 3.2%), transaminases increased (N=45; 72.6%), stupor (N=1; 1.6%), cystitis haemorrhagic (N=3; 4.8%), pneumonitis (N=1; 1.6%), pulmonary embolism (N=1; 1.6%) and pulmonary haemorrhage (N=7; 11.3%). Acute and chronic GvHD has been reported in 31 (50.0%) and 24 (38.7%) patients respectively. Adverse events leading to death were multi organ failure (N=1; 1.6%), GvHD (N=16; 25.8%), ejection fraction decreased (N=2; 3.2%), CNS haemorrhage (N=1; 1.6%), pulmonary haemorrhage (N=1; 1.6%) and pulmonary oedema (N=1; 1.6%).

Kirschbaum et al., 2012. A prospective, phase I dose-response without placebo study was conducted to determine the recommended phase II dose of clofarabine plus melphalan as a conditioning regimen for allo-SCT in adult patients with AML. Patients treated were 16 adults (median age, 63 years, range

30-66; 7 males, 9 females) receiving clofarabine plus melphalan (dose levels 1 and 2, 100 mg/m^2; dose level 3, 140 mg/m^2). Median follow-up period was 17 months. Safety objectives of this study were to determine the maximum tolerated dose and evaluate the toxicities of the combination of clofarabine plus high-dose melphalan as a conditioning regimen for allogeneic transplantation. Two types of toxicities were considered: dose-limiting toxicity (DLT) and graft failure, or graft rejection. Toxicities observed included cardiotoxicity (n=1; 6.3%), gastrointestinal toxicity (n=8; 50.0%), stomatitis (n=9; 56.3%), hepatotoxicity (n=15; 93.8%), acute GvHD (n=5; 31.3%), chronic GvHD (n=7; 43.8%), cerebrovascular accident (n=1; 6.3%), headache (n=2; 12.5%), nephropathy toxic (n=4; 25.0%), urinary bladder toxicity (n=2; 12.5%), perineal pain (n=1; 6.3%), pulmonary toxicity (n=2; 12.5%) and hypertension (n=2; 12.5%). Because the objective of engraftment had been satisfactorily achieved at the first 2 dose levels, authors decided to not accrue any more patients to dose level 3 and to expand dose level 2.

Other ADRs frequently reported in individual studies in adults were mucosal toxicity (n=13; 32.5% by Imataki et al., 2009), and infections (n=24; 47.1% by Gomez et al., 2014).

Yabe et al., 2015. This report describes the outcome of 30 paediatric patients with juvenile myelomonocytic leukemia (JMML) receiving HSCT with busulfan, fludarabine, and melphalan. Patient data were retrospectively collected. The conditioning regimen consisted of busulfan, fludarabine an melphalan (L-PAM) (90 mg/m^2 once daily for 2 days, total dose 180 mg/m^2). The regimen-related toxicity was scored according to the Bearman scale.
The most common organ toxicities were stomatitis (n=13; 43.3%; grades I–II, 12 patients; grade III, 1 patient) and gastrointestinal mucositis (grades I–II, n=7; 23.3%). Pulmonary, cardiac, renal, and bladder toxicities were uncommon and not serious adverse event (2 (6.7%), 1 (3.3%), 1 (3.3%), and 2 (6.7%) patients, respectively). Other toxicities were Epstein-Barr virus infection (N=1; 3.3%), post-transplant lymphoproliferative disorder (N=1; 3.3%), glomerulonephritis membranous (N=1; 3.3%), cystitis haemorrhagic (N=1; 3.3%), idiopathic interstitial pneumonia (N=1; 3.3%), bronchiolitis obliterans (N=2; 6.7%) and protein-losing gastroenteropathy (N=1; 3.3%). Acute and chronic GvHD were reported for 25 (83.3%) and 10 (33.3%) patients respectively.

Shenoy et al., 2018*.* Thalassemia Clinical Research Network and the Pediatric Blood and Marrow Transplant Consortium conducted a prospective, multicenter, phase II clinical trial of unrelated donor (URD) HSCT in children with transfusion-dependent thalassemia (TDT). The purpose of the trial was to test that RIC regimen was sufficient to establish donor hematopoiesis after URD bone marrow (BM) or umbilical cord blood (UCB) transplantation for TDT. All patients received hydroxyurea, alemtuzumab, fludarabine (30 mg/m^2/day i.v.), thiotepa and melphalan (140 mg/m^2 i.v.). The study accrued patients from 14 centers nationwide attended to the study enrolling 33 patients (age range: 1- 17 years): 17 received a MUD allo-SCT and the remain an umbilical cord blood transplant.
Two patients developed mild to moderate hepatic sinusoidal obstruction syndrome after UCBT (6.1%). Cytomegalovirus (CMV) reactivation in 13 of 16 UCB and 9 of 17 BM recipients (n=22; 66.7%). Adenovirus (n = 9; 27.3%) and Epstein-Barr virus (n = 9; 27.3%) viremia were also detected in the blood. Acute and chronic GvHD was documented for 11 (33.3%) and 14 (42.4%) patients respectively.

Overall ADRs reported in 18 publications

A summary of all ADRs reported in both adults and paediatric studies submitted in the MAA is presented in the Table below. Of note, the reported frequency is based on the total number of patients exposed to melphalan in the 18 publications but does not represent the actual incidence in individual studies as no systematic reporting of ADRs took place over the studies.

Most commonly reported ADRs were in the system organ class (SOC) immune system disorders of which all acute (n=611) or chronic (n=555) GvHD. Thereafter, events in the SOC gastrointestinal

disorders were the second most commonly reported ADRs, mainly nausea (n=47), vomiting (n=47) and diarrhea (n=29). ADRs in the SOC Investigations were mainly indicative of hepatic pathology (transaminases increased, n=45 and blood bilirubin increased, n=11) and ADRs reported in the SOC Hepatobiliary disorders included veno-occlusive liver disease (VOD, n=4) and hepatotoxicity without further details (n=15). Of the reported infections, over half were viral infections (n=41) whereas the rest (n=22) were reported without further details. ADRS in the SOC General disorders and administration site conditions included mucosal inflammation (n=30) and mucosal toxicity (n=13). A total of 16 ADRs were reported in the SOC Respiratory, thoracic and mediastinal disorders of which 6 ADRs (pulmonary toxicity, idiopathic interstitial pneumonia, pneumonitis) were indicative of inflammatory pulmonary disease.

Table 17 Summary table of adverse drug reactions for melphalan from relevant published literature in the allogenic indication

MedDRA System Organ Class (SOC) MedDRA Preferred Term (PT)	Total No. Patients Exposed to Melphalan N=1536	Frequency of ADRs [1] %	Percentage of ADRs[1] N=1589 %
Cardiac disorders			
Cardiotoxicity	2	0,1	0,1
Gastrointestinal disorders			
Nausea	47	3,1	3,0
Vomiting	47	3,1	3,0
Diarrhoea	29	1,9	1,8
Stomatitis	22	1,4	1,4
Gastrointestinal toxicity	8	0,5	0,5
Gastrointestinal mucosal inflammation	7	0,5	0,4
Pancreatitis	1	0,1	0,1
Protein-losing gastroenteropathy	1	0,1	0,1
General disorders and administration site conditions			
Mucosal inflammation	30	2,0	1,9
Mucosal toxicity	13	0,8	0,8
Hepatobiliary disorders			
Hepatotoxicity	15	1,0	0,9
Venoocclusive liver disease	4	0,3	0,3
Immune system disorders			
Acute graft versus host disease	611	39,8	38,5
Chronic graft versus host disease	555	36,1	34,9
Infections and infestations			
Infection	24	1,6	1,5
Cytomegalovirus infection	22	1,4	1,4
Epstein-Barr virus infection	10	0,7	0,6
Adenovirus infection	9	0,6	0,6
Investigations			
Transaminases increased	45	2,9	2,8
Blood creatinine increased	32	2,1	2,0
Blood bilirubin increased	11	0,7	0,7
Ejection fraction decreased	6	0,4	0,4
Neoplans benign, malignant and unspecified (incl cysts and polyps)			
Post transplant lymphoproliferative disorder	1	0,1	0,1
Nervous system disorders			
Headache	2	0,1	0,1
Cerebrovascular accident	1	0,1	0,1
Stupor	1	0,1	0,1
Renal and urinary disorders			
Cystitis haemorrhagic	4	0,3	0,3
Nephropathy toxic	5	0,3	0,3
Urinary bladder toxicity	4	0,3	0,3
Glomerulonephritis membranous	1	0,1	0,1
Reproductive system and breast disorders			
Perineal pain	1	0,1	0,1
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage	7	0,5	0,4
Pulmonary toxicity	4	0,3	0,3
Obliterative bronchiolitis	2	0,1	0,1
Idiopathic interstitial pneumonia	1	0,1	0,1
Pneumonitis	1	0,1	0,1
Pulmonary embolism	1	0,1	0,1
Vascular disorders			
Hypertension	2	0,1	0,1
Total Number Adverse Drug Reactions	**1589**		
Total Number of Patients Exposed to Melphalan	**1536**		

Note: [1] Within each MedDRA SOC, MedDRA PTs are displayed in order of descending frequency.

EudraVigilance

Most commonly reported individual ADR (> 5% of all ADRs reported) from the EudraVigilance output are shown in Table 18. Most commonly reported ADRs are various forms of GvHD and infections. Of note, no information is available on the number of patients exposed so no data on the actual incidence of ADRs is available.

Table 18 Most frequent (>5%) adverse drug reactions retrieved in EudraVigilance

MedDRA PT [1]	N=421	Percentage of all ADRs%
Off label use	76	18,1
Cytomegalovirus infection	48	11,4
Acute graft versus host disease	46	10,9
Graft versus host disease	44	10,5
Diarrhoea	28	6,7
Pyrexia	27	6,4
Sepsis	25	5,9
Febrile neutropenia	25	5,9
Stomatitis	24	5,7
Multiple organ dysfunction syndrome	24	5,7
Acute graft versus host disease in skin	24	5,7
Adenovirus infection	22	5,2

Note: [1] for source table please refer to Appendix Table 2.7.4.7-3.

Deaths

There were 223 ADRs associated with deaths reported in the publications. However, for some individual patients there were often multiple pathologies and clear-cut causes of death were often not reported. For some individual patients multiple concomitant causes leading to death have been reported. Therefore, it was not possible for any individual ADR to ascribe an exact outcome. An overall summary of ADRs leading to death by MedDRA System Organ Class and Preferred Term is shown in Table 19. Frequencies are calculated based on the total number of ADRs reported and do not represent actual incidences reported within the individual studies. The most frequent ADRs leading to death were GvHD (36 ADRs, 2.3%) and infection (35 ADRs, 2.3%). The other ADRs leading to death were reported with a percentage lower than 2.0%.

Table 19 Summary table of transplant related deaths in patients exposed to melphalan from relevant published literature in allo-HSCT.

MedDRA System Organ Class (SOC) MedDRA Preferred Term (PT)	Total No. Patients Exposed to Melphalan N=1536	Frequency of ADRs % (1) (2)
Blood and lymphatic system disorders		
Haemolytic uraemic syndrome	3	0,2
Microangiopathic haemolytic anaemia	2	0,1
Thrombotic microangiopathy	2	0,1
Thrombotic thrombocytopenic purpura	1	0,1
Bone marrow failure	1	0,1
Cardiac disorders		
Cardiac failure congestive	2	0,1
Cardiac failure	1	0,1
Cardiac arrest	1	0,1
Cardiomyopathy	1	0,1
Myocardial Infarction	1	0,1
Myocarditis	1	0,1
Gastrointestinal disorders		
Gastrointestinal perforation	1	0,1
General disorders and administration site conditions		
Multiple organ dysfunction syndrome	20	1,3
Organ failure	4	0,3
Sudden cardiac death	2	0,1
Hepatobiliary disorders		
Venoocclusive liver disease	1	0,1
Immune system disorders		
Graft versus host disease	36	2,3
Acute graft versus host disease	12	0,8
Chronic graft versus host disease	12	0,8
Anaphylactic reaction	1	0,1
Infections and infestations		
Infection	35	2,3
Sepsis	10	0,7
Pseudomonas infection	8	0,5
Enterococcal infection	4	0,3
Fungal infection	4	0,3
Adenovirus infection	3	0,2
Pneumonia	3	0,2
Pneumonia cytomegaloviral	3	0,2
Aspergillus infection	2	0,1
Cytomegalovirus infection	2	0,1

Table 18- continued. Summary table of transplant related deaths in patients exposed to melphalan from relevant published literature in allo-HSCT.

MedDRA System Organ Class (SOC) MedDRA Preferred Term (PT)	Total No. Patients Exposed to Melphalan N=1536	Frequency of ADRs % [1] [2]
Klebsiella infection	2	0,1
Pneumonia adenoviral	2	0,1
Scedosporium infection	2	0,1
Acinetobacter infection	1	0,1
Coccidioidomycosis	1	0,1
Metapneumovirus infection	1	0,1
Myelitis	1	0,1
Pneumocystis jirovecii infection	1	0,1
Staphylococcal infection	1	0,1
Stenotrophomonas infection	1	0,1
Injury, poisoning and procedural complications		
Vascular injury	2	0,1
Investigations		
Ejection fraction decreased	2	0,1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Post transplant lymphoproliferative disorder	1	0,1
Second primary malignancy	1	0,1
Nervous system disorders		
Central nervous system haemorrhage	1	0,1
Dementia	1	0,1
Encephalopathy	1	0,1
Psychiatric disorders		
Completed suicide	1	0,1
Eating disorder	1	0,1
Respiratory, thoracic and mediastinal disorders		
Pulmonary haemorrhage	3	0,2
Idiopathic interstitial pneumonia	1	0,1
Obliterative bronchiolitis	1	0,1
Pulmonary alveolar haemorrhage	1	0,1
Pulmonary oedema	1	0,1
Vascular disorders		
Haemorrhage	11	0,7
Venoocclusive disease	2	0,1

Note: [1] Within each MedDRA SOC, MedDRA PTs are displayed in order of descending frequency;

[2] Transplant related deaths could be not necessarily attributable to melphalan.

EudraVigilance

For the EudraVigilance output seriousness death was reported most commonly for infections (20.9% of all fatal ADRs were within the infections SOC) of which cytomegalovirus and sepsis (not further specified) each represented 3.1% of fatalities. Seriousness death for GvHD in various forms represented nearly 10% of fatalities. Respiratory failure was reported as fatal in 3.1% of cases. Various haematological ADRs as represented by ADRs within the blood and lymphatic system disorders SOC represented 5.2% of fatal ADRs. ADRs of potentially inflammatory pulmonary disease were reported as fatal in 12 cases (interstitial lung disease 5 ADRs, idiopathic pneumonia 4 ADRs, pneumonitis 3 ADRs, pulmonary fibrosis 1 ADR). In hepatobiliary disorders there were three (3) ADRs of veno-occlusive disease with fatal outcome representing 0.7% of all fatal ADRs.

Other significant adverse events

Graft versus Host Disease (GvHD), pulmonary toxicity and veno-occlusive disease of the liver (VOD) are known important complications of allogenic HSCT and were therefore chosen for further review.

Graft versus Host Disease (GvHD)

Various forms of GvHD were the most commonly reported ADR in the literature, representing over 75% of all reported ADRs in the total population, and was the second most commonly reported cause of death. In the paediatric population similar frequencies of GvHD ADRs were reported. From EudraVigilance data various forms of GvHD represented nearly 30% of ADR reports and approximately 12% of all fatal ADR reports. Similar proportions of ADRs of GvHD were reported in the paediatric population, although the proportions of ADRs of GvHD in the elderly populations were slightly lower. GvHD was second only to infection as the most commonly reported ADR with outcome fatal as reported in the EudraVigilance data. GvHD is not added to the SmPC or risk management plan (RMP) of melphalan by the applicant as it is considered a result of the procedure itself rather than as a result of effects of medicines used for myeloablation prior to transplantation.

Pulmonary toxicity

Inflammatory and subsequent fibrotic effects of cytotoxic medicines such as melphalan are well-established. The data retrieved from use of melphalan as conditioning in allo-SCT demonstrated that ADRs indicative of pulmonary toxicity were reported in this population. There were three ADRs indicative of pulmonary toxicity (one each of pulmonary toxicity, idiopathic interstitial pneumonia and pneumonitis) were reported in the literature. Two of these events (pulmonary toxicity and idiopathic interstitial pneumonia) were reported from the paediatric population. These latter events were reported as fatal.

From EudraVigilance 21 cases of pulmonary toxicity. There were 8 reports of interstitial lung disease representing 1.9% of all reported ADRs. There were 5 cases each of idiopathic pneumonia syndrome and pneumonitis (1.2% of all ADRs), and 1 case ADR each of pulmonary fibrosis, pulmonary toxicity, diffuse alveolar damage (0.25% of all ADRs). Of these ADRs reports, 14 were reported with fatal outcome. Of these reports 8 were in the paediatric population. In this population there were 3 reports of interstitial lung disease representing nearly 2.0%, 2 reports of each of idiopathic pneumonia syndrome and pneumonitis (1.3% of ADRs), and 1 case ADR of diffuse alveolar damage (0.7% of all ADRs). Pulmonary toxicities are already mention in section 4.8 of the SmPC of the reference product. Given its often fatal outcome, it is also added as an important identified risk in the RMP.

Veno-occlusive disease of the liver (VOD)

Veno-occlusive disease of the liver (VOD) is a well-known and often early reaction to conditioning using melphalan in allo-SCT. From the literature there were 4 (0.3% of patients) reports of VOD. Of these 2 (0.7% of patients) were in the paediatric population. One report in the adult population and 1 in the paediatric population had fatal outcomes. From ADRs in EudraVigilance 10 were reports of VOD (2.4% of all ADRs). Four of these were from paediatric patients (2.6% of all ADRs). Three of the 10 ADRs of VOD were reported as having fatal outcome. VOD is added to the SmPC and as an important identified risk in the RMP.

Laboratory findings

Laboratory results are only available from the study by De Lima *et al.,* 2004. Blood bilirubin increased (N=11; 17.7%), blood creatinine increased (N=32; 51.6%), ejection fraction decreased (N=6; 3.2%), and transaminases increased (N=45; 72.6%).

Supportive data

An additional literature search was performed in the allo-HSCT setting focusing on safety reporting. A total of 59 publications containing safety reports were identified. Safety data from these publications were combined, independent of diseases and/or conditioning regimens. Overall, 1,606 patients were exposed to melphalan within these publications. Age range was provided for 1,472 patients: 1,058 adults (18-65 years), 64 elderly (>65 years) and 350 paediatric (<18 years). Of the 1,606 patients exposed to melphalan, 586 patients have been reported with at least a safety report (440 adults, 27 elderly and 119 paediatric patients). A minority of the safety reports had an associated severity/grade reported.

The most frequent SOCs were Immune system disorders (23.5%, 15.6% and 12.3% in the adult, elderly and paediatric populations respectively) and Infections and infestations (11.5%, 14.1% and 12.6% in the adult, elderly and paediatric populations respectively). As expected, within the SOC Immune system disorders, different forms of acute and chronic graft versus host disease (GvHD) were reported as the most frequent complications. With few exceptions, the other MedDRA SOCs were quite balanced between the different populations. Safety reports of blood and lymphatic system disorders were more frequent in the adult population (7.8%) than in the elderly (3.1%) and paediatric (4.0%) populations. Cardiac disorders and General disorders and administration site conditions were noted to be most frequent in the elderly population (1.6% and 12.5% respectively) than in the adults (0.7% and 7.0% respectively) and paediatric population (0.3% and 2.9% respectively). Most of the ADRs under the MedDRA SOC General disorders and administration site conditions were "deaths" of unknown cause. Pyrexia and mucosal inflammation were the other most frequent reported ADRs.

Safety in special populations

Safety results are presented for paediatric patients and elderly. Safety results in other special populations, such as populations defined by gender, race, renal function and hepatic function have not been presented.

Safety in paediatric patients

Safety data from four studies were available that included paediatric patients only in an overall range of 0.6-17.9 years. Patients included received melphalan 140 mg/m^2 in combination with Flu/thiotepa/alemtuzumab to treat thalassemia (n=33), melphalan in combination with flu and alemtuzumab to treat severe aplastic anemia (n=17), melphalan in combination with Bu/CY to treat AML (n=133), or melphalan in combination with flu to treat juvenile myeolomocytis leukemia.

A summary of ADRS reported is shown in Table 20 and a summary of causes of death is shown in Table 21.

The most commonly reported ADRs in these studies were in the SOC immune system disorders and all were various forms of GvHD (acute GvHD n=122, chronic GvHD n=77). Within the SOC infections reported ADRs included cytomegalovirus infection (n=22), Epstein barr virus infection (n=10) and adenovirus infection (n=9). The SOC infections represented 14.9% of ADRs in the paediatric population, which is a higher proportion than was seen in the total population (4.1%). ADRs in the gastrointestinal SOC included stomatitis (n=13) and gastrointestinal mucosal inflammation (n=7). ADRs in the SOC gastrointestinal disorders were reported less commonly in the paediatric population (7.6%) vs total population (10.2%). Events in the SOC respiratory disorders were reported in 1.8% of paediatric patients.

Table 20 Summary table of adverse drug reaction for melphalan from relevant published literature in the paediatric population in the allogenic indication.

MedDRA System Organ Class (SOC) MedDRA Preferred Term (PT)	Total No. Patients Exposed to Melphalan N=213 [1]	Frequency of ADRs[2] %	Percentage of ADRs[2] N=275%
Cardiac disorders			
Cardiotoxicity	1	0,5	0,4
Gastrointestinal disorders			
Stomatitis	13	6,1	4,7
Gastrointestinal mucosal inflammation	7	3,3	2,5
Protein-losing gastroenteropathy	1	0,5	0,4
Hepatobiliary disorders			
Venoocclusive liver disease	2	0,9	0,7
Immune system disorders			
Acute graft versus host disease	122	57,3	44,4
Chronic graft versus host disease	77	36,2	28,0
Infections and infestations			
Cytomegalovirus infection	22	10,3	8,0
Epstein-Barr virus infection	10	4,7	3,6
Adenovirus infection	9	4,2	3,3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Post transplant lymphoproliferative disorder	1	0,5	0,4
Renal and urinary disorders			
Urinary bladder toxicity	2	0,9	0,7
Nephropathy toxic	1	0,5	0,4
Cystitis haemorrhagic	1	0,5	0,4
Glomerulonephritis membranous	1	0,5	0,4
Respiratory, thoracic and mediastinal disorders			
Pulmonary toxicity	2	0,9	0,7
Obliterative bronchiolitis	2	0,9	0,7
Idiopathic interstitial pneumonia	1	0,5	0,4
Total Number Adverse Drug Reactions	**275**		
Total Number of Paediatric Patients Exposed to Melphalan	**213**		

Note: [1] cumulative number of pediatric patients from studies conducted only in pediatric population (Shenoy *et al*, 2018; Ngwube *et al*, 2015; Lucchini *et al*, 2017; Yabe *et al*, 2015).

[2] Within each MedDRA SOC, MedDRA PTs are displayed in order of descending frequency

Infections and GvHD were the most common cause of the deaths reported (19).

Table 21 Summary table of transplant related deaths in paediatric patients exposed to melphalan from relevant published literature in the allogenic setting.

MedDRA System Organ Class (SOC) MedDRA Preferred Term (PT)	Total No. Patients Exposed to Melphalan N=213	Frequency of ADRs %
Gastrointestinal disorders		
Gastrointestinal perforation	1	0,5
General disorders and administration site conditions		
Multiple organ dysfunction syndrome	2	0,9
Hepatobiliary disorders		
Venoocclusive liver disease	1	0,5
Immune system disorders		
Graft versus host disease	8	3,8
Infections and infestations		
Infection	10	4,7
Pneumonia cytomegaloviral	2	0,9
Pneumonia adenoviral	2	0,9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Post transplant lymphoproliferative disorder	1	0,5
Respiratory, thoracic and mediastinal disorders		
Pulmonary haemorrhage	2	0,9
Idiopathic interstitial pneumonia	1	0,5
Obliterative bronchiolitis	1	0,5
Pulmonary alveolar haemorrhage	1	0,5
Vascular disorders		
Haemorrhage	1	0,5
Venoocclusive disease	1	0,5

The additional literature search provided cumulative safety data in the paediatric population and assessment was performed according to the paediatric age groups. Of the paediatric population, 29 patients were infants (28 days-23 months), 63 children (2 ≤age <12 years), 12 adolescents (12 ≤age <18 years). For 246 paediatric patients the age group was not specified.

Out of 29 infants exposed to at least one dose of melphalan, 17 (58.6%) had at least a safety report, cumulatively including a total number of 31 ADRs. Out of 63 children exposed to at least one dose of melphalan, 48 (76.2%) had at least a safety report, cumulatively including a total number of 139 ADRs. Out of 12 adolescents exposed to at least one dose of melphalan, 8 (66.7%) had at least a safety report, cumulatively including a total number of 18 ADRs.

In the paediatric population the most frequent SOCs were Immune system disorders (12.3%) and Infections and infestations (12.6%). Within the SOC Immune system disorders, acute GvHD with unspecified site of occurrence was 3.7%, chronic GvHD 1.7%. Safety reports of Gastrointestinal disorders were reported with a higher frequency in the paediatric population (8.9%) than in the adults (0.8%). Gastrointestinal disorders were more frequent in children (12.7%) than in the adolescents (8.3%). Respiratory thoracic and mediastinal disorders were reported with a higher frequency in the paediatric population (4.3%) than in the adult (1.5%) and elderly (1.6%) populations. Respiratory failure, interstitial lung disease and acute respiratory distress syndrome were the most frequent ADRs within this SOC for the paediatric population: 1.4%, 1.1% and 0.9% respectively. In particular, safety reports noting respiratory complications were higher for infants (24.1%) than for children (6.3%).

EudraVigilance

Within EudraVigilance, 153 individual cases were identified from the paediatric population (under the age of 18 years) with a total of 629 suspect ADRs. Most ADRs were reported in the SOC Infections and infestations (n=89), followed by the SOC immune system disorders (n=65), SOC injury, poisoning and procedural complications (n=45), SOC General disorders and administration site conditions (n=30), SOC respiratory thoracic and mediastinal disorders (n=23), and SOC investigations (n=22). Twenty ADRs were reported in the SOC Gastrointestinal disorders and 18 in the SOC Blood and lymphatic disorder. There were some small differences when compared to the adult population. The proportion of ADRs within the infections SOC was slightly higher in the paediatric population (21.8%) than in the adult population (16.9%). ADRs in the blood and lymphatic system disorders represented as a proportion of ADRs reported at least once in different SOCs were lower in the paediatric population (4.4%) than in the adult population (7.7%). Review of individual ADRs did not identify any ADRs which appeared to be reported at substantially different frequencies between the adult and paediatric population.

Safety in elderly

EudraVigilance data was also used to compare the ADRS by SOC for the adult and elderly (>65 years) population. There were only minor differences between the adult and older populations. Elderly patients had a slightly higher proportion of reports in the SOCs (8.2%) gastrointestinal disorders than adult patients (5.8%), in SOC infection (adult 16.9%, elderly 19.4%), and in the SOC hepatobiliary disorders (adults 2.9%, elderly 5.1%). There was a lower proportion of ADRs in the SOC immune disorders for elderly patients than for adult population (elderly 7.1%, adults 12.7%). Review of individual ADRs (data not shown in the report) did not identify any ADRs which appeared to be reported at substantially different frequencies between the adult and elderly population.

Safety related to drug-drug interactions and other interactions

No data were available from the literature or EudraVigilance outputs.

Discontinuation due to AES

No data were available from the literature or EudraVigilance outputs. Melphalan is either administered as a single i.v. injection or on two consecutive days and patients will in general receive the total dose in the setting of conditioning regimen for allogenic transplantation.

Post marketing experience

The hybrid generic marketing authorisation application for melphalan includes a new strength of melphalan 200 mg not included in any other EU melphalan marketing approvals and in addition to the usual 50 mg strength of the product. The possibility of medication errors and unintended overdose has been evaluated and is considered unlikely as for each strength a specific identification colour has been selected for external (carton box) and inner labels, the final packs will be different also in terms of dimensions for the 50 mg and 200 mg doses and the product is administered only under close supervision in hospital environment.

2.4.6. Discussion on clinical aspects

To support the safety profile in the newly proposed indication, the applicant summarised safety data from 18 literature publications in the period of 2005 to 2018 which were also discussed for efficacy. Overall, safety data were available from 1,536 patients of whom 213 were from studies reporting results only in the paediatric population. The underlying diseases for which allogeneic SCT was being undertaken were diverse and included mainly malignant haematological diseases whereas exposure in non-malignant haematological diseases is limited. The latter is acceptable from a safety point of view as the dose administered is independent of the underlying disease and the safety profile can be excepted to be comparable. Melphalan was administered as a single dose of 100-180 mg/m^2 i.v. (mostly 140 mg/m^2) or two daily doses of 70 mg/m^2 iv in combination with other cytotoxic agents. The proposed dosing regimen is already part of the currently licensed dosing regimen for adults for the treatment of various malignancies and for autologous HSCT and in childhood neuroblastoma together with autologous HSCT.

The safety data available in the publications focused on serious ADRs in the allo-HSCT setting, mainly GvHD and NRM. Therefore, information is available on major toxicities impacting the BR in the new indication. Few studies reported on other toxicities, mostly gastrointestinal events, mucosal inflammation and hepatotoxicity. A major shortcoming of the safety data provided is the lack of a systematic reporting of all AEs as well as a specific definition of ADRs within the publications. This results in a considerable underreporting of the safety profile of melphalan in the newly proposed indication which may affect both serious and more likely none-serious adverse events. The latter is not considered to impact the BR given the seriousness of the underlying condition. The data do not allow calculation of frequencies of occurrence of ADRs and a distribution of ADRs by severity grade is lacking. Further, the safety profile of melphalan cannot be disentangled from that of other agents in the combination. Given the long-standing use of melphalan in general and its wide-spread use as a conditioning regimen in HSCT, the risk of missing important serious ADRs may be considered low, but remains unknown. The applicant complemented the safety data with a search in the EudraVigilance for ADRs in the allogenic SCT setting for the period 2004-2018. A total of 421 individual cases were identified in EudraVigilance of which 153 were from the paediatric population whereas age was unspecified in 68 cases. However, this database has inherent limitations as it depends on reporting of ADRs by individuals. Nevertheless, it can be informative for identifying new signals. To support the safety profile, the applicant performed an additional literature search identifying 59 publications containing safety reports. Data from these publications in general support the safety profile based on the initial publications. However, the same limitations as identified above apply to these publications.

Despite the identified limitations, it should be taken into account that melphalan has been licensed over 50 years in the EU. Therefore, the safety profile of melphalan is considered well-known when used alone or in combination with other cytotoxic agents and/or extensive TBI. The safety profile is characterised by its myelosuppressive action (e.g. leukopenia, thrombocytopenia, anemia, and resulting infections), gastrointestinal side effects and hepatotoxicity. Rare cases of interstitial pneumonitis and fibrosis have been reported. It is reasonable to assume that the safety profile in the new setting as a conditioning regimen for allo-SCT is comparable to its use in the licensed indications. Therefore, treating physicians will be well aware of the toxicities associated with melphalan in the newly applied indication/setting whereas treatment is performed in specialised centres. Supported by the additional literature review, the safety profile in the allogenic setting is considered sufficiently characterised based on available data in the public domain. The presentation of adverse events in the SmPC needs, however, to be revised to provide concise information to the treating physicians.

Taking into account the abovementioned limitations, acute as well as chronic GvHD were in general reported in about 30-50% of patients. Although it is associated with the procedure and may not be

related directly to treatment with melphalan, GvHD is included in the SmPC as it is a major cause of morbidity and mortality related to the reduced intensity conditioning regimen and transplant process, in line with other conditioning agents. It is also be added to the important identified risk in the RMP. Another serious ADR reported was veno-occlusive disease, a well-known complication of conditioning regimens with potential fatal outcome. Inclusion in the SmPC section 4.8 and as important identified risk in the RMP is supported. In addition, a warning is added to section 4.4. Further, ADRs indicative of pulmonary toxicity were reported in the studies and in EudraVigilance database as well. Inflammatory and subsequent fibrotic effects of cytotoxic medicines such as melphalan are well-established and already included in the SmPC.

Other adverse events reported frequently (>25%) in individual studies included gastrointestinal toxicities (diarrhea, nausea, vomiting, stomatitis), mucosal toxicity/ inflammation, hepatotoxicity and infections. Also, blood creatinine increased and transaminases increased were reported frequently. These ADRs are in general in line with the known safety profile of melphalan and mostly reported in the SmPC of the reference product, except for mucosal inflammation and blood creatinine increased. These are added to section 4.8. Further, infections are commonly occurring ADRs and also a frequent cause of death and included in the SmPC as well. Myelo-suppression and immuno-suppression were not reported as ADRs in the studies, most likely because these are considered the desired therapeutic effects of the conditioning regimen. However, these are already included in the SmPC. The most frequent ADRs leading to death reported in the publications were GvHD and infection which are as expected for the allo-SCT setting and there appeared to be no new safety signals.

Elderly were included in the studies as these are especially candidates for RIC given the lower toxicity of these regimens compared to myeloablative regimens. Elderly patients may have more comorbidities which might impact the frequency of ADRs. This may explain the higher frequencies of AEs in the SOC Cardiac disorders and General disorders and administration site conditions reported for elderly in the supportive literature review. Further, elderly may have reduced renal clearance requiring close monitoring; the latter is already part of the SmPC. Based on EudraVigilance data, gastrointestinal and hepatobiliary ADRs appear more common in elderly than for the total adult population. However, limited information is available on severity and duration of these events compared to the total population and the clinical relevance is unknown.

Most commonly reported serious ADRs in the paediatric population were GvHD (both acute and chronic), infections and stomatitis. Infections and GvHD were also most commonly reported as cause of death. There appear no new safety signals in the pediatric data compared to the adult population, although a separate presentation of safety data in adults only is lacking. Supportive safety data revealed that respiratory complications were more frequently reported in the paediatric population and more frequently below 2 years of age compared to the age of 2 to <12 yrs. In the absence of a control group and prospective studies, these data are difficult to interpret. As these data are of importance for the treating physician, it is proposed to include this information in section 4.8 instead of section 4.4. This also holds true for gastrointestinal complications.

In general, type of ADRs and causes of death reported in the EudraVigilance database were in line with those reported in the literature. ADRs in the SOC infections and infestations (mostly cytomegalovirus infection) and SOC immune system disorders (mostly GvHD) were reported most frequently which were also among the most commonly reported causes of death. Identification of a different characterisation of the known ADRs (e.g. more severe etc.) related to the applied indication was not possible as this information was not recorded. Most ADRs in Eudravigilance not reported in the literature were single cases and a causality assessment was not provided. Paediatric patients with pulmonary toxicity were reported in EudraVigilance. Most frequently reported AEs leading to death in the paediatric population were infections. This is primarily related to immune compromised status due

to underlying condition. These findings are in line with the known safety profile for melphalan. No new safety signals were identified based on EudraVigilance data.

Within clinical practice, choice of conditioning regimen will be based on various factors including patient disease and performance status, physician's preferences but also on the known toxicities of the agents used. In general, type of AEs will mostly overlap between conditioning regimens given its intended use, however, quantitative differences may exist for certain AEs. A comparison of the safety profile between different regimens is hampered by the lack of prospectively controlled trials including a reasonable number of patients. No firm conclusions can be drawn from the presented data. In clinical practice, the physician's preference is (partly) based on their experience with a certain conditioning regimen.

2.4.7. Conclusions on clinical safety

GvHD and VOD are known complications from conditioning regimen and allo-HSCT with a major impact on morbidity/mortality. A major shortcoming of the safety data provided is the lack of a systematic reporting of all AEs as well as a specific definition of ADRs within the publications which limits characterization of the safety profile in the new indication. However, the safety profile of melphalan is well known from its long-standing use in the treatment of malignancies and as conditioning regimen for HSCT in clinical practice at dose ranges including the currently proposed dose.

2.5. Risk Management Plan

Safety concerns

None.

Pharmacovigilance plan

None.

Risk minimisation measures

None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. 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.

3. Benefit-risk balance

This application concerns a hybrid version of melphalan powder and solvent for concentrate for solution for infusion. The reference product Alkeran is indicated for the treatment of multiple myeloma, malignant lymphoma (Hodgkin, non-Hodgkin lymphoma), acute lymphoblastic and myeloblastic leukemia, childhood neuroblastoma, ovarian and mammary adenocarcinoma.

In the context of this application for a hybrid marketing authorisation application, the applicant is submitting also supportive data to include a new therapeutic indication concerning the use of melphalan as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (HSCT).

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

No bioequivalence studies were provided to support the application. The proposed product 50 mg/10 ml has the same qualitative composition with same concentration of melphalan at the moment of infusion, same type of solution (i.e. aqueous), same method and means of administration for the current approved indications of Alkeran 50 mg/10 ml. The excipients used for the test product are qualitatively the same and quantitatively comparable to the reference product according to the information available to the assessors. The composition and concentration of the other proposed formulation 200 mg/40 ml is identical to the 50 mg/10 ml formulation and has same final concentration after reconstitution and dilution corresponding to 5 mg/ml. The requirements stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) are fulfilled and, in principle, the absence of a bioequivalence study can be accepted.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

Nonclinical studies have been provided for this application and considered sufficient. From a clinical perspective, this application does contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these

clinical aspects based on information from published literature was considered sufficient.

A benefit/risk ratio in the indications already approved for the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

This application concerns also an additional indication of melphalan in the all-HSCT setting, the benefit – risk of which is analysed below.

3. 1 Therapeutic Context

3.4.1 Disease or condition

The current application concerns a "hybrid application" according to the Article 10(3) of Directive No 2001/83/EC as amended.

Together with the indications of the originator, the applicant seeks an additional new therapeutic indication for the use of Phelinun. The applicant has developed an additional new strength presentation (200 mg), specifically for use in the new indication.

Phelinun in combination with other cytotoxic drugs in adult is indicated as reduced intensity conditioning (RIC) treatment prior to allogeneic haematopoietic stem cell transplantation (allo-HSCT) in malignant haematological diseases in adults.

Phelinun in combination with other cytotoxic medicinal drugs is indicated as conditioning regimen prior to allogeneic haematopoietic stem cell transplantation in haematological diseases in the paediatric population.

- Myeloablative conditioning (MAC) treatment in case of malignant haematological diseases
- RIC treatment in case of non-malignant haematological diseases.

The proposed posology for the new indication is:

Adult population:

Malignant haematological diseases before allogeneic haematopoietic stem cell transplantation

The recommended dose range is 140 mg/m^2 as a single daily infusion or 70 mg/m^2 once daily for two consecutive days.

Paediatric population

Haematological diseases before allogeneic haematopoietic stem cell transplantation:

- *Malignant haematological diseases 140 mg/m^2 as a single daily infusion*
- *Non-malignant haematological diseases: 140 mg/m^2 as a single daily infusion or 70 mg/m^2 once daily for two consecutive days.*

The aim of allo-HSCT is to eradicate the underlying disease by replacing a "defective/diseased" bone marrow with a healthy donor's marrow and to prolong survival.

3.4.2 Available therapies and unmet medical need

Patients undergoing allo-HSCT are prepared with chemotherapy alone or chemotherapy combined with radiotherapy, the so-called conditioning regimen, before infusion of donor stem cells.

Myeloablative conditioning (with or without radiation) is associated with significant toxicity. Due to its lowered toxicity, non-myeloablative transplants can be appropriate for older or patients with co-morbidities that would otherwise exclude them from myeloablative transplantation. Fludarabine (FLU) has been widely used because it is highly immunosuppressive, has anti-tumour activity in haematologic malignancies and a low non-haematologic toxicity profile. Regimens that rely on FLU or lower doses of the conditioning agents are referred to as either non-myeloablative (NMA) or reduced intensity conditioning (RIC). There are several NMA and RIC regimens available but the optimum regimen remains to be defined.

The regimen of melphalan in combination with fludarabine is considered a RIC.

There is no standard choice for conditioning regimens in allogeneic HSCT and clinical practice varies across countries and institutions. A decision regarding the use of a particular conditioning regimen takes into consideration a range of factors; recipient co-morbidities, underlying condition and disease status, donor, and graft source, and presumably also physicians' preference.

For paediatric patients with malignant haematological diseases, addition of melphalan to busulfan and cyclophosphamide is considered intensification of the conditioning regimen. For children with non-malignant haematological diseases, melphalan is used as part of a RIC regimen.

3.4.3 Main clinical studies

To support the application, the applicant performed a PubMed search and selected publications from 2000 to 2018 reporting efficacy and safety data on the use of melphalan as conditioning regimen in allogeneic haematopoietic stem cell transplantation (HSCT). From the literature search 20 publications were identified which reported data on use of melphalan in allogeneic HSCT published between 2005 and 2018. No main or pivotal studies were defined. No randomised controlled trials have been performed comparing a reduced intensity conditioning (RIC) regimen containing melphalan to other conditioning regimes prior to allogeneic HSCT in haematological diseases. The included studies are mainly retrospective**.**

Of the studies included, 18 reported on safety data, mainly GvHD and NRM. In support of efficacy, for the adult population, the study by **Baron et al.,2015,** is the only large study performed in European patients and as such considered important for evaluation of the benefit/risk of melphalan in the EU and assessed as the main study. The study performed by **Kawamura et al.,2017,** is a very large retrospective study including not only ALL patients but also patients with AML or MDS, therefore this study is also considered important in view of the applied broad indication. **Eom et al.,2013,** is the only prospective comparative study included in the dossier.

For the paediatric population, two large retrospective registry studies compared conditioning regimens in AML (**Lucchini et al., 2017**) and ALL (**Kato et al., 2015**). These were assessed as the main studies.

Adults

Baron et al., 2015, is a retrospective study, performed by the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT), comparing the outcomes for a cohort of acute AML patients receiving a sibling HSCT after fludarabine-busulfan (n=218) or fludarabine-melphalan (n=176, melphalan dose 130-150mg/m2 i.v.). Both are considered RIC.

Kawamura et al., 2017, is a retrospective study performed in Japan, to compare the transplant outcomes of patients aged 50 years or older with AML, ALL or MDS after fludarabine with melphalan (140 mg/m2 i.v.) (FM140, n=423), fludarabine with intermediate doses of busulfan (6.4 mg/kg i.v.) (FB2, n=463) and fludarabine with higher doses of busulfan (12.8 mg/kg i.v.) (FB4, n=721). FM140 and FB2 are considered RIC-regimens, and FB4 is considered a MAC regimen.

Eom et al., 2013, is a case-control study performed in South Korea in high-risk ALL patients in first or second complete remission, comparing outcomes after RIC (melphalan 140 mg/m2 and fludarabine 150mg/m2; n=60) or MAC (TBI 13,2 Gy + cyclophosphamide 120mg/kg***;*** n=120) allo-HSCT.

Paediatrics

Lucchini et al., 2017, is a retrospective study, performed by the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT), comparing the outcomes for children >2 to <18 years of age undergoing a first allogeneic HSCT from a matched sibling or unrelated donor for AML in CR1 after either Busulfan-Cyclophosphamide-Melphalan (140mg/m2) (n=133), Busulfan-Cyclophosphamide (n=389) or TBI-cyclophosphamide (n=109). All are considered MAC.

Kato et al., 2015, is a retrospective study, performed in Japan, comparing the outcomes for children <15 years of age undergoing a first allogeneic HSCT from a matched sibling or unrelated donor for ALL in CR1 or CR2 after myelo-ablative conditioning with one of five cytostatics added to TBI: Cyclophosphamide (CY) (n=74) or melphalan (L-PAM) (n=139) or Cyclophosphamide + etoposide (Cy+VP16) (n=408) or Cyclophosphamide + AraC (Cy+AraC) (n=73) or Others: melphalan + etoposide, Cyclophosphamide + fludarabine, Fludarabine (n=73). For melphalan, 180 mg/m2 of was given in 73 cases (52.5%) of HSCT, whereas 200 mg/m2 or more was used in 45 cases (32.4%).

Marsh et al., 2015, is a retrospective study in which a total of 210 children received a RIC regimen of Alemtuzumab, Fludarabine, and melphalan 140mg/m^2. Included diseases were HLH and X-linked lymphoproliferative disease (n=91), combined immune deficiency and common variable immunodeficiency (n=23), severe combined immune deficiency (SCID) (n=24), non-Fanconi anaemia marrow failure disorders (n=25) and metabolic disorders (n=22). The main outcome was survival rate.

3.5 Favourable effects

The endpoints of the main studies are overall survival (OS), disease-free survival (DFS), non-relapse mortality (NRM) and relapse rate (RR). These endpoints are considered clinically relevant. It is not clear whether statistical analysis plans for the main studies were developed beforehand, and if the schedule of assessments was pre-specified and comparable between treatment groups for each study. OS and NRM are considered the most robust endpoints, as difference in the timing of assessment could have had impact on DFS and RR.

Adults

Statistically significant reduction in relapse risk at 2 years for fludarabine-melphalan (FM) versus fludarabine-busulfan (FB) in AML patients (FM 20%, FB 30%; p=0.007), confirmed in multivariate analysis (HR 0.5, 95%CI 0.3-0.8, p=0.01) (**Baron et al., 2015**)**.**

Statistically significant reduction in relapse risk at 3 years for fludarabine-melphalan (FM) versus fludarabine-busulfan intermediate dose (FB) in AML/ALL/MDS patients (FM 27.4%, FB 37.2%; p=0.0027), confirmed in multivariate analysis (HR 0.56, 95% CI 0.42-0.74, p<0.001) (**Kawamura et., al 2017**).

No statistically significant difference in OS-rate at 5 years for fludarabine-melphalan (FM, RIC) versus TBI-cyclophospohamide (TBICy, MAC) in high-risk ALL patients (FM 54.5%, TBICy 58.0%; p= 0.838; HR 1.38, 95% CI 0.82–2.32; P=0.227), despite RIC-patients being older or having more co-morbidities (and therefore ineligible for MAC) (**Eom et al., 2013**).

Paediatrics

For AML-patients (**Lucchini et al., 2017**):

Statistically significant reduction in relapse rate at 5 years for busulfan-cyclophosphamide-melphalan (BuCyMel) versus TBI-cyclophosphamide (TBICy) and busulfan-cyclophosphamide (BuCy): (BuCyMel 14.7%, TBICy 30%, BuCy 31.5%; p<0.01) confirmed in multivariate analysis (OR 0.44, 95% CI 0.25-0.80; p<0.01).

Statistically significant increase in OS-rate at 5 years for busulfan-cyclophosphamide-melphalan (BuCyMel) versus TBI-cyclophosphamide (TBICy) and busulfan-cyclophosphamide (BuCy): (BuCyMel 76.6%, TBICy 64.5%, BuCy 64%; p<0.041), but non-significant p-value in multivariate analysis (OR 0.61, 95% CI 0.36-1.03; p=0.07)

No statistically significant difference in NRM-rate at 5 years for busulfan-cyclophosphamide-melphalan (BuCyMel) versus TBI-cyclophosphamide (TBICy) and busulfan-cyclophosphamide (BuCy):(BuCyMel 10.8%, TBICy 8.1%, BuCy 10.5%; p=0.79), confirmed in multivariate analysis (OR 1.22, 95% CI 0.45-3.32; p=0.70).

For MDS patients (**Strahm et al., 2011**):

After MAC allo-HSCT (BuCyMel): OS-rate at 5 years was 63%, EFS-rate was 59% and relapse rate was 21%.

For JMML patients (**Yabe et al., 2015**):

After MAC allo-HSCT with busulfan, fludarabine, and melphalan: The 5-year OS-rate at 5 years was 72.4% and EFS rate was 53.1%.

For children with non-malignant diseases (**Marsh et al., 2015**):

After RIC allo-HSCT (alemtuzumab/fludarabine/melphalan): OS-rate at 3 years was 69% and re-transplantation-rate due to graft loss 5%.

Uncertainties and limitations about favourable effects

The studies have several methodological shortcomings related to the retrospective nature, being lack of randomisation, blinding, standardisation of treatment regimens and pre-defined timing of outcome assessments. Prognostic factors could differ between treatment groups despite correction in multivariate analysis, biasing the observed effect sizes.

As it is unclear if the schedule of assessments was pre-specified, and comparable between treatment groups, lead-time bias should be taken into account in interpretation of event-free survival and relapse rate.

Statistically significant increase in non-relapse mortality at 3 years for fludarabine-melphalan (FM) versus fludarabine-busulfan intermediate dose (FB) in AML/ALL/MDS patients (FM 28.0%, FB 19.4%; p=0.001), confirmed in multivariate analysis (HR 1.71, 95% CI 1.25-2.32, p=0.00067). Suggesting the reduction of relapse risk goes at a cost of higher toxicity of FM versus FB.

Statistically significant increase in relapse risk at 5 years for fludarabine-melphalan (FM, RIC) versus TBI+cyclophosphamide (TBICy, MAC) in high risk ALL-patients in multivariate analysis (FM 34.2%, TBICy 26.4%; HR 2.07, 95% CI 1.13–3.81; P=0.019).

As only 5 adult patients with non-malignant haematological diseases were included in the submitted publications, efficacy in this population is not supported by literature data. The applicant restricted the indication to adult patients with malignant haematological diseases only.

For children with AML treated with the BuCyMel regimen below the age of two, data on OS, safety or treatment-related mortality were not reported separately. Furthermore, for children >12 years of age BuCyMel was reported to lead to a higher TRM compared to younger patients.

No comprehensive efficacy data in paediatric patients with malignant haematological diseases other than AML. The trial in ALL-patients (Kato et al., 2015) did not report OS-estimates.

Other studies with melphalan RIC in non-malignant haematological diseases besides Marsh et al., 2015, are relatively small.

3.6 Unfavourable effects

Safety data provided in the publications focused on serious ADRs, mainly GvHD and NRM, allowing assessment of major and life-threatening adverse events in the new indication. Few studies reported on other toxicities, mostly gastrointestinal events, mucosal inflammation and hepatotoxicity.

A major and frequently occurring risk of melphalan when used as conditioning regimen for allo-SCT is graft-versus-host disease (acute and chronic). In addition, veno-occlusive disease is a well-known complication of conditioning regimens with potential fatal outcome, reported at low frequencies. Fatal cases indicative of pulmonary inflammation (interstitial pneumonia and pneumonitis) have been reported.

Infections are commonly occurring ADRs and also a frequent cause of death.

Gastrointestinal adverse events including nausea, vomiting, diarrhoea and stomatitis were commonly reported and are known side effects of melphalan.

Type of ADRs reported for the paediatric population appear comparable to that of the adult population.

The safety profile of melphalan is well-known due to its long-standing and wide-spread use at dose-ranges including the currently proposed dose. It is characterised by its myelosuppressive action (e.g. leukopenia, thrombocytopenia, anemia, and resulting infections), gastrointestinal side effects and hepatotoxicity.

3.7 Uncertainties and limitations about unfavourable effects

The reporting of ADRs in the publications is limited and it is unclear how adverse events were assessed. A systematically reporting of ADRs is lacking. This results in underreporting of adverse events in the newly proposed indication. Reliable frequencies of occurrence cannot be determined.

Well known side effects as myelo-suppression and immuno-suppression were not reported as ADRs, most likely because these are considered the desired therapeutic effects of the conditioning regimen. Nevertheless, relevant information is included in the SmPC.

Uncertainty remains whether there are any new safety signals compared to the well-known safety profile of melphalan. Given the long-standing use of melphalan in general and its wide-spread use as a

conditioning regimen in HSCT, the risk of missing important serious ADRs that could impact the BR is unknown, but also considered to be low.

The contribution of melphalan to the toxicity of the combination remains unknown. Safety data comparing melphalan based regimens with other regimens, being other RIC or myeloablative regimens, is limited and there is a lack of prospective studies.

The dose of melphalan is independent of the underlying disease, however safety data in non-malignant diseases is limited.

3.8 Benefit-risk assessment and discussion

3.8.1 Importance of favourable and unfavourable effects

The revised additional indication encompasses RIC for malignant haematological diseases for adults and as part of myelo-ablative conditioning regimen for paediatric patients with malignant haematological diseases and as part of reduced intensity conditioning for non-malignant haematological diseases.

Adult population

RIC for adults with malignant haematological diseases

In adults with malignant haematological diseases, OS for a melphalan-based conditioning regimen was at least comparable to that of a busulfan-based RIC regimen. The data reflect clinical practice with many patient and disease factors and physician's preference influencing the choice of treatment. Making an allo-HSCT possible for a patient group not eligible for myelo-ablative conditioning because of age or co-morbidities, by using a melphalan containing RIC regimen, is considered important and clinically relevant as a RIC conditioning regimen is considered less toxic compared to a MAC regimen. The major risks associated with conditioning regimens are well known and include GvHD and complications of the myelosuppressive/immunosuppressive effects (e.g. infections) which can be fatal. The data provided confirmed the high risk of GvHD and NRM. The likely underreporting of adverse events based on the studies submitted does not preclude assessment of the B/R given the well-known safety profile of melphalan and its long-standing use at a comparable dose for autologous SCT.

Paediatric population

Conditioning regimen for paediatric patients with malignant haematological diseases (MAC)

For paediatric patients with haematological malignancies, addition of melphalan to the conditioning regimen is an intensification of therapy with the aim of improving survival and reducing risk of relapse, which is of importance. In paediatric patients with AML between 2 and 12 years of age, the intensified conditioning regimen reducing relapse risk was not accompanied by a higher treatment-related mortality, suggesting that treatment toxicity did not negatively impact survival. For children with MDS and JMML data are less comprehensive, though support efficacy and use in these areas is part of EU consensus-based guidelines. For children with ALL, the data are less comprehensive whereas uncertainties remain on AML <2 yrs. For these paediatric patients, appropriate warnings need to be included in section 4.4 of the SmPC. For children with AML ≥12 yrs uncertainties remain due to potential increased treatment-related mortality.

Extrapolation to other malignant haematological diseases with warnings in section 4.4 and limitations of data in section 5.1 is acceptable. This as data have been provided for the largest haematological malignant disease areas in the paediatric population and it is not likely that more comprehensive data

will become available. Moreover, the main effect of the conditioning regimen before allo-HSCT is immunosuppression by eradication of the patient's bone marrow which is likely independent of the underlying disease and treatment is performed according to pre-specified protocols in specialised centres.

Conditioning for paediatric patients with non-malignant haematological diseases (RIC)

For children with non-malignant haematological diseases, melphalan is used in a reduced intensity regimen. Publications including about 500 children support the use of melphalan as RIC and it is understood that a melphalan-containing RIC regimen is one of the treatment options already used for paediatric non-malignant haematological diseases in current clinical practice. A reduced intensity conditioning regimen might make an allo-HSCT possible for paediatric patients with comorbidities and residual toxicities from earlier treatment, who would not be able to tolerate a MAC allo-HSCT. The choice for a conditioning regimen in these rare diseases is made based on doctor and patient's preference, and treatment guidelines and protocols are continuously adapted across European academic treatment centres.

Overall, the broad indication of melphalan as part of conditioning treatment for allo-HSCT in paediatric patients with haematological diseases, including non-malignant diseases, can be supported. The type of regimen is reflected in the indication.

3.8.2 Balance of benefits and risks

For adult patients with malignant haematological diseases, the benefit of making an allo-HSCT possible with a less toxic RIC-regimen for otherwise ineligible patients, outweighs the uncertainties pertaining to the lack of a prospective controlled trial.

For the paediatric population with malignant haematological diseases, based on a similar effect of bone marrow eradication irrespective of the underlying disease, the benefits of melphalan as part of the conditioning regimen (MAC) as reported in the literature outweigh the risks.

For paediatric patients with non-malignant haematological diseases, the benefits of a reduced intensity treatment making an allo-HSCT possible for children with comorbidities and residual toxicities from earlier treatments outweigh the uncertainties associated to the type of studies available in this disease area.

3.8.3 Additional considerations on the benefit-risk balance

N/A

3.9 Conclusions

Efficacy of Phelinun in combination with other cytotoxic drugs in adults as RIC prior to allo-HSCT in malignant haematological diseases and in the paediatric population as MAC (in malignant diseases) or RIC (in non-malignant diseases) regimen prior to allo-HSCT in haematological diseases is established and the safety of the melphalan-based regimens is well-known.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Phelinun is favourable in the following indication:

High-dose of Phelinun used alone or in combination with other cytotoxic medicinal products and/or total body irradiation is indicated in the treatment of:

- multiple myeloma,
- malignant lymphoma (Hodgkin, non-Hodgkin lymphoma),
- acute lymphoblastic and myeloblastic leukemia,
- childhood neuroblastoma,
- ovarian cancer,
- mammary adenocarcinoma.

Phelinun in combination with other cytotoxic medicinal products is indicated as reduced intensity conditioning (RIC) treatment prior to allogeneic haematopoietic stem cell transplantation (allo-HSCT) in malignant haematological diseases in adults.

Phelinun in combination with other cytotoxic medicinal products is indicated as conditioning regimen prior to allogeneic haematopoietic stem cell transplantation in haematological diseases in the paediatric population as:

- Myeloablative conditioning (MAC) treatment in case of malignant haematological diseases
- RIC treatment in case of non-malignant haematological diseases.

The CHMP therefore recommends the granting of the marketing authorisation.

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Phelinun is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Farydak (panobinostat), Ninlaro (ixazomib), Imnovid (pomalidomide), Kyprolis (carfilzomib), Mylotarg (gemtuzumab-ozogamicin), Besponsa (inotuzumab-ozogamicin), Vyxeos (cytarabin-daunorubicin), Iclusig (ponatinib), Blincyto (blinatumomab), Xaluprine (mercaptopurin), Dacogen (decitabine), Rydapt (midostaurin), Xospata (gilteritinib), Qarziba (dinutuximab beta), Poteligeo (mogamulizumab), Kymriah (tisagenlecleucel), Yescarta (axicabtagen ciloleucel), Gazyvaro (obinutuzumab), Imbruvica (ibrutinib), Adcetris (brentuximab vedotin), Ledaga (chlormethine), Zejula (niraparib), Tepadina (thiotepa) and Mozobil (plerixafor).

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.