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Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

BEGEDINA

International non-proprietary name: begelomab

Procedure No. EMEA/H/C/004144/0000

Note

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

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List of abbreviations

ABA	Anti- BEGEDINA Antibodies
ADA	Anti-Drug Antibodies
AEC	Anion Exchange Chromatography
allo-HSCT	allogeneic-Hematopoietic Stem Cell Transplantation
aGvHD	acute Graft versus Host Disease
AUC	Area Under the Curve
BSA	Bovine Serum Albumin
cGMP	Current Good Manufacturing Practice CV Coefficient of Variation
cIEF	Capillary Isoelectrophocusing
CL	total Body Clearance
Da	Dalton
DDI	Drug-Drug Interaction
DL	Dose Level
DP	Drug Product
DPBS	Dulbecco Phosphate Buffer Saline
DPP-IV	Dipeptidyl peptidase-IV
DS	Drug Substance
ECG	Electrocardiogram
ELISA	Enzyme-Linked ImmunoSorbent Assay
EOPC	End of Production Cell
FBS	Foetal Bovine Serum
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GLP-1	Glucagone like peptide-1
GMP	Good Manufacturing Practices
GvHD	Graft versus Host Disease
HAMA	Human Anti-Murine Antibodies
HC	Heavy Chain
HCP	Host Cell Protein
HLA	Human Leukocyte Antigen
HPCT	Haematopoietic Progenitor Cells Transplantation
HRP	Rabbit anti-mouse Horseradish peroxidase
HSCT	Hematopoietic Stem (Progenitor) Cell Transplantation
ICH	International Conference on Harmonisation
IEF	Isoelectrophocusing
Ig	Immunoglobulin
IGF-1R	Insulin-Like Growth Factor-1 receptor
IV	Intravenous
LC	Light Chain
LLOQ	Lower Limit Of Quantitation
mAb	monoclonal Antibody
MCB	Master Cell Bank
MED	Minimum Effective Dose
MFI	Mean Fluorescence Intensity
MFIR	Mean Fluorescence Intensity Ratio
MHC	Major Histocompatibility Complex

MLC	Mixed Lymphocyte Culture
MRD	Minimum Required Dilution
MSC	Mesenchymal Stem Cells
NIH	National Institutes of Health
NK	Natural Killer
OD	Optical Density
ORD	Office of Rare Diseases
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamics
PHA	Phytohemagglutinin
PhEur/EuPh	European Pharmacopeia
PK	Pharmacokinetics
PPC	Post Production Cells
PRV	Pseudorabies Virus
PT	Preferred Term
QCH	High Quality Control
QCL	Low Quality Control
QCM	Medium Quality Control
RE	Relative Error
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SEC	Size Exclusion Chromatography
SOC	System Organ Class
SR	Steroid Resistant
T0	Initial Time
T1/2	Terminal Half-Life
TCA	Trichloroacetic Acid
TCR	T cell receptor
UB	Unprocessed Bulk
ULOQ	Upper Limit Of Quantitation
UPLC	Ultra Pressure Liquid Chromatography
Vd	Volume of Distribution
vs.	versus
WCB	Working Cell Bank
X-MLV	Xenotropic Murine Leukemia Virus

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for BEGEDINA, an orphan medicinal product, in the treatment of *steroid-resistant acute Graft-versus-Host Disease (GvHD) in adult patients who underwent allogeneic haematopoietic progenitor cell transplantation (HPCT)*, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The details of these major objections are provided in the preliminary list of questions.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Quality

- Characterisation of the cell substrate used for production of begelomab is insufficient
- Characterisation of the drug substance (DS) is incomplete.
- The analytical comparability between material produced according to the proposed phase III clinical study/commercial process and material used in both clinical studies has been insufficiently demonstrated.
- Sufficient evidence to demonstrate viral safety has not been submitted.
- The manufacturing process is insufficiently laid down in the dossier and process parameters and process controls are insufficiently defined, justified and controlled.
- The production process can not be considered as validated.
- The proposed specifications of Begelomab are insufficient to control its complex purity/impurity profile
- The quality of the excipient Dulbecco Phosphate Buffered Saline (DPBS) is insufficiently ensured.
- Sufficient evidence to ensure the sterility of the drug product (DP) has not been submitted.
- Stability of the DP is insufficiently ensured.

Non-Clinical

- Preclinical pharmacology of begelomab is not sufficiently addressed to support its use in treatment of steroid-resistant acute GVHD.
- Due to its compromised design, and in the absence of a separate safety pharmacology study, the pivotal toxicity study is not conclusive on the preclinical identified safety risks.

Clinical

- The PK/PD of begelomab has insufficiently been characterised.
- Sufficient evidence of efficacy has not been provided for a conditional marketing authorisation.
- At present it is not possible to adequately characterise the safety profile of begelomab.

Inspection issues

GMP inspection(s)

The European Medicines Agency Compliance and Inspection Sector will recommend a GMP inspection of one manufacturer (back up cell bank storage site) due to invalid GMP documentation.

GCP inspection(s)

A request for (routine) GCP inspection has been adopted for the following clinical studies EUDRACT 2007-005809-21 (pilot study) and EUDRACT 2012-001353-19 (dose finding study). Following assessment of the clinical dossier, a number of concerns have been identified that bring into question the validity of the data from these clinical trials. Therefore, the outcome of this inspection and the satisfactory responses to its findings are considered to be an integral part of this procedure and will be needed by Day 121 (preferably earlier), which is in line with a triggered inspection.

New active substance status

Based on the review of the data, the CHMP consider that the active substance begelomab contained in the medicinal product BEGEDINA is to be qualified as a new active substance in itself.

Questions to be posed to additional experts

None

Inspection issues

The BEGEDINA GCP inspection is anticipated to take place in the third week of February 2016 and in the first week of March 2016. The reporting inspectorate is Italy and the Co-inspectorate is Germany (PEI). There will be a clinical site inspected in Italy (two clinical trials, protocol ADN-GvHD DF BT 5/9 – EudraCT 2012-001353-19 and protocol ADN-GvHD DF BT 5/9 – EudraCT 2007-005809-21) and the sponsor. Furthermore one CRO (Quintiles) will be included in the sites to be inspected. The integrated inspection report - IIR (including applicant's responses to the questions from the inspectors) is due on 11th April 2016.

2. Executive summary

2.1. Problem statement and about the product

Rationale for the product

BEGEDINA contains the active substance begelomab, a murine monoclonal antibody against CD26 produced in a hybridoma cell line. It has been developed by ADIENNE S.A. as a treatment of steroid resistant acute Graft-versus-Host Disease (SR-aGvHD) in adult patients undergoing hematopoietic progenitor (or stem) cell transplantation (HSCT).

Graft versus host disease

Acute graft versus host disease (aGvHD) is a potentially life threatening complication of hematopoietic allogeneic stem cell transplantation (HSCT) or the infusion of donor lymphocytes (DLI). Acute GvHD is a result of an alloimmune effect whereby immune cells from the HSCT graft recognize the recipient (the host) as "foreign" and mount an immune response against the host.

Acute GvHD usually occurs within the first 3 months after a transplant, and is characterised by symptoms associated with inflammatory reactions primarily in the skin, gastrointestinal tract and the liver. The syndrome can range from a mild self-limiting condition to a serious and potentially fatal disorder. The major risk for occurrence is the presence of HLA disparity between the donor (graft) and the recipient. Other risk factors include older patient age, the use of female donors for male recipients, the use of unrelated donors, prior alloimmunisation of the donor and the nature of GvHD prophylaxis.

Several strategies are available to prevent aGvHD, namely removal of donor allo-reactive T cells from the graft (*ex vivo* T cell depletion), post-graft infusion of cyclophosphamide or administration of T-cell antibodies (such as anti-thymocyte globulin (ATG) or Campath) to the patient (*in vivo* T cell depletion), or administration of immunosuppressive medications such as cyclosporine A, tacrolimus or methotrexate.

The incidence of the severity of acute GvHD is determined by the extent of involvement of the above three principal target organs according to Glucksberg criteria (Glucksberg et al. 1974). The overall grades are classified as I (mild), II (moderate), III (severe) and IV (very severe). Grade III-IV aGvHD have an extremely poor prognosis despite therapeutic intervention. Grade I aGvHD, by definition affecting only the skin, may be effectively treated with topical steroids alone. More advanced grades require systemic therapy and the mainstay of treatment remains high dose methylprednisolone, usually at a dose of 2 mg/kg/day, which may be combined with calcineurin inhibitors. The chance of response decreases with increasing grade of GvHD, but in general approximately 40–50% of patients will demonstrate a response (EBMT handbook 2011).

Failure to respond to standard steroid doses or refractory recurrence after initial steroid dose reduction will necessitate second line treatment. In this context many agents have been tried alone or in combination with corticosteroids. None have shown convincing long-term efficacy. Thus, second line therapy is unsatisfactory and overall survival of these refractory patients is poor.

Mode of action

The mechanism of action of BEGEDINA is associated with its ability to bind CD26, which is expressed on activated lymphocytes. It's binding to CD26 activity results in blocking of T cell expansion CD3+CD26+ T lymphocytes and consequently reduces the immune response occurring during steroid-resistant aGvHD.

CD26 is a multifunctional glycoprotein expressed both as a soluble form and as well as surface antigen in various tissues, including activated T lymphocytes with DPP-4 peptidase activity in its extracellular domain. This dipeptidyl peptidase IV (DPP-IV) enzymatic activity belongs to a subgroup of prolyl oligopeptidases that can cleave N-terminal dipeptides from many biologically active polypeptides, e.g. hormones, cytokines and chemokines. CD26 regulates multiple biological processes and has been studied in the fields of immunology, endocrinology, cancer biology and nutrition owing to its ubiquitous and enzyme activity.

The role of DPP IV/CD26 within the immune system is a combination of its exopeptidase activity and its interactions with different molecules. CD26 is both a T cell co-stimulatory molecule as well as a T cell activation marker. Accumulations of CD26+ T cells have been demonstrated in inflamed tissues in patients with autoimmune diseases. Soluble CD26 was found to modulate *in vitro* T-cell proliferation. Furthermore, CD26/DPP4 has been implicated in regulating the *in vitro* and *in vivo* functional activities of a number of hematopoietic active molecules, and has been studied in efforts to enhance HSC haematopoiesis after stress in mouse models, and in the clinical setting of single-unit cord blood (CB) HSCT (Broxmeyer et al 2013). Activated lymphocytes are thus the target of this anti-CD26 antibody therapy and their partial depletion was suggested to lead to clinically relevant modulation of steroid-resistant aGvHD.

Claimed indication and recommendation for use and posology

The claimed indication is: *BEGEDINA is indicated for the treatment of steroid-resistant acute Graft-versus-Host Disease (GvHD) in adult patients who underwent allogeneic haematopoietic progenitor cell transplantation (HPCT).*

The recommended dose is 2.7 mg/m^2 body surface area. The recommended schedule is daily administration for 5 consecutive days. The administration should then be repeated on days 10, 14, 17, 21, 24 and 28 for a total of 11 doses (starting from day 1 of administration).

The product is administered after dilution in 0.9% saline solution for injection, by intravenous infusion via a central venous catheter over 1 hour. All patients should be pre-medicated with 40 mg of prednisolone and an antihistamine agent by parenteral route.

2.2. The development programme/compliance with CHMP guidance/ scientific advice

The development programme

The Applicant stated that clinical development of BEGEDINA has followed the ICH Efficacy Guidelines and EU GCP standards and includes two uncontrolled studies conducted in the EU population, i.e.

- a Phase I/II open-label pilot study in patients submitted to hematopoietic progenitor cells transplantation (HPCT) with grade II-IV Graft versus Host Disease (GvHD) (Study EUDRACT 2007-005809-21) and
- a Phase II open-label dose-finding study for treating steroid-resistant aGvHD patients who had previously undergone HPCT (Study EUDRACT 2012-001353-19).

An open-label, uncontrolled study design was considered adequate to determine pharmacokinetic variables of begelomab, to assess dose dependent effects as well as to determine the preliminary efficacy and safety profile in these studies.

A confirmatory phase II/III efficacy and safety trial is planned (Study EUDRACT 2015-001360-19).

Scientific advice

The Applicant discussed quality, non-clinical and clinical issues during a Protocol Assistance meeting in **January 2012** (EMEA/H/SA/2241/1/2011/PA/SME/III). The clinical development program of Begelomab was also presented to EMA and FDA during a Parallel Scientific Advice procedure in order to achieve a shared design of the confirmatory study entitled "A prospective, phase II/III, randomized study to compare BEGEDINA versus conventional treatment for Steroid Resistant Acute Graft Versus Host Disease" (Meeting References EMEA/H/SA/2241/1/FU/1/2013/PA/SME/III).

Regarding the non-clinical development, the design (animal model and the duration) of the repeat dose toxicity study was discussed. While the CHMP could agree with the proposed model (mini-pig), the proposed duration of 14 days was considered too short. In principle a 1 month study was recommended. It was also noted that the dose level should be better justified. The CHMP agreed that genotoxicity studies and carcinogenicity studies were not needed. Furthermore, it was also concurred that repeat dose toxicity studies might not be needed if justified with appropriate data, e.g. pre-treatment sterility.

Regarding the clinical development, the phase II dose-finding study was discussed, in particular the use of day 100 treatment related mortality (TRM) as primary endpoint. The CHMP considered that while TRM was interesting, it was not suitable as the primary endpoint. The use of a pharmacodynamic

surrogate (level of circulating CD3+CD26+ cells) was recommended, so that the next dose level could be started earlier, and it was advised to increase the sample size above the proposed 3 patients at each dose level to aid interpretation of the data. As a consequence, the Applicant has indeed changed the endpoint and included 7 more patients after determination of the appropriate dose level.

Also the definition of steroid-resistance was discussed. The Applicant proposed to define steroid-resistance – progression after 3 days, or - no change after 7 days, or – incomplete response after 14 days. This was deemed acceptable by the CHMP.

In this advice the Applicant proposed to submit the confirmatory randomised controlled study as pivotal trial to the MAA. This was endorsed by the CHMP. A comment on the choice of comparator was made. In this respect, it was noted that while CHMP could accept a superiority trial with the proposed comparator (rATG), it could also reduce the feasibility of the study. The Applicant apparently changed the strategy for registration as the current application for marketing authorisation concerns an application for conditional approval for which the here proposed confirmatory phase II/III trial is used to fulfil the requirement (condition) to provide comprehensive data after registration.

Further discussions in this protocol assistance concerned the design of the confirmatory study. The CHMP considered that transplant related mortality at 6 months was an acceptable primary endpoint, and commented that while the statistical hypothesis seemed plausible, it was based on a very optimistic estimation of efficacy. Furthermore, it was considered that the proposed safety database of 77 treatment patients was likely to be acceptable for MAA, and it was agreed that overall the proposed clinical development program with the suggested amendments, was likely to be adequate for an MAA in the proposed therapeutic indication where no drug is currently approved.

In **April 2013** follow-up issues were discussed during an EMA/FDA Parallel Protocol Assistance.

Quality: Regarding the viral safety evaluation of the cell banks it was noted in the CHMP answer that all retrovirus infectivity assays results are negative. Furthermore, the scientific advice indicated that further testing might be needed in case materials of human and/or animal origin have been used in the establishment of MCB, WCB or used during production and which may not be accounted for in the proposed test program..

Non-clinical: It was generally noted that the applicant had followed previous scientific advice by the CHMP. New data indicated that marmoset might be a better model than minipig. Some further comments were made on the design of the repeated dose toxicity study, in particular on the need of necropsy and histopathology data, and on the PK/PD assessment in the marmoset. Not all these recommendations were followed by the Applicant.

Clinical: the Applicant proposed some rewording of the definition of steroid-resistance as previously discussed. This proposal was considered acceptable. The definition of steroid-resistance in the final protocol of the dose-finding study and the confirmatory study is in line with the here discussed proposal, albeit with (again) some rewording. The comparator was again marked for discussion. The CHMP agreed to the Applicant's proposal to use the "best conventional second-line therapy" as comparator. The choice of TRM at 6 month as primary efficacy endpoint was endorsed and the proposal for the secondary endpoints was considered acceptable: i.e. staging of GvHD by organ on day +28, frequency of responders on day +28, overall survival at 6 and 12 months, incidence of chronic GvHD at 6 and 12 months, steroid tapering, relapse and relapse related mortality at 12 months, Karnofsky index at 12 months.

The choice of dose level was discussed using the available data from the dose-finding study. The CHMP noted that at the time of the advice the available data were too limited to establish the best possible dose and that more work on the dose and schedule was needed.

2.3. General comments on compliance with GMP, GLP, GCP

GMP

The European Medicines Agency Compliance and Inspection Sector has reviewed the manufacturer information contained in the application form (Module 1) and available from the EEA National Competent Authorities and determined that all relevant sites have valid manufacturing authorizations or valid GMP certificates as appropriate., with the exception of one back up facility for cell bank storage for which an inspection will be recommended to the CHMP.

GLP

The pivotal 28 days repeated dose toxicity study was the only preclinical study for which GLP was claimed. The study was conducted by Research Toxicology Centre, in Pomezia RM Italy, which was inspected and regarded GLP compliant.

GCP

According to the Applicant, both the pilot and the dose-finding study were conducted in compliance with the principles of GCP. No GCP inspections have taken place. Since the submission of the MAA, the EMA has selected the phase II dose-finding study (ADN-GvHD DF BT 5/9 or 2012-001353-19) for routine GCP inspection. The request for this inspection was initiated on the basis of general triggers including the indication (orphan), that both clinical trials submitted in support of the application included very few patients and that no inspections have been performed by any EU inspectorate on either trial and the sponsor (academic) was not inspected before. As the data from both studies are essential for the assessment of the dossier also the pilot study (ADN-GVHD vs BT5/9 or 2007-005809-21) was included in the IREQ of the inspection.

However, following assessment of the clinical dossier a number of concerns have been identified that bring into question the validity of the data from the 2 clinical trials. This includes a large number of incomplete datasets, changes to the baseline data for one of the efficacy endpoints and a number of changes to the final analyses. The CHMP consider the outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 121. The outcome of the GCP inspection will be required before any final conclusions on the clinical data can be made and before any marketing authorisation can be granted.

2.4. Type of application and other comments on the submitted dossier

- Legal basis

The current application concerns an Application for marketing authorisation (MAA) of an orphan designated medicinal product that fits within the mandatory scope of the centralised procedure (Article 3(1) of Regulation (EC) No 726/2004).

The legal basis is defined as Article 8(3) of Directive 2001/83/EC as amended – full application; new active substance.

- Accelerated procedure

A request for an accelerated assessment was considered by the CHMP in June 2015. A decision was adopted that did not recommend the granting of an accelerated assessment procedure.

- Conditional approval

The Applicant applies for a conditional approval.

- Exceptional circumstances

Not applicable.

- Biosimilar application

Not applicable.

- 1 year data exclusivity

Not applicable.

- Significance of paediatric studies

A Paediatric Investigation Plan (PIP) was submitted to the Paediatric Committee (PDCO) (procedure number: EMEA-001744-PIP01-14). The PIP for the indication of acute GvHD was agreed in accord with Regulation (EC) 1901/2006 with (i) a grant of deferral for a quality measure and 2 paediatric clinical studies and (ii) a grant of a waiver for the neonatal paediatric population from birth to less than 28 days on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subsets. The PIP was approved on 2nd of October 2015; decision number P/0226/2015.

3. Scientific overview and discussion

Introduction

Begelomab is a murine monoclonal antibody against CD26. CD26 is a multifunctional glycoprotein expressed both as a soluble form and as well as surface antigen in various tissues, including activated T lymphocytes. CD26 is both a T cell co-stimulatory molecule as well as a T cell activation marker. Activated lymphocytes are the target of anti-CD26 antibody therapy and, according to the Applicant, their partial depletion may lead to clinically relevant modulation of steroid resistant aGvHD.

The Applicant seeks a conditional MAA for BEGEDINA (begelomab) for 'the treatment of steroid-resistant acute Graft-versus-Host Disease (GvHD) in adult patients who underwent allogeneic haematopoietic progenitor cell transplantation (HPCT)'.

Treatment with begelomab consists of a daily dose of 2.7 mg begelomab/m^2 body surface area administered for 5 consecutive days, and then on days 10, 14, 17, 21, 24 and 28 for a total of 11 doses.

The clinical development of BEGEDINA includes two uncontrolled studies: a Phase I/II open-label pilot study in patients who received prior HSCT and with grade II-IV Graft versus Host Disease (GvHD) (Study EUDRACT 2007-005809-21) and a Phase II open-label dose-finding study for treating steroid-resistant aGvHD patients who previously underwent haematopoietic stem cell transplantation (HSCT) (Study EUDRACT 2012-001353-19). In total, 28 patients affected by steroid-resistant acute GvHD have been treated with begelomab.

The Applicant has provided a comparison of the results from begelomab-treated patients in the clinical studies with historical controls from the same treatment centre and two published studies (Knop et al 2007, Sanchez-Guijo et al 2014) to evaluate treatment of steroid resistant acute GvHD based on a similar overall GvHD grade at baseline.

It is recognised by the Applicant that the available efficacy and safety data will require confirmation with new studies and collection of data from marketing use. For this purpose the Applicant has

included one study in adult patients in the submitted risk management plan. The proposed study is a phase II/III confirmatory efficacy and safety study in adult patients (Study EUDRACT 2015-001360-19).

Of note: After the completion of the clinical studies an empirically established experimental molecular extinction coefficient of begelomab has been applied. As result, the concentration of 1 mg/ml in the clinical studies corresponds to an actual dose of 0.9 mg/ml. Similarly, the dose of 2 mg/day or 2 mg/m2/day corresponds actual doses of 1.8 mg, or 1.8 mg/m2/day, the dose of 3 mg/m2/day in the studies corresponds to an actual dose of 2.7 mg/m2/day and the dose of 4.5 mg/m2/day in the studies corresponds to an actual dose of 4.05 mg/m2/day. In the following sections, the original values of doses were used.

3.1. Quality aspects

3.1.1. Introduction

BEGEDINA contains the active substance begelomab, a murine monoclonal antibody against CD26 produced in a hybridoma cell line. BEGEDINA is formulated as a concentrate for solution for infusion 0.9 mg/ml and is intended to be administered by intravenous route. It has been developed by the Applicant as a treatment of steroid resistant acute Graft-versus-Host Disease (SR-aGvHD) in adult patients undergoing hematopoietic progenitor cell transplantation (HPCT). The mechanism of action is associated with its ability to bind CD26, mainly expressed on activated lymphocytes. Its binding to CD26 activity results in blocking expansion of T CD3+CD26+ lymphocytes and consequently reduces the immune response occurring during steroid-resistant aGvHD.

3.1.2. Active Substance

General Information

The active substance in BEGEDINA (INN begelomab) is a murine monoclonal antibody against CD26 with molecular weight of around 150 kDa. It consists of a heavy chain (HC, 456 amino acids) and a light chain (LC, 213 amino acids). Begelomab is N-glycosylated at position 306 of the heavy chain. Its chemical name is Immunoglobulin G 2b, anti-human CD26 (antigen) (*Mus musculus* monoclonal heavy chain), disulfide with *Mus musculus* monoclonal light chain, dimer; also known as monoclonal antibody BT 5/9 and murine monoclonal antibody against CD26.

Manufacture, characterisation and process controls

Begelomab is manufactured by Adienne S.r.l. S.U (Adienne), Caponago, Italy.

Source, history and generation of the cell substrate

A MCB and a WCB were established. The Applicant has stated that both cell banks were manufactured, controlled and labelled according to cGMP.

Manufacturing process

The upstream manufacturing process (Figure 1) starts from WCB vials which are expanded.

Begelomab is obtained by a purification process that comprises a series of chromatography and viral inactivation and filtration steps.

Process validation

Process validation was carried out on three consecutive batches produced according to standard batch size and process.

Specification

The active substance specification includes control of identity, purity, potency and other general tests.

Comparability exercise for Active Substance/Finished Medicinal Drug Product

Analytical comparability between material produced according to the proposed phase III clinical study/commercial process and material used in both clinical studies has been insufficiently demonstrated. This is considered **a major objection.**

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is a glass vial containing 6 mL 0.9 mg/ml clear, colourless concentrate for solution for infusion. One vial contains 5.4 mg of begelomab.

BEGEDINA is provided in a 10 mL type 1 glass vial with a chlorobutyl rubber stopper and aluminium flip-off crimp cap. The amount of BEGEDINA solution to be administered should be diluted in 100 ml 0.9% saline solution for injection prior to administration.

Manufacture of the product and process controls

The finished product manufacturing process consists of sterile filtration and aseptic filling of the active substance using a disposable system.

The finished product manufacturing process underwent a validation exercise.

Product specification

The finished product specification includes control of identity, purity, potency and other general tests.

Stability of the product

For unopened vials, a shelf life of 18 months at 2-8 °C is claimed.

The batches stored for 18 months at 2-8 °C do not show any signs of degradation.

Adventitious agents

Viral testing was conducted primarily at MCB, EOPC and unprocessed bulk. No testing was performed at WCB level as the EOPC were tested.

GMO

Not applicable

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

As a general remark, Begedina is an orphan medicinal product and the Applicant has requested a conditional marketing authorisation based on a phase 1/2 study and a phase 2 study. They have committed to conducting a confirmatory post-authorisation phase 2/3 safety and efficacy trial. Due to the limited clinical experience with this product, the clinical qualification of the manufacturing process and the finished product for this marketing authorisation application is also limited. The information submitted to support the quality dossier is also minimal.

Overall, based on assessment of the information provided by the Applicant, the product is not considered approvable from a quality perspective for the following reasons:

- There are concerns that could have a major impact on the quality and/or safety of the product.
- A high number of issues have been identified with this application.
- The Applicant's development program has not been systematic and is not appropriate in the context of a marketing authorisation application.
- The development of the product in its entirety is not considered as completed.

Active substance

Information about the characterisation of the hybridoma cell line, MCB, WCB and EOPC is insufficient, which is a Major Objection (MO1). The company has not provided sufficient information and scientific data about how the hybridoma cell line was generated and established and how the monoclonality of the cell line was confirmed. Questions are outstanding regarding the characterisation of the MCB and WCB, which are related to cell line stability.

The Applicant used a very minimalistic approach for characterisation of the active substance and this is considered a Major Objection (MO2). Characterisation should be completed.

The mechanism of action has not been described in the quality dossier, which makes it difficult to correlate quality attributes to biological function. Data should be submitted to show that binding of the antibody correlates with the therapeutic effect through immunomodulatory action; residual CDC/ADCC activity should be characterised; it should be investigated how bioactivity is influenced by different quality attributes .

Analytical **comparability** between material produced according to the proposed phase 3 clinical study/commercial process and material used in the clinical studies **has been insufficiently demonstrated**.

Therefore, additional data should be provided to fully assess the comparability of clinical and commercial batches. If differences are identified and a possible adverse impact on safety and efficacy profiles cannot be excluded, the Applicant should perform non-clinical and/or clinical bridging studies. Considering the numerous process modifications made after manufacturing of clinical study material, which may potentially affect the efficacy and safety of future product, this issue is considered as **Major Objection (MO3)**.

With regards to ICH Q11 the applicant has followed a "traditional" approach for the development of Begelomab. A traditional process development is acceptable provided the manufacturing process is well controlled, i.e. set points, operating ranges and in-process controls should be set narrowly on the basis of proper process validation data to ensure product quality and process consistency. Also in a traditional approach more emphasis is placed on assessment of CQAs at the stage of the drug

substance, i.e., end-product testing. In other words, an acceptable overall control strategy should be applied. However, for BEGEDINA this is not the case.

The absence of a detailed description of the manufacturing process with a clear identification of all process parameters, set points, well-justified operating ranges and in-process controls is considered a major objection. (MO5)

According to the Applicant the downstream purification process of begelomab is reproducible and robust. However, hardly any data has been supplied to substantiate this conclusion. Actual results for operational process parameters, most in-process controls and performance parameters have not been provided. **The process cannot be considered as validated and this is considered a Major Objection. (MO6)**

The proposed active substance and finished product specifications of begelomab are considered insufficient to control its complex purity/impurity profile. The appropriateness of the proposed assays should be justified **(part of MO2). The lack of an appropriate set of specifications is considered a Major Objection (MO7)**. In addition, many of the analytical methods have been poorly designed, justified and/or validated.

Finished product

In relation to the description and control of the manufacturing process, the Major Objection raised for the active substance also applies to the finished product: an adequate description and justification of process parameters and in-process controls should be provided together with their acceptance ranges and criticality status.

Process validation data for the finished product in terms of comparison of in-process controls demonstrating that the process is able to meet established acceptance ranges and is consistent has not been submitted. The batch testing data for all available batches should be presented for assessment as a part of the demonstration that the process has been validated. **The Major Objection raised for process validation of the active substance also applies to the finished product**.

The company has stated that the Dulbecco's Phosphate Buffered Saline (DPBS) used as excipient is commercially sourced. Specifications for the excipient Dulbecco's phosphate buffered saline (DPBS) have been provided however questions are outstanding about how the quality of the individual ingredients of DPBS is controlled. Moreover, since DPBS is the formulation buffer and its manufacture is an essential part of the DS and DP manufacture, the applicant should provide evidence that the manufacturing process of DPBS adheres to GMP. **Since the quality of the excipients can have a major impact on product quality, the BWP considers this to be a Major Objection (MO8)**.

Sufficient evidence to ensure the sterility of the DP has not been submitted. The applicant should clarify what procedures are in place to control the consistent sterility of these components. **The currently insufficient evidence for ensuring sterility is considered a major objection, particularly because the product is administered to immunosuppressed GvHD patients (MO9)**.

A complete set of stability data based on an improved testing strategy for a sufficient number of full-scale batches manufactured by the proposed commercial process should be submitted for MA unless otherwise justified. **The absence of appropriate stability data is considered a major objection (MO10)**.

Adventitious agents

Sufficient evidence to demonstrate viral safety has not been submitted and this is considered a **Major Objection (MO4).**

In conclusion, a positive opinion cannot be recommended for this product and significant deficiencies are identified in almost all parts of the quality dossier. The product development, characterisation and control strategy (as described in the application) are incomplete. Insufficient assurance is provided that the commercial product is of adequate quality and a large number of major objections are identified that could have a significant impact on safety or efficacy. It should be noted that some of the proposed major objections are multifactorial and should be addressed in conjunction with other questions as listed under other concerns.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

Several Major Objections have been identified, which precludes approval of BEGEDINA at this stage.

3.2. Non clinical aspects

3.2.1. Pharmacology

Begelomab's target: CD26 / DPP IV

Begelomab is a murine IgG2b monoclonal antibody targeted against CD26. CD26 or DPP-IV is a dipeptidyl peptidase, member of the DASH family (DPP-IV activity and/or structure homologues). It is a ubiquitous protein that has a membrane bound and a soluble variant. CD26/DPP-IV can act as a serine exopeptidase with a dipeptidyl peptidase activity that regulates various physiological processes by cleaving peptides in the circulation. Via its enzyme activity it has roles in nutrition, metabolism, the immune and endocrine systems, bone marrow mobilization, cancer growth and cell adhesion. Over 30 substrates are known to be cleaved by CD26/DPP-IV of which GLP-1 is most studied, but also include many chemokines, mitogenic growth factors, neuropeptides and peptide hormones. In association with FAP it is involved in the pericellular proteolysis of the extracellular matrix (ECM), the migration and invasion of endothelial cells into the ECM. It may also be involved in the promotion of lymphatic endothelial cells adhesion, migration and tube formation.

Besides its peptidase activity, CD26/DPP-IV has also been shown to bind, but not cleave, adenosine deaminase, binds to the kidney Na+/H+ ion exchanger and fibronectin and plays a role in cell surface localization of these molecules. In addition, CD26/DPP-IV acts as a positive regulator of T-cell co-activation, by binding at least ADA, CAV1, IGF2R, and PTPRC. Its binding to CAV1 and CARD11 induces T-cell proliferation and NF-kappa-B activation in a T-cell receptor/CD3-dependent manner. Its interaction with Adenosine Deaminase also regulates lymphocyte-epithelial cell adhesion. When CD26 is overexpressed, it may enhance cell proliferation, a process inhibited by GPC3 (adapted from http://www.genecards.org/cgi-bin/carddisp.pl?gene=DPP4).

Primary pharmacology - *In vitro*

One *in vitro* primary pharmacology study has been submitted. In this study, the expression of CD26, recognized by begelomab, was studied in human, marmoset and minipig blood lymphocytes. Begelomab did not recognize CD26 on minipig lymphocytes, thus this animal is not appropriate for preclinical studies with begelomab. Begelomab recognizes CD26 on T-lymphocytes in marmoset and human. Marmoset can thus be used as a species for preclinical testing. It has however, not been shown whether begelomab binds to the soluble variant of CD26/DPP IV.

In human and marmoset CD26 is expressed on subsets of CD3+CD4+ and CD3+CD8+ T-lymphocytes. In Marmoset, CD56+ Natural Killer cells express CD26, recognized by begelomab, whereas this

population is not found in human. For both species a CD3+, CD4+ CD26+ CD45RA+ lymphocyte population could be detected. In human, also a CD3+ CD26 bright population is found, which is positive for CD4 and for CD45 RO as well. This CD3+, CD4+ CD26+ CD45 RO+ T-lymphocyte population was not detected in marmoset. In the study report it was noted that the lack of expression of CD45RO by marmoset T lymphocytes could be related to a lack of significant antigenic stimulation of marmosets T lymphocytes, which did not allow for specific differentiation of circulating effector/memory T lymphocytes.

In 2013 the CHMP advised to provide a discussion on the differences in CD26 positive T-lymphocyte populations in marmoset and human and on the subsequent relevance for the extrapolation of the non-clinical efficacy/safety data towards the clinics. This discussion was not provided by the applicant.

In the report it is stated that binding of begelomab to human and marmaoset CD26 was tested over a concentration range of 0.5 µg/ml - 500 µg/ml. For human the optimal concentration was 5 µg/ml and for marmoset 2.5 µg/ml. However, the data are not shown.

Primary pharmacology - *In vivo*

Mouse – proof of concept

The efficacy of begelomab murine monoclonal antibody against human CD26 was examined in a xenograft graft-versus-host disease (GvHD) model based on the transfer of human peripheral blood mononuclear cells in irradiated NOD/ShiLtSz-Scid/IL2Rgamma null mice. These mice completely lack T, B and NK cells and have qualitative defects in macrophage and dendritic cell functioning, and therefore these mice do not oppose substantial immunological barriers to the transfer of human cells. The applicant claims that begelomab is proven to have a positive effect on the delay of lethal GvHD in this model, but the study design limits conclusions on dose dependency, a potential mode of action and the difference in effect with a CD26 inhibitor. In addition, results from the first set of three experiments are not in line with results obtained in a second set of two experiments, which questions effectivity of the antibody in this xenograft graft versus host disease model. These issues are addressed below.

According to the applicant, therapeutic effect of 0.01 – 0.02 – 0.03 mg begelomab at inhibiting the early development was dose dependent. The final endpoint is hardly different for the three doses and the mid dose seems most effective. The doses do not differ substantially to conclude a dose dependent effect.

In mice injected with human PBMC and treated with begelomab there is a trend of reduced circulating human CD3+ T cells and a failure of CD4+ T cells to up-regulate the begelomab target CD26 *in vivo*. According to the applicant the mechanism of action of begelomab may include *in vivo* down-regulation of CD26 on activated T cells possibly resulting in reduced proliferation and differentiation into effectors cells. *In vivo* CD26 down-regulation on CD4+ T cells may be used as an efficacy biomarker, although statistical significance is lacking, and the observation is not done for CD8+ cells.

The dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin (Januvia®) was introduced as a comparator and was shown to be ineffective at inhibiting early development of GvHD. The applicant suggested therefore that the therapeutic effects of begelomab are independent from a putative anti-enzymatic activity against DPP-4.X-GvHD model. However, given the dosing regimen of 2 days BID and the short half life [half life of sitagliptin in rodents is approximately 1 hr (EPAR Januvia®)], exposure to sitagliptin was too short to have measurable activity on day 7 or 14. Begelomab is a murine antibody and likely eliminated via the murine Fc mediated pathway, resulting in a much longer half life. The lack of toxicokinetic (TK) data makes the study inconclusive on the effect of sitagliptin in delay of lethal GvHD.

In the first study, there was evidence of prolongation of survival in mice given BEGEDINA compared to mice given only saline and there was also evidence that survival was better at the higher dose of BEGEDINA (0.03 mg/kg) than the lower dose (0.01 mg/mouse). Mice given BEGEDINA showed reductions in CD3+ T cell counts in the peripheral blood and the applicant indicated this proves the mode of action of the product. It was also noted that there was downregulation of CD26 expression following exposure to BEGEDINA. However, a second study, of similar design, did not replicate these results. Across the two studies the profile of the saline control group was markedly different, and this was not explained. At day 21, there appears to be a difference between saline and each BEGEDINA dosing posology, in the measure of CD3+ cells and this difference is less at day 28 and disappears by day 35 and later – thus, it appears that the early effect of BEGEDINA is still present but does not result in either it being sustained or in activity to extend life. The key difficulty is that the effect of BEGEDINA to reduce CD3+ T cells at days 14 and 21 with this effect being lost gradually from day 28 onwards, is apparent in both studies, but in only one study is there an effect of BEGEDINA to prolong survival. In particular, the saline group in the second experiment survived to day 35 (median) whereas in the first this was 14 days and this difference in the saline group could explain the inability of the second study to show an effect of BEGEDINA to extend life due to a ceiling type of effect: the inference is that the saline group performances in this testing are not robust. If this conclusion is accepted, it calls into question the evidence supporting the action of BEGEDINA from the first set of testing results. The applicant should explain this apparent inconsistency.

Marmoset – pharmacological analysis

Binding of begelomab to CD3+ CD4+ CD26+ or CD8+CD3+CD26+ T-lymphocytes has been followed in the single, and the two repeated dose toxicity studies for begelomab. Binding to CD26 is 100%. CD26 cell surface levels decrease during treatment, which may be antibody mediated. It is anticipated that cell surface expression of CD26 is upregulated again when antibody levels decrease due to new synthesis of the protein. However, on day 42 in the pivotal study only absolute binding to CD26 was measured whereas relative levels of begelomab bound CD26 were not analysed. It can thus not be concluded how long the antibody mediated downregulation of CD26 is maintained after the last dose and how long the effect may hold.

Secondary pharmacology

A short discussion on the secondary pharmacodynamic aspects of begelomab has been submitted. Since primary pharmacology of begelomab is limited and not conclusive with regard to the effect of the binding of the antibody to CD26, and due to the absence of a cross reactivity studies it is complicated to predict and discuss potential secondary pharmacology effects.

The applicant refers to the observation of increased blood glucose which is regarded a proof that begelomab is not involved in GLP-1 cleavage and thus insulin secretion. However, a change in glucose levels is not necessarily due to GLP-1 levels alone. The increase of glucose, the observed decrease of urine volume and glucosuria could indicate that the function of kidneys is compromised, which is not unlikely seen the high CD26 expression in the kidney. As a direct indication of the effect of begelomab on GLP-1 cleavage, the sponsor should have tested the peptidase activity *in vitro* as part of the primary pharmacology.

Safety pharmacology

It is agreed that safety pharmacology assessment is conducted within the repeated dose study in marmosets. Begelomab is a murine antibody and is likely not transported over the Blood Brain Barrier and therefore CNS effects are not anticipated. Absence of remarkable behavioural effects upon treatment with begelomab confirms this assumption. In the pivotal study no remarkable observations were done with regard to the ECG, which supports that cardiovascular function is not affected. In the

pivotal repeated dose study one animal showed extramedullary haematopoiesis in heart and in both male and female animals an increase in the incidence of abscess and thrombi in lungs were observed. The clinical relevance of these findings was not discussed. Since CD26 is widely expressed and among other tissue also in lung, heart and kidney, the safety pharmacology addressed within the toxicology study was too limited.

3.2.2. Pharmacokinetics

Method of analysis

Two validated assays and one qualified assay were used to detect levels of begelomab and levels of anti-drug antibodies (ADA) in serum. To detect begelomab in serum a sandwich ELISA (assay 88840) was developed. The test item containing the murine antibody begelomab was applied to wells coated with Rabbit anti Mouse IgG followed by the incubation with an anti mouse antibody coupled to Horse Radish Peroxidase. The assay was validated and the levels of accuracy and precision are in line with the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009).

To detect ADA against begelomab, first a bridging (human anti-mouse antibody, HAMA) ELISA was used. Sera with begelomab and ADA were applied to wells that were coated with anti mouse IgG and thereafter incubated with anti mouse HRP for detection purposes. This method was validated but not successful in detecting ADA. Therefore another ADA detection assay, a competitive sandwich ELISA, was developed. Sera, either or not spiked with begelomab, were applied to wells that were coated with the target, CD26, followed by incubation with anti mouse –HRP to detect begelomab. In order to detect whether ADA were bound to begelomab resulting in a decreased signal, the sera were spiked with begelomab to assess the maximal binding signal. The results of unspiked and spiked sera were compared and when inhibition of binding /detection took place, the presence of ADA was confirmed. This assay was not validated but turned to be more specific than the HAMA assay in detecting ADA.

Absorption

Analysis of begelomab serum concentration showed that all animals were amply exposed to the product for the entire period of the study. On day 1, the values of AUC0-tlast and Cmax increased with dose in a supra-proportional manner. Quantifiable amounts of begelomab were still measurable at 24 hours from the end of the infusion.

Levels observed on day 28 were characterized by measurable levels at pre-dose sample and small serum concentrations were still measurable after 1 week of treatment-free period in most of the animals. After repeated administration for 28 days, gender differences were observed in PK parameters, with exposure (AUC) being higher in males than in females at both dose levels, due to stronger immunogenicity in 1/3 female animals per group. It is unlikely that it has anything to do with gender related mechanism. In the high dose group accumulation of the antibody occurs which is most prominent (approximately 3-fold) in male.

In the high dose group, males and females are exposed up to 4 mg*hr/mL and 2.5 mg*hr/mL. Cmax, most of the times reached after one hour, was 176 µg/mL for male and 111 µg/mL for female animals on day 28. T1/2 could only be calculated for the high dose group being 18 hr for females (based on 2 animals) and 25 hr for males (based on 3 animals).

Clinically only limited PK data were available. At a dose of 3 mg/m^2, the elimination half life was < 2.5 days and the Cmax was 200 ng/mL. Cmax levels reached in marmoset are > 500 fold higher. However, in humans, the elimination half life turned to > 2.5 times longer. Absence of clinical exposure

levels makes comparison imposable. It is expected however, that based on the 500 fold higher Cmax and the ± 2.5 times lower T ½ of begelomab in marmoset that these animals in toxicity studies have been exposed higher than human.

Elimination of the antibody is likely target mediated. The mouse IgG2b is only weakly bound by human FcRN receptor (Ober RJ et al, Int Immunol., 2001).

Distribution

The applicant did not discuss the tissue distribution of the target, which could have been helpful in understanding the toxicity. A tissue distribution study could have been used to analyse whether the distribution of the target and the distribution of the antibody were similar between human and test species or not. The absence thereof is limits in the understanding of the toxicity findings.

Other PK studies

The absence of studies addressing metabolism, excretion and pharmacodynamic drug interactions or other pharmacokinetic studies is agreed taken into account the nature of the product.

3.2.3. Toxicology

Repeated dose toxicity

Both a 7 days preliminary and a 28 days pivotal toxicity study were conducted for begelomab in marmoset.

Preliminary 7 day toxicity study.

In the preliminary study, 3 females were given a high dose of begelomab via a 1 hr-during infusion with was repeated for 7 days. Saline was given to three females as control group. Seven days after the last treatment all clinical pathology observations were done. All analyses were done after a recovery period of one week. This limits the observation of treatment related findings. In addition, the two treatment groups are not sufficiently equal before dosing, which further compromises the identification of treatment related findings. Decreases in haemoglobin and haematocrit and increase in neutrophils were observed. Findings are not discussed by the applicant and the relation to the mode of action of begelomab cannot be made, since the MoA is not sufficiently investigated.

Pivotal 28 days toxicity study

In the pivotal study 3 animals per sex, per group were used to test two different concentrations of begelomab. Animals were infused for 1 hr daily, which was repeated for 28 days. On day 28 haematology, clinical chemistry and urinary analysis were conducted. At day 42 this was repeated and the animals were sacrificed for macro- and micro pathology, thus after a recovery period. Normally, the main group is analysed at the end of treatment and a recovery group is introduced and analysed after an additional recovery period. In this case, no main group was included, thus no data on the treatment related effects is available. This makes a conclusion on begelomab related adverse effects not possible. In the scientific advice of 2013 the CMHP notes that that necropsy and macro- and micro-scopical analyses of animals is expected at the end of treatment, n this case on day 28. Necropsy after a recovery period (recovery group) would only yield relevant information when necropsy at the end of treatment (main group) has been performed as well. The CHMP also notes that a 28 days necropsy of

3 animals/sex/group leaves no animals for a recovery group. For recovery analysis additional animals should have been included in the study. This CHMP advice was thus not followed.

All animals groups (including the control group) in the study lost more then ten percent of body weight over the course of the study (either 14 days or 28-42 days). Weight loss and possibly related effects (eg leukocyte decrease) during study may be signs of unfavourable conditions (housing) or illness (wasting disease) for the animals and mask potential treatment related effects. To exemplify: animals showed extramedullary haematopoiesis on day 42. This may be a manner to compensate for the decreasing levels of leukocytes because of weight loss due to housing condition. However, it could also be related to treatment or have masked treatment-related effects. Notably, in the preliminary toxicity study, extramedullary haematopoiesis was a treatment related finding.

Overall, the identification of treatment related effects in this study is complicated. Effects in Treatment groups have to be compared to the control group. In addition, results from measurements conducted at week 4 and week 6 have to be compared with pre-dose measurement results. To enable identification of treatment related effects, the applicant should have presented and compared the data between the different groups and in time in one overview table. This was only done for four RBC parameters. The absence of such a comparison table limits interpretation of the study findings and the assessment of the data.

The pivotal study includes two doses and for each dose three animals per sex. The presence of ADA may have affected the exposure in some animals and thus have may have influenced the lack of dose dependency for certain findings. Therefore, incidental findings and findings without dose dependency should also be taken into account in the safety evaluation.

In the pivotal study a decrease of haemoglobin, haematocrit and platelets (male at end of study) and an increase of reticulocytes were noted. Leukocytes levels also decreased. Liver enzymes, blood glucose, cholesterol, blood urea and bilirubin were increased, albeit the latter three in one male only. Males show a decreased urine volume and urinalysis revealed glucosuria, ketonuria and increased bilirubin levels was observed in some females. Macroscopically adrenals, right femoral vein, liver, spleen, thymus and starting from the last dose the testis and ovary appeared abnormal, either in size, shape or colour. Main microscopic findings were haemorrhage of femoral veins and thrombus, abscess and thrombus in lungs, congestion and subchronic inflammation of mesentheric lymph nodes, subchronic inflammation of and thrombus in skeletal muscle. Also subchronic inflammation and epidermal hyperplasia of the hind limb, extramedullary haematopoiesis of the heart, extramedullary haematopoiesis and subchronic inflammation of the spleen and, cortical mineralization of kidney and haemorrhage of ovary has been observed. The applicant regarded above findings as incidental, not dose dependent or not treatment related due to similar observation in control animals and a relation to begelomab mode of action was not made. This is not agreed because of study design limitations, as explained before. A relation between mode of action of begelomab and toxicity findings upon treatment with begelomab in the toxicity study cannot be laid, since the MoA is not sufficiently investigated.

Antigenicity

At day 42, Anti Drug Antibodies (ADA) were detected in all animals. At day 28, ADA were detected in only two animals, but may have been underestimated. For example for one female (No 9) in the low dose group very low levels of begelomab before the last dose, as well as very low begelomab positive T-lymphocytes were observed. No ADA were detected, but exposure levels and pharmacodynamic measurement strongly suggest ADA in this animal. Results may suggest that ADA are formed mainly after end of treatment / dosing, when begelomab levels will decline again, but this is not likely. Instead, underestimation of levels of ADA formed during the study is more plausible. Antibody

interference in the ADA detection assay may have occurred in measurements conducted during or shortly after dosing due to high levels of begelomab in serum.

Tissue Cross Reactivity

No cross reactivity studies have been conducted by the applicant. Instead, the applicant discusses the result for histopathological tissue staining from a study conducted and published by Hatano and coworkers (2013). First of all, this study is conducted with a humanized anti-human CD26 monoclonal antibody (mAb), instead of a murine variant. Thereby it is not discussed whether the murine begelomab and the humanized antibody against CD26 recognizes the same CD26 epitope. In addition, the applicant remarks in the pharmacology written summary: 'these models cannot be used to evaluate begelomab efficacy due to the fact that murine T lymphocytes express very low levels of CD26 (begelomab target) and that the murine CD26 is not recognized by begelomab.'

It is unlikely that the above presented results can be used as data for cross reactivity data for begelomab. Instead, a study addressing begelomab tissue cross reactivity in human and marmoset is missing and would have been valuable for interpretation of the findings in the toxicity study with begelomab. In addition, the distribution of CD26 in marmosets should have been investigated and discuss this in comparison with that of humans to verify that CD26 has similar tissue distribution in humans and marmosets. By not conducting a CD26 distribution analysis nor a begelomab tissue cross reactivity studyfor human and marmoset tissues, the applicant has not followed the advice from the CHMP in 2013. Results of these analyses could have an impact on the conclusions of the safety studies.

Absent studies

The absence of genotoxicity is agreed seen the nature of the product and the absence of carcinogenicity studies is agreed since the product is only given for a short period.

The absence of studies addressing the affect of begelomab on fertility and early embryonic development, embryo foetal development, prenatal and postnatal development and juvenile toxicity is agreed. The therapy before begelomab treatment would become relevant already impairs fertility. In addition, patients are severely ill and pregnancy will likely not occur. Begelomab should not be used during pregnancy and breastfeeding should be discontinued while using begelomab.

The absence of local tolerance and other toxicity studies with begelomab is agreed. The absence of studies addressing specific immunogenicity, dependence, metabolites, impurities.

3.2.4. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Begelomab is not expected to pose a risk to the environment. An ERA is therefore not deemed necessary.

3.2.5. Discussion on non-clinical aspects

Pharmacology

As a whole, the *in vitro* pharmacology is insufficiently addressed. Only the binding to CD26 present on T-lymphocytes have been investigated. It is not investigated whether begelomab can bind the soluble variant. Also the influence of begelomab binding on the function of CD26 / DPP IV has not been addressed, which may vary from the peptidase activity of CD26 / DPP IV on several substrates (such as GLP-1 degradation), to T-cell co stimulation and proliferation and binding to kidney NA+/H+ (NHE3) ion exchanger, fibronectin or adenosine deaminase and even more as can be found in literature. This limits the understanding of the mode of action of the antibody.

The *in vivo* POC study suggests an effect for begelomab in delaying lethal GVHD. However, the study is rather preliminary due to its limits in study design, and efficacy should be demonstrated by clinical use. In addition, results from the two different sets of experiments are conflicting, which further questions an effect of begelomab in delaing lethal GVHD in the xenograft GVHD model in mice.

CD26 cell surface levels decrease during treatment, which may be antibody mediated. Due to limitation in analysis of relative binding at end of the study, it can not be concluded how long antibody mediated downregulation of CD26 is maintained after the last dose and how long the effect may hold.

A proper discussion on secondary pharmacology is missing.

Discussion on the toxicology findings as extramedullary haematopoiesis in the heart and abscess and thrombi in lungs was lacking. An article on Safety assessment of mAb's (Brennan, 2014) states that *'For candidates with concerns, e.g., where the target is expressed in lung or heart, more detailed assessments (including blood gases and mucous membrane colour) may be required, possibly including plethysmography if the rodent is a relevant toxicological species. Renal assessments are easily assessed via inclusion of urinalysis in repeat dose toxicity studies and an accompanying histopathology assessment of the kidney, urinary bladder and urethra'*. Since CD26 is widely expressed and among other tissue also expressed in lung, heart and kidney, the safety pharmacology addressed within the toxicology study was too limited.

Preclinical pharmacology of begelomab is not sufficiently addressed to support its use in treatment of steroid resistance GVHD**:**

a. The characterisation and functional consequences of binding of begelomab to CD26, e.g. binding affinity of begelomab for human and marmoset CD26, binding to soluble CD26 / DPP-IV, effects of binding on peptidase activity of DPP-IV and the effect of binding on antibody-mediated downregulation of target, have been characterised insufficiently in *in vitro* studies.
b. The design and results of the *in vivo* studies in mice do not allow any conclusion on the mode of action of begelomab in treatment of steroid refractory GVHD. With regard to the study design the linearity of and small difference between chosen test-doses for begelomab and the chosen dose regimen for the DPP-IV inhibitor do not allow any conclusion on efficacy and on mode of action of begelomab. With regard to the results the results for the survival of control groups in experiments 4-5 are markedly different from those in experiments 1-3. This also holds true for the values of CD26 on each of CD4+ and CD8+ cells. The robustness of these results supporting the activity of begelomab is questioned.

The applicant is requested to provide additional experimental data or a suitable justification for the lack of data, which may include evidence from on additional clinical data.

Toxicology

The toxicity of begelomab was not sufficiently addressed. The body weight loss of the animals during the study, the variability of the groups pre dose (WBC and liver enzymes) and the lack of microscopic analysis at the end of treatment, although advised by the CHMP, comprises the quality of the design and thus the outcome of the pivotal toxicology study. The applicant regarded the toxicity findings as incidental, not dose dependent or not treatment related due to similar observation in control animals and a relation to begelomab's mode of action was not made. This is not agreed, because of above described study design limitations. In addition, the Mode of Action is not sufficiently investigated, which complicates interpretation of toxicity findings.

Anti Drug Antibodies are detected in all animals at day 42, but only in two animals at day 28, which maybe underestimated. It is not likely that the majority of animals only start developing ADA when antibody levels are already declining. In addition, it is plausible that high levels of begelomab interfere with ADA measurement during dosing at day 28. Therefore, ADA detection during dosing maybe less reliable.

Studies addressing begelomab tissue cross reactivity in human and marmoset or CD26 tissue distribution in human and marmoset are missing, although advised by the CHMP, and would have been valuable for interpretation of the findings in the toxicity study with begelomab. Due to its compromised design, made explicit below,, and in ~~the~~ absence of a separate safety pharmacology study, the pivotal toxicity study is not conclusive on the preclinical identified safety risks**.** The following issues are identified:

a. Microscopic analysis was only done after a period of non-treatment (called recovery), when antibody levels were much lower compared to end of treatment, limiting the identification of treatment related findings.

b. All animals showed >10 % weight decrease and possibly related effects (decrease in leukocytes and related extramedullary haematopoiesis) during study which may be a sign of unfavourable conditions (housing) or illness (wasting disease) for the animals and likely mask treatment related findings.

c. Predosing-differences between groups interfere with the interpretation of treatment related findings. In combination with the low number of animals per group, this compromises the ability to detect treatment-related effects.

d. The limited knowledge on begelomab pharmacodynamics does not allow understanding of the observed toxicity findings such as the extramedullary haematopoiesis and the findings in the kidney.

~~e.~~ Absence of a cross reactivity study in a set of human tissues with begelomab itself hinders identifying the target organ specificity of begelomab. Lack of data on tissue distribution of the target (CD26) in humans and marmosets (as requested in in SA procedure EMEA/H/SA/2241/1/FU/1/2013/PA/SMEIII) does not allow any interpretation of the marmoset toxicology data.

The applicant is requested to comment on the relevance of the toxicity study and the noted pharmacodynamic limitations and discuss the possible value of additional toxicity studies.

3.2.6. Conclusion on non-clinical aspects

Major objections to the marketing authorization of begelomab are currently formulated from the non clinical part of the dossier. The non clinical information submitted for application of marketing authorisation is not sufficient. Based on non clinical data, begelomab can not be authorised for market admission.

3.3. Clinical aspects

Clinical development of begelomab in steroid resistant aGvHD is currently limited to two uncontrolled studies both of which were conducted in a single centre in Italy:

- A Phase I/II open-label pilot study in patients who received prior HPCT and with grade II-IV GvHD. Patients were followed for 365 days after the first dose of treatment.
- A Phase II open-label dose-finding study for treating steroid-resistant aGvHD patients who previously underwent HPCT. Patients were followed for 180 days after the first dose of treatment.

In total, 29 adult patients have been treated with begelomab, of whom 28 with acute GvHD are included in the efficacy full analysis set.

Tabular overview of clinical studies

Table 8 Overview of clinical studies

Study ID	**No St. Centres** Location	**Design**	**Dose, route**	**Duration of treatment**	**Number of subjects** Enrolled/evaluable	**Study Objective** (Primary Endpoint)
Study EUDRACT 2007-005809-21	1 Italy	Pilot, open-label, uncontrolled study	2 mg/day IV,	5 consecutive days	14/12	Efficacy and Safety (frequency of responder patients at Day +10)
Study EUDRACT 2012-001353-19	1 Italy	Dose-finding, open-label, uncontrolled study	DL 1: 2mg/m^2 IV,	5 consecutive days	16 patient DL 1: 3/3	Efficacy and Safety (MED and PD/PK assessment[a])
			DL 2: 3mg/m^2 IV	5 consecutive days	DL 2: 3/2	
			DL 2bis: 3mg/m^2 IV	5 consecutive days and day+10,+14, 17,+21,+24, +28	DL 2bis: 7/0	
			DL 3: 4.5 mg/m^2 IV	5 consecutive days	DL 3: 3/3	

DL: dose level, MED: minimal effective dose, PD/PK: pharmacodynamic/pharmacokinetic,
a: BEGELOMAB® positive cells staining with anti-mouse IgG within Day +5 of BEGELOMAB® treatment

The Applicant is aware that more and controlled data are needed for a full MA, and therefore applies for a conditional MA (CMA). Therefore a confirmatory phase II/III study is also planned.

Table 9 Confirmatory study

Study ID	**No. of study centres / locations**	**Design**	**Begelomab** **Dose, route and regimen**	**Study objective**	**Primary endpoint**	**Key secondary endpoint**
ADN011	Approx 30 bone marrow transplant units in Europe, US and Canada	Phase II/III, multicenter, open label, randomized control study comparing begelomab with 'conventional treatment'.	2.7mg/m^2 for 5 consecutive days from study day 1 to 5 and on day+10,+14,17,+21,+24,+28	Efficacy, safety, PK	Overall response at 28 days and TRM up to 180 days	Overall survival up to 180 days

According to principle outlined in of EMA/509951/2006, at least one of the following three requirements are needed for eligibility for conditional marketing authorization, i.e.

- seriously debilitating diseases or life-threatening diseases;

- medicinal product to be used in emergency situation;

- orphan medicinal product.

The Applicant argues that BEGEDINA fulfils the requirements for conditional approval based on its designation as an orphan drug and because of the unmet medical need in the treatment of the condition, i.e. steroid-resistant acute GvHD. It is agreed with the Applicant that the first and third of the above requirements are fulfilled, and thus that BEGEDINA (begelomab) is eligible for a CMA.

A conditional approval may be granted where, although comprehensive clinical data have not been supplied, all of the requirements (a)-(d), as defined in Article 4 of Commission Regulation (EC) No. 507/2006, are met. These comprise:

(a) the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive;

(b) it is likely that comprehensive data can be provided;

(c) unmet medical needs will be fulfilled (no satisfactory methods or major therapeutic advantage);

(d) benefits of immediate availability outweigh risks due to additional data to be provided.

These aspects will be addressed in this overview when applicable, and especially in the benefit/risk section (section 5).

3.3.1. Pharmacokinetics

BEGEDINA is formulated as 0.9 mg/ml begelomab concentrate for solution for infusion and is intended to be administered by intravenous route. The recommended daily dose is 2.7 mg/m^2 body surface area (Extinction coefficient of begelomab was determined later in the development: 3 mg/m^2 used in this report equals 2.7 mg/m^2 in the SmPC). Begelomab should be administered daily for 5 consecutive days. The administration should then be repeated on days 10, 14, 17, 21, 24 and 28 for a total of 11 doses.

Pharmacokinetic, pharmacodynamic and immunogenicity data of begelomab in humans were assessed from two clinical studies in patients developing aGvHD after HPCT. The proposed dose and schedule have been applied in 7 patients in the pivotal phase 1 / 2 study 2012-001353-19.

Studies to evaluate excretion, metabolism and interactions have not been conducted, which is acceptable because begelomab is a murine immunoglobulin and not subject to metabolism by P450 enzymes or subject to excretion by the kidneys. Studies in hepatic and renal impaired patients are also not required.

Methods

The method to determine begelomab in serum seems to be based on a general detection of mouse IgG and not a specific assay for detection of begelomab. The method to detect anti-begelomab antibodies was a general method for human anti-mouse antibodies using a commercial kit. The methods were not described detailed enough to allow full evaluation. Bioanalytical reports of studies 2007-003809-21 and 2012-001353-19 should be submitted.

Mainly pre-dose and 15 min after end of infusion samples were collected for pharmacokinetics, which is not optimal to describe the pharmacokinetic profile of begelomab. Sample collection was not frequent enough to conduct a non-compartmental analysis. P-Pharm was used for parametric modelling. Pharmacokinetic parameters may depend on the parametric modelling program used (Staatz, Eur J Clin Pharmacol. 2002). The correlation between predicted and observed data using P-Pharm was not optimal (*Slope = 0.68 (SE 0.046); Intercept =73.021 (SE 12.6395); R = 0.7799 (144 df).* Further, unexpected serum concentrations were observed e.g. mis-match pre-dose and post-dose values, increase in serum concentrations in the elimination phase. Therefore, quantitative description of the pharmacokinetics of begelomab should be considered very cautiously.

Formulation

The to-be-marketed formulation is manufactured by a different process than the formulation used in the clinical studies. Clinical comparative studies with the commercial manufacturing process may be required as analytical comparability between the formulation used in the clinical studies and the to-be-marketed formulation has insufficiently been demonstrated.

Results

Study 2012-0011353-19 was a dose-finding, open-label, single-centre, phase II, uncontrolled study of begelomab dose escalation for treating steroid-resistant aGvHD subjects. Three subjects per group received 2 mg/m^2, 3 mg/m^2 or 4.5 mg/m^2 for five consecutive days. **Figure** 4 shows the mean profile of begelomab concentration per group. Begelomab concentrations were higher in subjects treated with 4.5 mg/m^2 than in subjects who received 3 mg/m^2 of drug and than those treated with the 2 mg/m^2 dose.

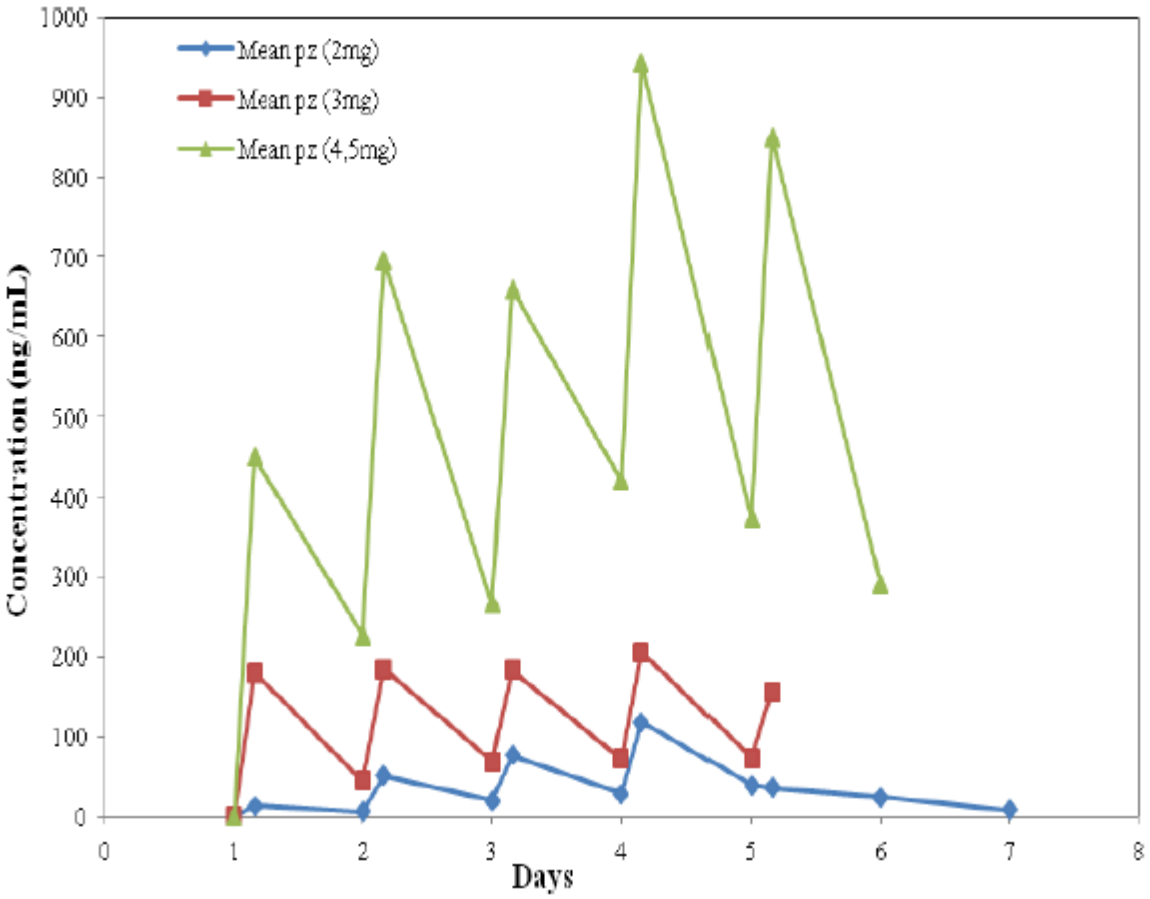


Figure 4 Dose dependency of begelomab pharmacokinetics. Mean serum concentration-time profile in subjects (N=3 per group) treated with 2 mg/m^2, 3 mg/m^2 or 4.5 mg/m^2 begelomab for five consecutive days.

Pre- and post-dose begelomab concentrations from the seven subjects who received 3 mg/m^2/day of begelomab for 5 consecutive days with 6 additional 3 mg/m^2/day doses at Days: +10; +14; +17; +21; +24; +28 are shown in Figure 3. Concentrations of begelomab varied greatly between subjects and a considerable variability was observed within one subject: post-dose begelomab serum concentrations ranged from 0.05 to 1.25 µg/ml. In most subjects post-dose begelomab concentrations were higher following multiple dosing compared to the first dose. Predose begelomab concentrations

were higher during the first 5 days when begelomab was administered daily compared to the predose values at days 10-28 when begelomab was administered every 3-5 days.

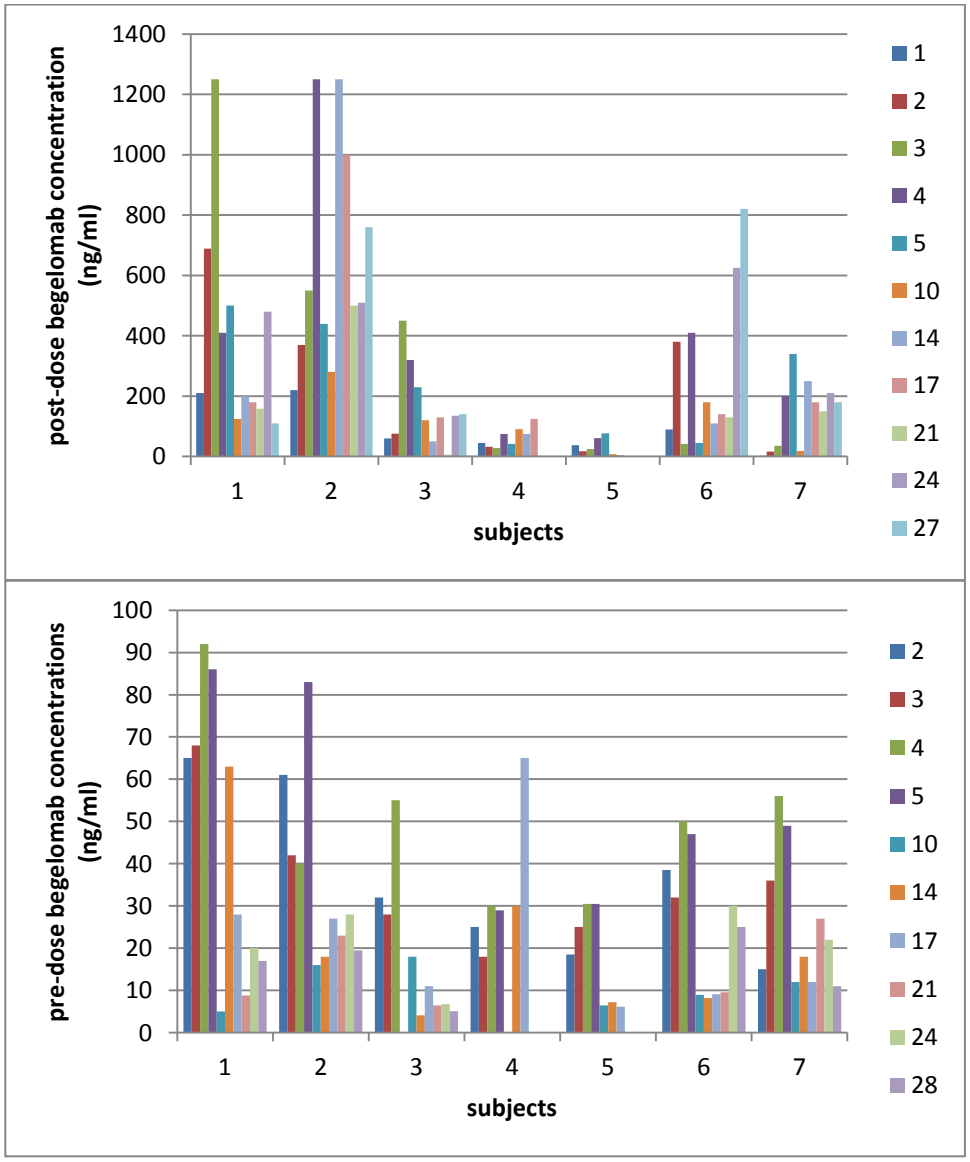


Figure 5 Begelomab concentrations post-dose (top) and pre-dose (bottom) in 7 subjects treated with 3 mg/m^2 begelomab for 5 consecutive days followed by doses at days+10; +14; +17; +21; +24; +28 (study 2012-001353-19)

Immunogenicity of begelomab was evaluated in 28 patients. Eight out of 28 patients (28%) developed detectable HAMA levels, which is in line with reported incidences for a murine antibody. Given the high intra-subject variability observed, the unknown drug tolerability of the HAMA assay, no conclusions can be drawn if the HAMAs affected pharmacokinetics of begelomab.

3.3.2. Pharmacodynamics

The mechanism of action of begelomab is associated with its ability to bind CD26, which is mainly expressed on activated lymphocytes. Begelomab is thought to act by down regulation of activated

lymphocytes. Proof for use of begelomab in treatment of aGvHD was derived from in a xenograft murine model of human aGvHD.

The clinical pharmacology program included *in vitro* pharmacodynamics studies to evaluate CD26 expression in resting T, B and NK cells purified from healthy donors and patients after allogeneic-hematopoietic progenitor cell transplantation with /without onset of aGvHD. Further, begelomab binding to CD3+CD26+lymphocytes was evaluated following treatment with begelomab in studies 2007-003809-21 and 2012-001353-19. Begelomab exposure CD3+CD26+lymphocytes binding relationships were explored. No secondary pharmacology or pharmacodynamic interaction studies were conducted.

Compared with healthy controls, allo-HPCT patients showed an increase of CD26 expression within the CD3+ CD16+ and CD3+ CD56+ T cell subpopulations and NK cells.

The aim of the dose finding study 2012-001353-19 was to determine the minimum effective dose of begelomab in steroid resistant aGvHD using a pharmacodynamic surrogate (level of circulating CD3+CD26+ cells), because the dose used in the explorative study 2007-005809·21 was able to bind only the 25% of circulating CD3+CD26+ cells. The lymphocyte counts and begelomab binding to CD3+CD26+ cells were performed using flow cytometry by staining with anti-mouse IgG. Percentage of begelomab binding to circulating CD3+CD26+ cells of subjects treated with begelomab for 5 consecutive days is presented in **Table 10**. The percentage of binding varied between 20% and 76%, but an overlap in binding between doses was observed.

Table 10 Binding results from subjects treated with begelomab doses 2, 3, and 4.5 mg/m^2 for 5 consecutive days (study 2012-001353-19)

Subject ID	BEGEDINA® Dosage	Median % CD3+CD26 binding
01	2 mg/m^2/day	46,8%
02		20%
03		n.a.
04	3 mg/m^2/day	47%
05		63%
06		63%
07	4.5 mg/m^2/day	76%
08		45%
09		20%

The relation between begelomab exposure and binding to CD3+CD26+ lymphocytes was evaluated in study 2012-001353-19 following 2, 3, and 4.5 mg/m^2 begelomab administration for 5 consecutive days. No relation between begelomab exposure and percentage binding to CD3+CD26+ lymphocytes was apparent, however, the data could not be evaluated as the raw data of the bioanalytical binding assay could not be found.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetic, pharmacodynamic and immunogenicity data were assessed from two clinical studies 2007-005809-21 and 2012-001353-19 in 29 patients developing aGvHD after HPCT. No studies were performed in healthy volunteers, because of the differences in overexpression of the CD26 receptor between healthy volunteers and patients developing aGvHD.

Begelomab pharmacokinetics can only be described qualitatively. Due to the limited sampling, the high inter- and intra-subject variability observed, and the presence of implausible data, pharmacokinetic parameters of begelomab can not be quantified reliably. The analytical method to detect begelomab in serum needs also further discussion. In the planned phase II/III study, quantitative characterisation of begelomab pharmacokinetics by a more frequent sampling post-dosing should be conducted. The pharmacokinetic data of 2007-005809-21, 2012-001353-19 and phase II/III study can then evaluated by popPK analysis. At this moment, it only can be concluded that the terminal elimination of begelomab is rather short, approximately 1 to 3 days, which is in line with the elimination half-life reported for other murine antibodies. Begelomab concentrations appeared to increase 2-fold on average following daily dosing. This is in line with the estimated half-life, but might also be related to target availability. Incomplete saturation of target-binding sites may explain the apparent more than dose proportional increase in begelomab serum concentrations over the dose range 1.1 mg/m^2 to 4.5 mg/m^2. Dose and time dependency should be further discussed.

Following the recommendation of the CHMP, binding of begelomab to circulating CD3+CD26+ circulating cells was investigated as primary endpoint in the pivotal phase 1 / 2 study 2012-001353-19 to guide dose selection of begelomab. At day 5, the percentage binding varied between 20% and 76% and an overlap in binding between doses 2, 3, and 4.5 mg/m^2 begelomab was observed. Disease-burded, time dependency of the begelomab binding was not addressed and the individual binding data could not be found. Additional analyses are requested.

Selection of the 3 mg/m^2 begelomab dose has not been sufficiently substantiated. At 3 mg/m^2 dose, begelomab binding to CD3+CD26+ cells was incomplete, which is in line with *in vitro* binding data: begelomab serum concentrations at 3 mg/m^2 ranged from 0.05 to 1.25 µg/ml while *in vitro* data indicated an optimal binding of begelomab 5 µg/ml. Higher begelomab doses may be needed for complete occupancy of CD26+ target cells. Relation between binding of begelomab to CD3+CD26+ cells and response e.g. efficacy, reduction of activated (CD26 expressing) lymphocytes, inhibition of DDPIV as result of begelomab treatment is not clear. Relationship between exposure and CD3+CD26+ binding may be influenced by disease burden, dissociation rate of begelomab from CD26, internalisation of begelomab, and expression of CD26 on cell surface resulting in increased occupancy of target with repeated dosing of begelomab. Expression of CD26 on the CD3+CD26+ cells may be altered in response to begelomab treatment as was observed in marmosets treated with 7.5 mg/kg begelomab. Factors (including time) that affect the begelomab binding should be discussed.

Binding of begelomab to CD26 may inhibit the dipeptidyl peptidase IV (DDPIV) activity. Inhibitors of DDPIV are used for treatment of type 2 diabetes mellitus to improve glycaemic control. Therefore, begelomab may interact with glucose regulation when co-administered with other anti-diabetic medicines through DDPIV inhibition. This potential interaction should be discussed.

3.3.4. Conclusions on clinical pharmacology

The clinical pharmacology package to support the application of begelomab is very limited and the evaluation was hampered by the poor presentation of the data and the absence of the individual data. Additional data and further discussions should be provided to gain more insight into the effect of begelomab treatment.

3.3.5. Clinical efficacy

Data to support the clinical efficacy come from both studies submitted by the Applicant, a phase I study (EUDRACT 2007-005809-21) and a dose response study (EUDRACT 2012-001353-19) (see Table 8).

Dose-response studies and main clinical studies

Dose-response study

The Phase II study EUDRACT 2012-001353-19 was a dose-finding, open-label, single-centre, phase II, uncontrolled study assessing begelomab dose escalation for treating steroid-resistant aGvHD patients. The primary objective of this study (n=16) was to evaluate the minimum effective dose and PD/PK assessment.

Main clinical studies

The two studies submitted by the Applicant are essential for the evaluation of the safety and efficacy of begelomab treatment in the proposed patient population. Study EUDRACT 2007-005809-21 is a Phase I/II open-label pilot study in patients who received prior HSCT and with grade II-IV Graft versus Host Disease (GvHD). Next, study EUDRACT 2012-001353-19 is a Phase II open-label dose-finding study for treating steroid-resistant aGvHD patients who previously underwent HSCT.

Summary of main efficacy results

The following tables summarise the efficacy results from the pilot and the dose finding study, the two studies in which all the patients have been treated (n=29, with n=28 for efficacy evaluation). These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11 Summary of efficacy for the pilot study (2007-005809-21)

Title: Treatment of steroid-resistant Graft versus Host Disease (GVHD) with monoclonal antibody BT 5/9 (ANTI-CD26)			
Study identifier	EUDRACT 2007-005809-21		
Design	Pilot, open-label, uncontrolled phase, single arm I/II study		
	Duration of study:		Patients were followed up to D+365 after the first dose of treatment.
Hypothesis	Exploratory: evaluation of effect of treatment		
Treatments groups	Treatment group		2 mg begelomab, 5 consecutive days (14 patients were enrolled, 1 withdrew consent before receiving treatment and 1 was later found to have chronic GvHD and excluded from the FAS)
Endpoints and definitions	Primary endpoint	Frequency of responder patients at Day +10	The definition of response was based on the following criteria: – Complete response: complete resolution of all signs of GvHD; – Partial response: reduction of GvHD to a less severe grading, but still evidence of GvHD; – Stable disease: no change; – No response: progression of GvHD to a more severe grading.
	Secondary endpoint	Frequency of responders at Day +30	For classification of response, see above.

	Secondary endpoint	Overall survival	Defined as the time from the informed consent signature until date of death
	Safety	Adverse events Laboratory parameters Vital signs HAMA assessments	
Database lock	Final version study report: 2 February 2015 Addendum to study report: 2 September 2015		
Results and Analysis			
Analysis description	**Outcome analysis**		
Analysis population	Full analysis set: all patients with acute GvHD who received at least one dose of begelomab		
Outcome		Treatment group	
	Number of subject	12	
	Frequency of Day 10 responder patients	7 of 12 (58%)	
	Frequency of Day 30 responder patients	10 of 12 (83%)	
	Overall survival (at day 365)	4 surviving patients (of 12) (33%)	
Notes	This was a single arm open label study with one dose level; no comparison across groups within the study has been performed. The presentation of the study results is based on an unexplained re-review of main study parameters performed by the Applicant and provided in an addendum to the study report. While other endpoints were discussed by the Applicant (incidence of chronic GvHD, Karnofsky index, relapse), the collected data was generally limited to a very few patients, thereby prohibiting any conclusions.		

Abbreviation: HAMA: Human Anti-Murine Antibodies

Table 12 Summary of efficacy for the dose finding study (2012-001353-19)

Title: Dose finding study of BEGEDINA (murine monoclonal antibody against CD26) in patients with steroid resistant acute graft versus host disease (aGvHD)			
Study identifier	EUDRACT 2012-001353-19		
Design	Dose finding, open-label, single-centre, uncontrolled study		
	Duration of main phase:	Patients were followed up to day 180 after the first dose of treatment*	
Hypothesis	Exploratory: Dose-finding: to evaluate the minimal effective dose (MED) and PD/PK by assessing begelomab positive cells through staining with anti-mouse IgG within Day +5 of treatment.		
Treatments groups	Dose level 1 (DL1)	2 mg/m^2 for 5 consecutive days, 3 patients	
	Dose level 2 (DL2)	3 mg/m^2 for 5 consecutive days, 3 patients	
	Dose level 2bis (DL2bis)	3 mg/m^2 for 5 consecutive days and at Days: +10; +14; +17; +21; +24; +28, 7 patients	
	Dose level 3 (DL3)	4.5 mg/m^2 for 5 consecutive days, 3 patients	
Endpoints and definitions	Primary endpoint	Determine MED through PK/PD assessment	PD assessment consisted of calculating begelomab positive cells by staining with anti-mouse IgG within day +5 of begelomab treatment.

	Secondary endpoint	Frequency of responders at Day 28 and Day 56†	The definition of response was based on the following criteria: – Complete response: complete resolution of all signs of GvHD; – Partial response: reduction of GvHD to a less severe grading but still evidence of GvHD; – Stable disease: no change; – No response: progression of GvHD to a more severe grading.
	Secondary endpoint	Transplant Related Mortality	Defined as death from any cause without prior progression event
	Secondary endpoint	Overall survival	Defined as absence of death from any cause
	Safety	Adverse events Laboratory parameters Vital signs HAMA assessments	
Database lock	Final version study report: 2 February 2015 Addendum to study report: 2 September 2015		

Results and Analysis

Analysis description	**Primary Analysis**					
Analysis population	full analysis set: all patients with acute GvHD who received at least one dose of begelomab					
Outcome	Treatment group	DL1	DL2	DL2bis	DL3	Cumulative
	Number of subject	3	3	7	6	16
	% begelomab positive cells	20-47%	47-63%	Not done	20-76%	Not done
	frequency of responders at Day 28	2 (67%)	2 (67%)	5 (71%)	2 (67%)	11 (69%)
	frequency of responders at Day 56	1 (33%)	2 (67%)	6 (86%)	3 (100%)	12 (75%)
	Treatment related mortality at Day 180	1 (33%)	1 (33%)	2 (29%)	0 (0%)	4 (25%)
	Overall survival at day 180	0 (0%)	2 (67%)	5 (71%)	3 (100%)	10 (63%)
Notes	This was a single arm open label study; no comparison across the dose groups within the study has been performed. The presentation of the study results is based on an unexplained re-review of main study parameters performed by the Applicant and provided in an addendum to the study report. While other endpoints were discussed by the Applicant (incidence of chronic GvHD, Karnofsky index, relapse), the collected data was generally limited to a very few patients thereby prohibiting any conclusions.					

Abbreviation: HAMA: Human Anti-Murine Antibodies

*Patients in the DL2 bis extension cohort were followed up to D28 within the duration of the main study. Follow-up data up to D180 was then presented in a clinical study addendum report.

†The inclusion of stable disease in the definition of responders was a change to the analysis planned in the SAP and a re-analysis of the responder rates only including CR+PR will be required.

Clinical studies in special populations

No separate efficacy studies in special populations have been performed.

All of the patients in the 2 clinical trials were adults.

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

A direct comparison between the two clinical studies has the following limitations: (1) both studies used different doses and slightly different dosing schemes; (2) the primary endpoint defined for each study differs and (3) the limited number of subjects in each study included for this assessment. Specific issues regarding the between trial comparison are included in the discussion on efficacy.

For the comparison with historical controls the data from the pilot study and the dose finding study were pooled. This pooling of data is complicated by several factors, these are analysed in the discussion on the comparison with the historical controls.

Supportive study(ies)

In support of the application, the Applicant has discussed data from two published studies (Knop et al 2007, Sanchez-Guijo et al 2014), and data from a sr-aGvHD patient population who were treated within the same treatment centre in a specific time frame before the initiation of the begelomab trials. These are also further discussed in the discussion on clinical efficacy.

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Two studies were submitted in support of this CMA, a phase I 'pilot' study (EUDRACT 2007-005809-21), and a phase I/II 'dose-response' study, EUDRACT 2012-001353-19.

Patient population

Generally the patient population selected for inclusion in both clinical trials is representative of the intended licensed indication. In both studies the target population, as specified by the in- and exclusion criteria, were adult patients (18-65 years) who had received a HSCT and developed acute GvHD that was resistant to first-line steroid treatment. Patients with a life expectancy of < 10 days, chronic GvHD or lymphoproliferative disease after transplantation were to be excluded.

However, several differences in the in-and exclusion criteria between the studies have been noted, and the impact thereof on the included patient population is not clear. One of the major differences is the definition of steroid resistance. In the pilot study this is defined as the impossibility to reduce steroid dose after 5 days, while in the dose-response study steroid-resistance encompassed one of three options, i.e. progressive disease after 3 days, lack of response within 7 days of steroid treatment, or lack of complete response after 14 days of steroid treatment.

Other differences in the inclusion and exclusion criteria that could have resulted in differences in patient population were:

- the requirement to have GvHD of Grade II-IV in the pilot study, while grading was not specified in the dose-response study;
- the requirement that aGvHD had to develop within 100 days after transplant in the dose-finding, but not in the pilot study;
- the limitation on the number of transplants in the pilot study, but not in the dose-response study;
- the exclusion of patients with aGvHD following DLI in the dose-response study, but not in the pilot study;
- in the dose-response study it was specified that the HSCT donor had to be a sibling or a matched unrelated donor (MUD), while there were no restrictions in the pilot study.

In both studies, acute GvHD diagnosis staging and grading were performed according to the commonly used Glucksberg scoring system. This system consists of staging the level of aGvHD disease from 0 to 4 in three key organs (skin, gut and liver), and the resultant stages are then combined, together with the clinical performance of the patient (ECOG status) to provide an overall grade of aGvHD. However, diagnosing GvHD based on this system alone may be not straightforward, and it is generally recommended to consider and exclude possible causes for isolated abnormalities prior to diagnosis of acute GvHD. It is unclear whether this was required and has been done for the patients included in the studies.

Historically, the distinction between *acute* and *chronic* GvHD was made based on the timing of onset of symptoms (*before* or *after* day 100 post stem cell infusion respectively). Currently, this distinction is not as strict as symptoms associated with acute GvHD have also been noted beyond day 100. It is therefore surprising that in the most recent study (and also in the confirmatory phase II/III study), it was stipulated that aGvHD should have occurred within 100 days from transplantation.

Treatment

In the pilot study (2007-005809-21) patients received begelomab at a dose of 2 mg/day i.v. for 5 consecutive days.

The dose-response study (2012-001353-19) included the following treatment groups:

- Dose level 1 (DL1): 2 mg/m^2/day of begelomab for 5 consecutive days;
- Dose level 2 (DL2): 3 mg/m^2/day of begelomab for 5 consecutive days;
- Dose level 2bis (DL2bis): 3 mg/m^2/day of begelomab for 5 consecutive days, and at Days: +10; +14; +17; +21; +24; +28;
- Dose level 3 (DL3): 4.5 mg/m^2/day of begelomab for 5 consecutive days.

Overall 5 dose levels and dosing schedules have been tested in a total of 29 patients, each in only a limited set of patients: N=13 in the pilot study at the pilot dose level and 16 in the dose finding study using dose levels 1, 2 and 3 administered to 3 patients each and dose level 2bis to 7 patients. In the pilot study 3 patients received a second cycle of 5 consecutive days of begelomab treatment, and 1 patient received 3 additional days of therapy. The dose level to be tested in the confirmatory phase II/III study and as proposed in the SmPC is that of dose level 2bis in the dose-response study.

In both study reports/protocols information on concomitant aGvHD medication was only sparsely provided, and a clear overview of the used co-medication and (initiation of) next line treatment was not found.

Endpoints

While the primary endpoints differed between the studies, the overall set of endpoints was rather similar. Endpoints in both studies included frequency of responders at day +28 or 30, and day +56 or 60, where response was defined as reduction of aGvHD to a less severe grading. Furthermore, staging of GvHD (organ by organ), survival, Karnofsky index, relapses and chronic GvHD were collected as well. The dose-finding study was aimed to determine the minimal effective dose level (primary endpoint). For this, the level of circulating CD3+/CD26+ lymphocytes bound to begelomab was measured as pharmacodynamic surrogate endpoint. The primary endpoint of the pilot study was frequency of responder patients at 5 days after last dose of begelomab, i.e. at Day+10.

As both studies are considered to be exploratory and data are only descriptive, and as a confirmatory study will be performed, the difference in hierarchy of the endpoints in the two submitted studies will not be raised as a major issue.

Conduct of the study

For the pilot study, no protocol amendments were generated at any time during the study. For the dose-finding study one protocol amendment was generated during the study, this concerned the implementation of the DL2bis cohort.

In both studies, changes to the planned analysis resulted in a reduction of documentation of clinical endpoints and a change to not collect several outcome parameters in the case report form (CRF). As a consequence, the accuracy of (documentation of) clinical efficacy assessment parameters is questioned. In this respect it should be noted that on several occasions the overall aGvHD grade was based on incomplete information on the aGvHD stage in one or all key organs. Yet these organ-specific grades are the basis for the evaluation of the overall GvHD grade. This provides an additional level of uncertainty on the reliability of the documentation and claimed clinical outcome. A further complicating factor is the fact that the GvHD organ scores and overall grading were re-reviewed by the investigator (provided in an appendix to both studies). This resulted in several changes to the originally scored GvHD staging/grading. A justification for this re-review of the efficacy data was not provided, also no explanation was provided for the introduced changes ('corrections').

Please note that as the Applicant only discussed the adjusted data, these are the data that were used for discussion.

The Applicant's analysis of the protocol violations is limited to a statement in both study reports that all patients respected the inclusion and exclusion criteria. As protocol violations encompass more than compliance with in- and exclusion criteria, this statement is deemed insufficient. Furthermore, several examples of apparent violations of an in-or exclusion criterion were noted, therefore even the accuracy of the Applicant's statement is doubted.

A routine GCP inspection of both clinical trials is due to take place following adoption of the request, based on routine triggers, by the CHMP in November 2015. However, during the assessment of the clinical dossier a number of concerns have been identified that bring into question the validity and reliability of the data from the 2 clinical trials. This includes a large number of incomplete datasets in particular the PK and immunogenicity data, changes to the baseline data for one of the key efficacy endpoints in the dose-finding study and a number of changes to the final analyses e.g. classification of responders. The outcome of the GCP inspection will be required before any final conclusions on the clinical data can be made and before any marketing authorisation can be granted.

Dose finding data

The dose-finding study was aimed to determine a minimal effective dose (MED) and included several treatment groups. For this a pharmacodynamic/pharmacokinetic assessment was to be made with the fraction of begelomab positive T cells (%CD3+ CD26+ cells of all lymphocytes) as PD surrogate marker. Apparently, it was expected that 80 % begelomab positive T cells was needed for the minimal effective dose, as this was the cut-off value for dose escalation. An explanation for this assumption was not provided.

None of the patients treated with begelomab in any dose cohort study showed a % begelomab positive cells on Day +5 of treatment of ≥ 80%, and therefore the dose escalation to the next dose level was performed each time after treating three patients at a specific dose level. Binding levels were between 20% and approximately 76%. A clear correlation between begelomab dose and % of binding of circulating CD3+CD26+ cells is lacking. This observation combined with the limited patient numbers and the limited assay description, leads to the conclusion that the binding data do not support the selection of 3 mg/m^2 as the recommended dose.

Efficacy data and additional analyses

Participant flow

The patient flow for both studies is shown in Figure 6 (pilot study EUDRACT 2007-005809-21) and Figure 7 (dose finding study EUDRACT 2012-001353-19).

Figure 6 Patient flow study 2007-005809-21

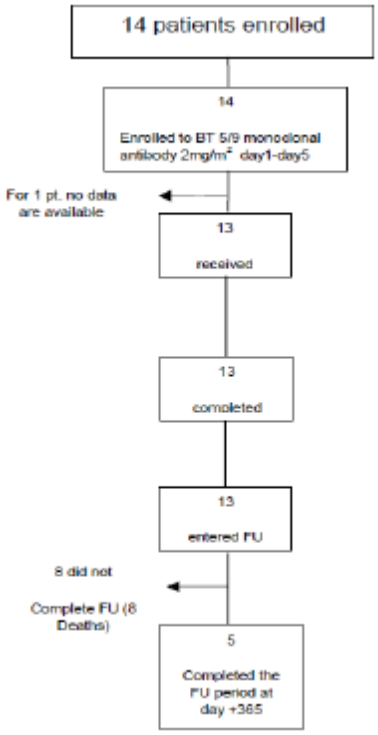
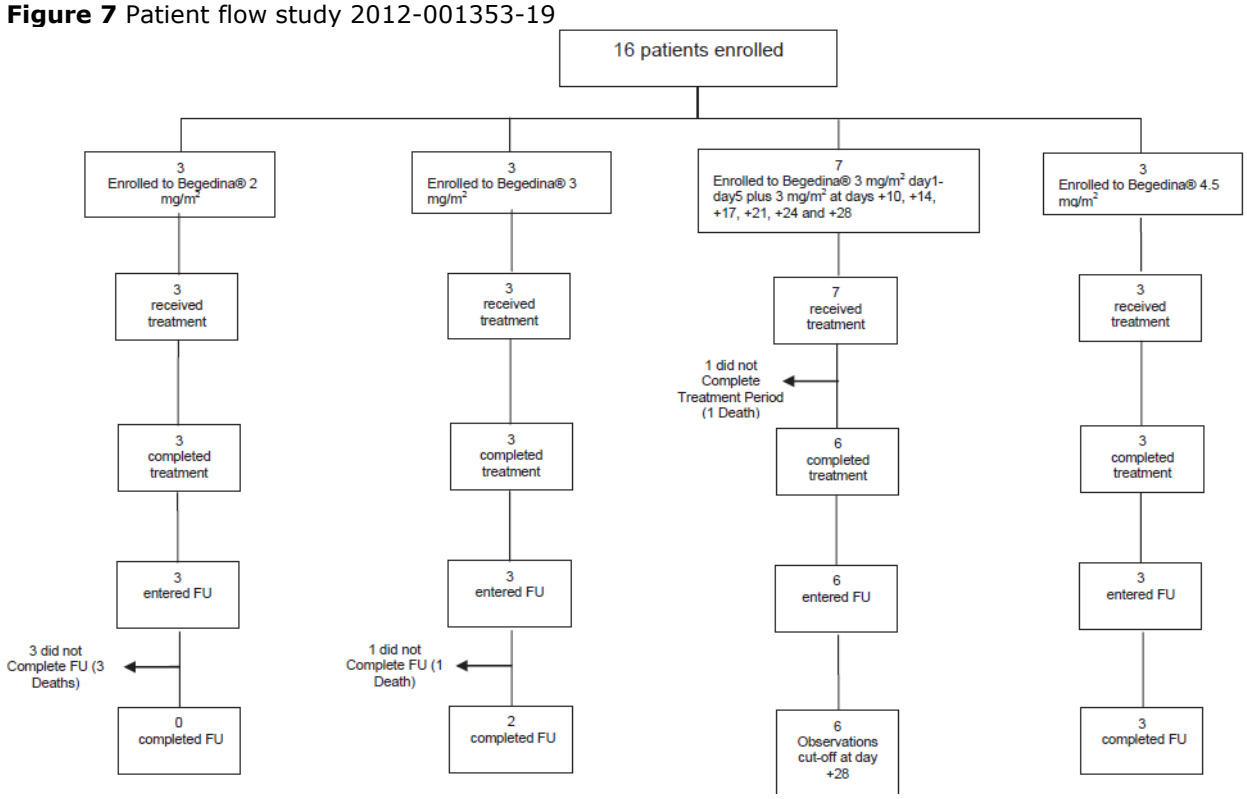


Figure 7 Patient flow study 2012-001353-19



Overall, in the pilot study 14 patients were enrolled and 13 were treated with begelomab. One of the 13 treated subjects in the pilot study was determined to have been enrolled with chronic, not acute GvHD, and is excluded from the efficacy Full Analysis Set (FAS). In this study 3 patients received a second cycle of 5 consecutive days of begelomab treatment, and 1 patient received three additional days of therapy. These additional administrations and their potential effect on efficacy outcome parameters were not discussed by the Applicant.

In the dose finding study, all patients received begelomab. All patients in DL1, DL2 and DL3 received the 5 doses as scheduled in the protocol. In the DL2bis cohort all but 1 patient received the 11 doses as scheduled in the protocol.

Baseline characteristics

The demographics of the study populations of both studies are presented in Table 13 **Demographics of patient populations in the 2 begelomab studies**.

Table 13 Demographics of patient populations in the 2 begelomab studies

Category n(%)	Study EUDRACT 2007-005809-21 Study EUDRACT 2012-001353-19 Cumulative (N= 28)
Sex,	
Male	13(46.4%)
Female	15(53.6%)
Age, years	
Median Age (range)	42(20-66)
Transplant Reason,	

Acute Leukaemia	1(3.6%)
Acute Lymphocytic Leukaemia	8(28.6%)
Acute Myeloid Leukaemia	5(17.9%)
Aplastic Anaemia	2(7.1%)
Large Granular Lymphocytosis	1(3.6%)
Multiple Myeloma	1(3.6%)
Myelodysplastic Syndrome	3(10.7%)
Myelofibrosis	3(10.7%)
Myeloprolipherative Disorder	1(3.6%)
Non-Hodgkin's Lymphoma	3(10.7%)
Donor Type,	
Haploidentical	10(35.7%)
Mud	11(39.3%)
Sibling	7(25.0%)
Stem Cell Source,	
Bone Marrow	20(71.4%)
PBSC	7(25.0%)
Not available	1(3.6%)
Overall Grade GVHD at Baseline	
Grade II	8(28.6%)
Grade III	18(64.3%)
Grade IV	3(10.7%)
Acute GVHD by organ involvement at Baseline	
Skin	26(92.9%)
Liver	12(42.9%)
Gut	19(67.9%)

The information on baseline characteristics and the discussion thereof is considered to be limited. In particular more information on the disease to be treated was expected, such as the onset of aGvHD relative to HSCT, the time between onset GvHD and start of begelomab treatment, the initial response to first-line therapy, the duration of steroid therapy prior to inclusion in the pilot study and, for the dose finding study, which criteria were fulfilled to consider the disease to be steroid resistant (progressive disease after 3 days or lack of response within 7 days of steroid treatment, or lack of complete response after 14 days of steroid treatment). Moreover, also other patient characteristics (e.g. race, ECOG status, time between leukaemia/lymphoma diagnosis and transplantation, disease status at transplantation and time of begelomab treatment etc.) were not included in the overview provided by the Applicant.

The provided information on baseline characteristic indicates that the included patient population in both studies was very heterogeneous. Overall, there is an (approximate) equal distribution between male and female subjects. The median (range) age of all patients was 42 (20-66) years. The most common reason (haematological condition) for bone marrow transplantation was leukaemia (ALL in N=8 and AML in N=5). There is an approximately equal number of haplo-identical and matched unrelated donors, and somewhat less sibling donors. Bone marrow was the most commonly used stem cell source. Acute GvHD grading varied between 2 and 4. Skin was the most affected organ (92% of subjects) followed by gut (67%) and liver (42%). For some patients the baseline aGvHD grading was not clear, and as a consequence it is not clear how a response to treatment could be determined in these patients.

Responses

Table 1 **Frequency of responders in the pilot study** shows the results of frequency of responders at Day +10, Day +30 and Day +60 in the FAS of the pilot study. Table 15 **Frequency of responders in the dose finding study** shows the results of frequency of responders at Day +28 and Day +56 in the

FAS of the dose finding study. Subjects in complete or partial response were considered as responders. Subjects who died before or at Day +28 were considered as non-responders.

Table 1 Frequency of responders in the pilot study

	(N=12)
Responders at Day +10, *N (%)*	
Yes	7 (58.3%)
No	5 (41.7%)
Responders at Day +30, *N (%)*	
Yes	10 (83.3%)
No	2 (16.7%)
Responders at Day +60, *N (%)*	
Yes	11 (91.7%)
No	1 (8.3%)

Table 15 Frequency of responders in the dose finding study

	DL 1 2 mg/m^2 (N=3)	DL 2 3 mg/ m^2 (N=3)	DL 2bis 3 mg/ m^2 Extended (N=7)	DL 3 (N=3) 4.5 mg/ m^2 (N=3)	Cumulative (N= 16)
Responders at Day +28, *N (%)*					
Yes	2 (66.7%)	2 (66.7%)	5 (71.4%)	2 (66.7%)	11 (68.7%)
No	1 (33.3%)	1 (33.3%)	2 (28.6%)	1 (33.3%)	5 (31.2%)
Responders at Day+ 56, *N (%)*					
Yes	1 (33.3%)	2 (66.7%)	6 (85.7%)	3 (100%)	12 (75.0%)
No	2 (66.7%)	1 (33.3%)	1 (14.3%)	0 (0%)	4 (25.0%)

The frequency of D60 responders in the pilot study as depicted in Table 1 does not fully match to the information in the addendum to the study report. In this addendum it is stated that at day 60 10 patients had responded, 1 patient had no response and data was not available for 1 patient.

Also the frequency of responder patient in dose finding study, as depicted does not appear to be fully correct. In the study report, data on aGvHD grade were missing for several patients on several days (day 28, and in particular day 56, almost all DL2bis cohort) after treatment, yet these patients are included in the above table. It appears that for this table the response seen at other time points was taken. This does not seem to be fully justified. The number of subjects evaluated should have been adjusted to the number of patients for which data are available. In addition, for several patients in this study it is unclear if and/or why they have been classified as responding to treatment.

In time, the overall aGvHD grading improved in both studiesTable . Furthermore, in the pilot study, 75% of the patients showed a stage 2-4 gut GvHD before treatment, which was reduced to 25% of patients at day +30 from begelomab treatment. In this study total mean bilirubin levels (mg/dL) were 3.33 (median 1.10) at baseline and 3.29 (median 0.70) at Day +10 and decreased to mean 2.0 (median 0.45) at Day +30. Also in the dose finding study reductions in mean and median total bilirubin values (mg/dL) were observed during the course of the study for three of the four cohorts (not for DL3). Information on gut aGvHD staging in this study appeared too limited to be discussed.

Table 16 Global grade of GvHD over time (both studies)

	Study EUDRACT 2007-005809-21	Study EUDRACT 2012-001353-19				
Category n(%)	2 mg (N= 12)	2 mg/m2 (N= 3)	3 mg/m2 (N= 3)	3 mg/m2 Extended (N= 7)	4.5 mg/m2 (N= 3)	Cumulative (N= 28)
Overall Grade GVHD At						
Baseline						
Grade 0						0(0.0%)
Grade I						0(0.0%)
Grade II						7(25.0%)
Grade III						18(64.3%)
Grade IV						3(10.7%)
Day 28-30						
Grade 0						2(7.1%)
Grade I						10(35.7%)
Grade II						8(28.6%)
Grade III						5(17.9%)
Grade IV						0(0.0%)
Day 56-60						
Grade 0						2(7.1%)
Grade I						13(46.4%)
Grade II						7(25.0%)
Grade III						1(3.6%)
Grade IV						0(0.0%)
Day 90-100						
Grade 0						3(10.7%)
Grade I						11(39.3%)
Grade II						4(14.3%)
Grade III						1(3.6%)
Grade IV						0(0.0%)

As a proper overview of co-medication and (initiation of) next-line therapy is lacking, it is not clear if the responses seen and the decrease in overall aGvHD grade can be attributed to begelomab treatment.

Survival

In the pilot study, overall survival at Day +180 after begelomab treatment was 7/12 (58.3%) subjects and 4/12 (33.3 %) at Day +365. Transplant related mortality (TRM: all deaths excluding deaths in patients with relapse after the relative transplant) was 4/12 (33.3%) at Day +180 after begelomab treatment.

In the dose finding study overall survival was 10/16 (63%) at day 180, and TRM was 4/16 (25%).

Whilst the overall survival seen in the pilot and dose-finding study at day +180 was similar, the overall survival in days for the patients that died was lower for the patients in the dose-finding study. This was despite the fact that the patients in the pilot study overall had a higher overall baseline GvHD grade and received a lower dose of begelomab. Five of the 6 deaths in the dose finding study occurring before day 90, compared with no deaths before day 90 in the pilot study. No discussion or potential explanation for these results has been provided.

Other endpoints

In the pilot study an improvement in Karnofsky score was only evident between day 30 and day 60. In this study, data at later time points were limited to a few patients only. Also in the dose finding study, Karnofsky data were only available for a limited set of patients, and only at day180. As the relationship between begelomab treatment and the improvement in this parameter is uncertain, this observation is of limited support for the claimed efficacy of begelomab.

In the pilot study, 1 of the 3 subjects evaluated for incidence of chronic GvHD (cGvHD) had developed limited skin chronic GvHD. In the dose finding study, 2 of the 5 subjects evaluated for incidence of

chronic GvHD had developed extended skin chronic GvHD, which was accompanied by extended liver involvement in 1 patient. Notably, the Applicant stated that in the pilot study cGvHD was evaluated at D365, yet the dates for 2 patients imply a different time point of evaluation (i.e. 170 and 531 days after HSCT, or 59 and 406 days after initiation of begelomab treatment, respectively), and for 1 patient the date of cGvHD evaluation were not present. Similarly, in the dose finding study, the Applicant stated that the cGvHD was assessed as the presence of GvHD post day 100, yet 1 patient was diagnosed with cGvHD prior to 100 days post transplant, and 2 patients were diagnosed with cGvHD < 100 days post begelomab treatment.

Based on the study reports only a few patients were evaluated for relapse (no data in the report of the pilot study, and not even half of the subjects in the dose finding study were evaluated for relapse). Based on the data provided in the comparison with historical controls, it is assumed that at least 3 patients experienced a relapse at day 180, and 6 patients died of relapse within 1 year.

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

To put the observed efficacy parameters in perspective, the Applicant has provided a comparison of the results from all begelomab treated patients in the clinical studies with historical controls from the same treatment centre and with two published studies (Knop et al 2007, Sanchez-Guijo et al 2014) that also evaluated a possible treatment option for steroid resistant acute GvHD with patients that had a similar overall GvHD grade at baseline. While this comparison would provide a clue towards the potential efficacy of begelomab treatment, it is accompanied by the inherent uncertainties that are associated with cross study comparisons.

Population

For this comparison, the data from the pilot study and the dose finding study were pooled. This pooling of data is complicated by several factors, the two most important being the possible differences in patient population between the studies and the variety of dosing regiments (5 different regiments) with which the begelomab population has been treated.

Furthermore, the control population for this comparison was retrieved from the transplant database of the same institution where patients were treated with begelomab (Genova San Martino) and consisted of adults HSCT patients treated between 2000 and 2010, i.e. before the initiation of the begelomab trials, for aGvHD (Grade II or higher) that did not (sufficiently) respond to first line aGvHD therapy. As such, this group literally encompasses *historical* controls which are accompanied by the bias that they can not have profited from improvements in supportive care that were available at the time of begelomab treatment.

The definition for GvHD resistant to standard therapy corresponded with that of the dose finding study.

Out of 712 allogeneic HSCT performed in the study centre, 54 historical control patients were identified that fitted the eligibility criteria of the begelomab trials. Of these 36 patients matched the inclusion criteria formulated for the historical controls. The reason why 18 subjects were excluded was not further discussed.

It is important to note that for the control populations no exclusion criteria appear to have been applied. For the begelomab studies patients with a life expectancy of <10 days, with chronic GvHD and/or lymphoproliferative disease after transplantation were to be excluded.

The final sample size for this comparison consisted of 36 control and 28 begelomab-treated patients. These two populations were compared by demographics, gender and transplant type (see Table). Their baseline aGvHD disease characteristics are shown in Table 18.

Table 17 Patient demographics of historical control patients and begelomab treated patients

Group	Control	*Begelomab*
N.of patients	**36**	**28**
Median age –years (range)	46 (18-66)	42 (20-66)
Gender mismatch (FM)	10 (28%)	(18%)
Median interval Dx-Tx (dd)	889	745
Stem cell source BM/PB	31/5	20/8
Myeloablative regimens	22 (61%)	20 (71%)
Donor Sib /UD / haplo	15/6/15	7/11/10
Alternative donors	58%	75%
Diagnosis		
Aplastic anemia	0	2
Acute Myeloid Leukemia	6	6
Acute lymphoblastic leukemia	7	8
Myelodyplastic syndrome (RAEB)	9	3
Myeloma	4	1
Myelofibrosis	3	3
Lymphoma	2	3
Chronic myeloid leukemia	4	0
LGL leukemia	0	1

Abbreviations: FM= female in to male donor recipient combinations; Dx-Tx: diagnosis-transplant. BM= bone marrow; PB= peripheral blood; SIB= matched sibling donor; UD= unrelated donor; haplo= family haploidentical donor

RAEB= refractory anemia with excess blasts

Table 18 Baseline aGvHD grade at time of second line treatment

Group	Control	*begelomab*
N.of patients	**36**	**28**
Skin 0-1/2/3-4	8/ 14/ 14	4/ 8/ 16
Skin 3-4	14 (47%)	16 (53%)
Liver 0-1/2/3-4	27/ 6/ 3	19/ 3/ 6
Liver 3-4	3 (8%)	6 (21%)
Gut 0-1/2/3-4	20/ 13/ 3	11/ 9/ 8
GUT 3-4	**3 (8%)**	**8 (29%)**
Overall Grade II,III,IV	11/ 24/ 1	7/ 18/ 3
Overall III-IV	69%	75%

The number of baseline and disease characteristics on which these two populations were compared is limited. As already discussed above, some basic characteristics (gender, race, stage of underlying malignant disease at diagnosis and HSCT), but also known risk factors for aGvHD, such as donor-recipient HLA disparity, and CMV status, are missing in the comparison. Furthermore, no information was provided on the onset of aGvHD relative to HSCT, the time between onset GvHD and start Begelomab treatment, the initial response to first-line therapy, the duration of previous steroid therapy and which of the criteria were fulfilled to consider the disease to be steroid resistant (i.e. progressive

disease after 3 days or lack of response within 7 days of steroid treatment, or lack of complete response after 14 days of steroid treatment). Remarkably, the here listed staging of organ aGvHD has different categories than was documented in the patient listings in the study report. In view of all this, a proper comparison between the populations cannot be performed.

The available information suggests that the control and begelomab-treated group encompass a heterogeneous patient population. A difference is noted in the percentage of alternative donors (i.e. non-sibling donors) and in the underlying malignant disease. This latter is likely to affect the risk of relapse, and as a consequence the risk of death. This provides a level of uncertainty on the interpretation in overall survival/leukemic free survival data. As death due to progression and transplant related mortality (TRM) are competing risks, also the interpretation of potential TRM is affected by this uncertainty. The majority of the patients suffered from grade III aGvHD, with a similar frequency of skin (~80%) and liver (~30%) involvement but a difference in the frequency of gut involvement which was slightly higher in the begelomab-treated population (61 vs 44%). The impact of these differences on the possibility to response to treatment and overall prognosis is not clear.

Responses

The overall response rate, patients with stable disease, patients with progressive disease, and patients who were dead by day +28, are outlined in Table 19 for both groups. The proportion of responders (patients who have improved by at least 1 grade in overall grading of GvHD) was found to be significantly higher in the begelomab arm (two-sided Fisher's exact test, p=0.0009). Of the 11 responders in the control group, 9 had their GvHD score decreased by 1 grade and 2 by 2 grades. In the begelomab group, the Applicant stated that of 21 responders 10 had their GvHD score decreased by 1 grade and 12 by 2 grades, however, as 10 + 12 is not 21, one patient was apparently counted twice.

Table 19 Overall response data on day +28 from second line treatment

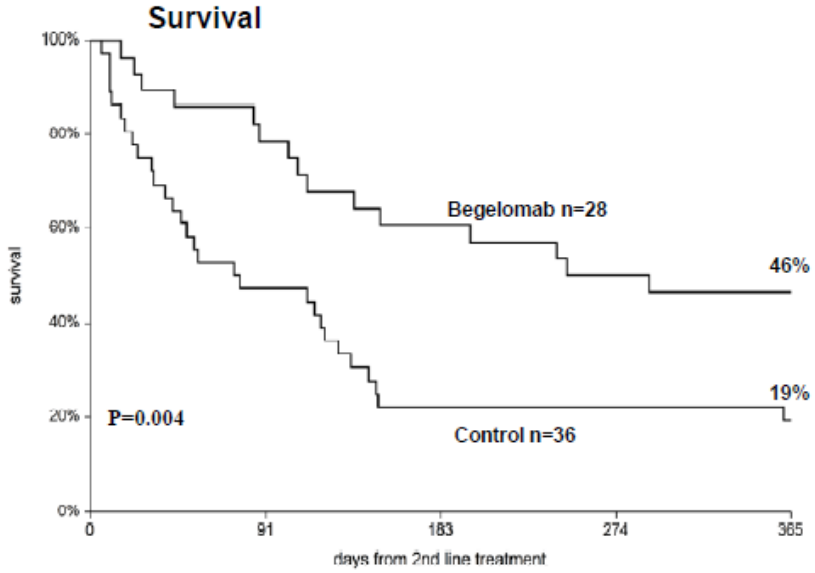
Group	Control	*Begelomab*	P
All patients	**36**	**28**	
Response	11 (31%)	21 (75%)	0.0009
Stable	10 (28%)	3 (11%)	
Progression	6 (17%)	1 (4%)	
Dead	9 (25%)	3 (11%)	
Progression+ Dead	15 (42%)	4 (14%)	0.03

Two-sided p-values of Fisher's exact tests

Survival

The overall survival for both groups is shown in Figure 8.

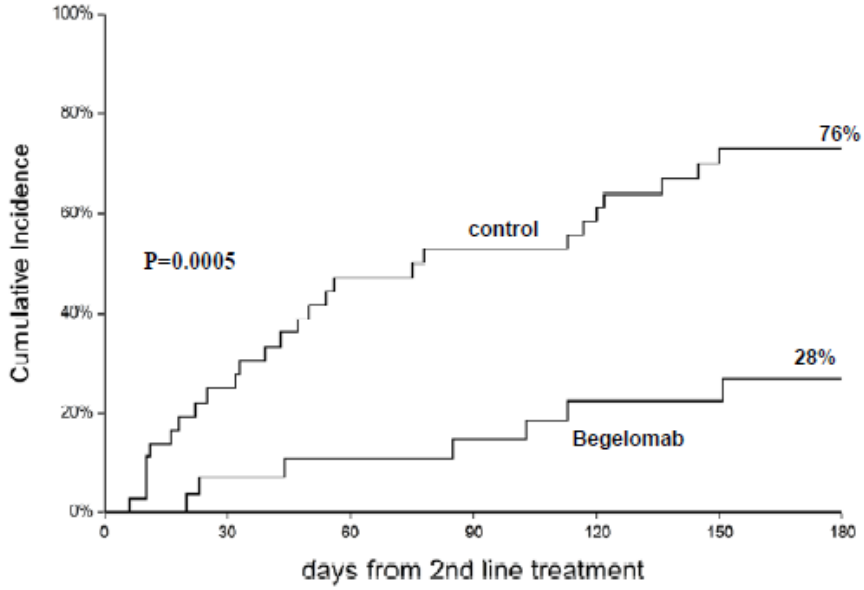
Figure 8 Overall survival in patients treated with begelomab and historical controls



Given the many uncertainties on the documentation of aGvHD staging and grading, survival may be the best available endpoint for comparison of the two populations at hand. However, also the interpretation of the data from this endpoint is hampered due to differences in the baseline characteristics between the populations. This may have consequences for the risk of death of the population. Furthermore, the difference in the curves may also have been biased, as patients with a life expectancy of < 10 days and lymphoproliferative disease after transplantation appear not to have been actively excluded from the control group, while it was an exclusion criterion for the begelomab trials.

Figure 9 shows the cumulative transplant related mortality (TRM) of begelomab treated patient versus the historical control group. For these results apply the same remarks as above.

Figure 9 Cumulative incidence of transplant related mortality in patients treated with begelomab and historical controls



Cumulative incidence of transplant related mortality in patients treated with begelomab, and in controls; relapse after the most recent transplant (if multiple) was treated as competing risk. Difference is statistically significant (P=0.0005, Fine and Gray).

The causes of death are outlined in Table 2.

Table 2 Causes of death at 180 days and 1 year after second line treatment

	CoD at day 180		**CoD at 1 year**	
Group	**Control**	**Begelomab**	**Control**	**Begelomab**
N of patients	**36**	**28**	**36**	**28**
Alive	8 (22%)	17 (61%)	7 (19%)	13 (46%)
Leukemia relapse	2 (6%)	3 (11%)	2 (6%)	6 (21%)
Acute GvHD	16 (44%)	4 (14%)	17 (47%)	4 (14%)
Infections	4 (11%)	2 (7%)	4 (11%)	2 (7%)
Multi-organ failure	6 (17%)	2 (7%)	6 (17%)	2 (7%)
Chronic GvHD			0	1 (4%)

CoD: cause of death

This table suggests that in the control group more patients died of aGvHD, while in the begelomab group mortality due to leukaemia relapse is higher. Interpretation of these frequencies is hampered, as death due to aGvHD or TRM and death due to leukaemic relapse are competing risks. Notably, it is not clear whether in this table only relapse due to leukaemia was included, or whether relapse of underlying haematological malignant disease was meant. Yet, also this comparison should be interpreted with caution as it is based on limited number of patients, patient populations may be different and it should be taken into account that treatment related mortality and death due to leukemic relapse are competing events.

Overall, the comparison of the pooled begelomab-treated population with a historical control population is insufficient due to too many uncertainties and lack of adequate data. This does not allow any conclusion on a clinical efficacy of begelomab treatment for steroid-resistant aGvHD.

Other (supportive) studies

In support of this Application, the Applicant has provided a comparison of the results from begelomab treated patients in the clinical studies with two published studies (Knop et al 2007, Sanchez-Guijo et al 2014) evaluating treatment of steroid resistant acute GvHD based on a similar overall GvHD grade at baseline. However, these publications cannot be used for a meaningful comparison as detailed information on the studies patient populations in these publications is lacking (for more detailed discussion see clinical AR).

3.3.7. Conclusions on clinical efficacy

The results from the 2 uncontrolled studies submitted would appear to show some promise in terms of the efficacy of Begelomab in the treatment of aGVHD. However, even when taking into consideration the rarity of the disease a conclusion on the effect of begelomab treatment on steroid-resistant aGvHD cannot be drawn as there are too many uncertainties on the data. There is a lack of (detailed) information on e.g. baseline characteristics, concomitant medication and next-line treatment that prohibit any conclusion on the relationship between treatment and observed responses. Furthermore,

the comparison with historical control is hampered due to lack of data and uncertainties on the similarity between the patient populations and is based on only a very limited set of patients treated with many different (begelomab) treatment regimes. In addition, the apparent inaccuracy of documentation, and the unexplained re-review of the data provide a major cause for uncertainty on the internal validity of the data. Moreover, also the external validity of the findings is uncertain as all the data come from a single study centre.

3.3.8. Clinical safety

The clinical safety of BEGEDINA was evaluated in a total of 29 patients treated within 2 uncontrolled studies, the phase I pilot study (2007-005809-21, n=13) and the phase I/II dose finding study (2012-001353-19, n=16). The patient population consists of the 28 patients discussed in the efficacy section plus one additional patient treated in the pilot study, but who was classified to have chronic GvHD.

Adverse events were pooled from all patients treated with begelomab. The evaluation of safety included the collection of adverse events (AEs), serious AEs (SAEs) and treatment-related AEs as well as clinical laboratory evaluation, vital signs, physical findings, and immunogenicity. These variables were collected for 180 days from the start of treatment.

Patient exposure

In Table 21 an overview of the patient exposure is shown. The safety analysis set (SAF) population consists of 13 treated subjects in the pilot study together with 16 patients from the dose finding study.

Table 21 Overall extent of exposure and duration of treatment

	Study EUDRACT 2007-005809-21	Study EUDRACT 2012-001353-19				
	2mg (N= 13)	2 mg/m2 (N= 3)	3 mg/m2 (N= 3)	3 mg/m2 Extended (N= 7)	4.5 mg/m2 (N= 3)	Cumulative (N= 29)
5 consecutive days, N (%)	9 (69.2%)	3 (100%)	3 (100%)	0 (0%)	3 (100%)	18 (62.1%)
7 days (5 days consecutive plus 2 days), N (%)	1 (7.7%)	0 (0%)	0 (0%)	1 (14.3%)	0 (0%)	2 (6.9%)
10 days (2 x 5 consecutive days), N (%)	3 (23.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (10.3%)
11 days (5 days consecutive plus 6 days), N (%)	0 (0%)	0 (0%)	0 (0%)	6 (85.7%)	0 (0%)	6 (20.7%)

**Note one patient in the 2007-005809-21 study received 8 days treatment (5+3 days and not 5+2 as stated in the table above)*

Treatment compliance was very high, all but one patient received the scheduled dose of begelomab, and several patients received additional doses (described earlier).

Overall, a total of 29 patients have received at least 5 doses of begelomab in open-label, uncontrolled phase I/II clinical trials, only 6 have received the dose and duration of treatment proposed for licensing.

One patient did not complete the scheduled treatment because of death due to respiratory failure. This death was considered to be due to an AE that was indicated as possibly treatment-related by the investigator. The Applicant indicated that the temporal relationship of the event with treatment with

begelomab (death 10 days after last administration) was not indicative of any acute effect of the drug. While it is agreed it is likely that death was not to begelomab treatment, a relationship with treatment cannot be excluded.

Adverse events

All adverse events

A total of 867 adverse events, irrespective of relationship to study treatment, were reported during the studies (Table 3). All subjects were reported as having experienced at least one grade ≥ 3 AE. A relative small fraction of all AEs was considered to be possibly treatment-related by the investigator (total of 14 AEs in 7 subjects). Sixteen (16) subjects (55.2%) were reported with at least one serious adverse event. Of these, 11 (37.9%) were subjects with fatal adverse events by day 180 from start of therapy with begelomab.

Table 3 Overview of incidences of adverse events

	Study EUDRACT 2007-005809-21	Study EUDRACT 2012-001353-19				
Category n(%) E	2 mg (N= 13)	2 mg/m2 (N= 3)	3 mg/m2 (N= 3)	3 mg/m2 Extended (N= 7)	4.5 mg/m2 (N= 3)	Cumulative (N= 29)
Number of Subjects with at least one AE	13(100.0%) 488	3(100.0%) 70	3(100.0%) 55	7(100.0%) 146	3(100.0%) 108	29(100.0%) 867
Number of Subjects with at least one SAE	9(69.2%) 27	1(33.3%) 2	2(66.7%) 3	2(28.6%) 3	2(66.7%) 4	16(55.2%) 39
Number of Subjects with one Grade>=III AE	13(100.0%) 70	3(100.0%) 22	3(100.0%) 8	7(100.0%) 22	3(100.0%) 31	29(100.0%) 153
Number of subjects with at least one Grade I-II AE	13(100.0%) 418	3(100.0%) 48	3(100.0%) 46	7(100.0%) 126	3(100.0%) 75	29(100.0%) 713
Number of Subjects with one Drug-related AE	5(38.5%) 8	0(0.0%) 0	0(0.0%) 0	1(14.3%) 6	0(0.0%) 0	6(20.7%) 14
Number of Subjects with at least one AE Leading to Discontinuation of Study Medication	0(0.0%) 0	0(0.0%) 0	0(0.0%) 0	0(0.0%) 0	0(0.0%) 0	0(0.0%) 0
Number of Deaths by Day 180	5(38.5%) 5	3(100.0%) 3	1(33.3%) 1	2(28.6%) 2	0(0.0%) 0	11(37.9%) 11

Percentages are based on the number of SAF Set; n=number of patients; E=numbers of events.

The most commonly involved system organ classes (SOCs - reported in at least 50% of patients overall) were Infections and infestations, Gastrointestinal disorders, General disorders and administration site conditions, Investigations (i.e. additional testing/investigations), Skin and subcutaneous tissue disorders, Blood and lymphatic system disorders, and Musculoskeletal and Connective Tissue Disorders.

The frequencies as mentioned by the Applicant in the clinical overview are assumed to be based on the pooled data. However, accuracy of the numbers is doubted as these could not be reproduced by the assessor using the incidences of AEs by SOC as reported in tables 14.3.1.2 of the study reports. Furthermore, several inconsistencies of AE reporting were noted both within and between studies. In the pilot study, an AE falling within the SOC of immune system disorders was noted for 10 (77%) patients. All the AEs noted in this SOC were graft versus host disease events. However, as GvHD was an inclusion parameter, it is not understood why this was noted as an AE in only 10 of the 13 patients. Remarkably, in the other (dose finding) study, a GvHD was listed as AE in only 1 patient. Similarly, in

the pilot study relapse was listed as an AE in SOC neoplasm in 3 patients. In the dose finding study 2 patients died of underlying disease prior to day 180, yet these were not captured as adverse events. Table shows the most commonly (≥10% of patients) reported AEs during treatment with begelomab.

Table 23 Commonly reported adverse effects (≥ 10% of patients) occurring during treatment with begelomab

Adverse Event (Preffered Term)	Number (%) of patients (Total 29)
Diarrhoea	11 (37.9%)
Cytomegalovirus infection	7 (24.1%)
Abdominal pain	6 (20.7%)
Graft versus host disease in intestine	4 (13.8%)
Rash	4 (13.8%)
Blood bilirubin increased	3 (10.3%)
Bacterial infection	3 (10.3%)
Anaemia	3 (10.3%)
Leukopenia	3 (10.3%)
Oedema peripheral	3 (10.3%)
Skin exfoliation	3 (10.3%)
Thrombocytopoenia	3 (10.3%)

Also the accuracy of incidences as reported by the Applicant in Table 23 is doubted. According to this table, diarrhoea occurred in 11 of the 29 patients, but was noted in 11 patients in the pilot study and in 7 patients in the dose finding study. Similarly, CMV infection was noted in 6 or 7 subjects in the pilot study and in 8 patients in the dose finding study, but reported here in 7 patients.

AEs related to treatment

Fourteen (14) AEs reported from six patients (20.7%) were judged as related to study medication by investigator (see Table 24), but no AE reported required treatment discontinuation.

Table 24 Drug related AEs

Adverse event (preferred term)	**Number (%) of patients (total 29)**
Anaemia	1 (3.4%)
Neutropenia	1 (3.4%)
Leukopenia	1 (3.4%)
Abdominal pain	1 (3.4%)
Malaise	1 (3.4%)
Oedema peripheral	1 (3.4%)
Hepatic stenosis	1 (3.4%)
Heart rate increased	1 (3.4%)
Neurological examination normal	1 (3.4%)

Protein total decreased	1 (3.4%)
Weight increased	1 (3.4%)
Dyslipidaemia	1 (3.4%)
Muscle spasms	1 (3.4%)
Dermatitis exfoliative	1 (3.4%)

AEs of special interest

Infection: The most commonly (≥10% of patients) reported infections during clinical trials with begelomab included viral, fungal and bacterial infections, i.e. CMV 51.7% of patients, bacterial infection 17.2%, cystitis 17.2%, Pseudomonas infection 17.2%, Escherichia infection 17.2%, fungal infections 13.8%, Staphylococcal infection 10.3% and Bronchopneumonia 10.3%.

Hypersensitivity/infusion-related reactions: AEs commonly associated with infusion-related reactions, such as systemic malaise, pyrexia, rash, nausea and vomiting, were relatively commonly reported during the course of the study. From the analysis of events occurring during treatment with begelomab (when these events are most likely to occur) there are only few reports of such events. There were no reports of anaphylaxis or anaphylactoid reactions. However, the analysis of hypersensitivity reactions/infusion reactions presented by the applicant lacks sufficient detail for assessment. The regimen of pre-medication for hypersensitivity reactions administered in both the phase I and phase II trial is unclear (timing prior to treatment, drugs administered and frequency of administration).

The Applicant did not evaluate possible AEs that could have occurred due to the interference of begelomab with processes in which CD26 is known to play a role (e.g. cardiovascular system, glucose levels) or in tissues where CD26 is expressed (e.g.CD26 on keratinocytes in skin).

Serious adverse events and deaths

Deaths

Overall, 11/29 (37.9%) of patients had died by day 180 of the studies. Of these, 8 (28.6%) were judged transplant-related deaths (see Table 25). None of the deaths has been attributed by the investigator to begelomab treatment.

Table 25 Numbers of death until D180 after start of treatment

	Study EUDRACT 2007-005809-21	Study EUDRACT 2012-001353-19				
Category n(%)	2 mg (N= 13)	2 mg/m2 (N= 3)	3 mg/m2 (N= 3)	3 mg/m2 Extended (N= 7)	4.5 mg/m2 (N= 3)	Cumulative (N= 29)
Number of subjects who died within 180 days	5(38.5%)	3(100.0%)	1(33.3%)	2(28.6%)	0(0.0%)	11(37.9%)

In the pilot study: The causes of death were progression of underlying disease (2 patients), infections (1 patient) or GvHD (2 patients of whom one was also reported to have suffered a fatal GI haemorrhage). In addition, there were three further deaths by one year follow-up.

In the dose finding study: The causes of death by day 180 were due to progression of underlying disease in 2 patients, acute GVHD in 2 patients, systemic infection and associated multi-organ failure in 1 patient and respiratory failure associated with pulmonary oedema in 1 patient.

Serious adverse events

All patients enrolled in the studies experienced at least one severe adverse event (Table 3). Sixteen (16) subjects (55.2%) were reported with at least one serious adverse event. Of these, 11 (37.9%) were subjects with fatal adverse events by day 180 from start of therapy with begelomab. Thirteen (13) subjects (44.8%) were reported with at least one severe adverse event during actual treatment with begelomab.

The most commonly involved SOCs for SAEs were infections and infestations (10 patients, 34.5%), nervous system disorders (4 patients 13.8%), respiratory, thoracic and mediastinal disorders (4 patients, 13.8%) and general disorders and administration site conditions (3 patients, 10.3%), blood and lymphatic system disorders (2 patients, 6.9%) and immune system disorders (2 patients, 6.9%). No other SOCs involved more than one patient reporting an SAE.

There were only two SAEs reported during actual treatment with begelomab – 'GvHD' in one patient in the DL3 cohort and one report of 'Influenza A virus test positive' in the DL2bis cohort. Both the SAEs reported during actual treatment and those occurred after treatment with begelomab did not indicate any specific drug related effects and represent typical SAEs expected from the population treated.

Laboratory findings and other observations

The overall laboratory measurement profiles observed in both studies are typical of those for the patient group treated and no marked laboratory abnormalities led to any study drug intervention.

Some individual abnormalities of safety laboratory parameters required by protocol were considered as clinically significant and were reported as AEs.In both studies a (slight) decrease from baseline in the mean value of leukocyte and neutrophil count was observed. Also a decrease from baseline was seen in the mean values of glucose and bilirubin levels. The mean values of alkaline phosphatase increased from baseline. Several other changes in laboratory parameters were noted, however, most effects were not similar between the two studies. Only one case of haematological values indicating anaemia was considered as treatment-related in the pilot study. In the dose-finding study one report of low white cell count reported as neutropenia and one report of total protein decrease in a patient in the 3 mg/m2/day extended treatment cohort were considered as treatment-related.

The only consistent effect seen across the studies is a reduction in (mean) bodyweight and in temperature. This could be related to the improvement in disease status to an overall less severe aGvHD grading.

Safety in special populations

No studies were performed in special populations.

Adverse events by gender

An overview of the incidence of adverse events did not indicate any differences in the safety profile of begelomab between males and females.

Adverse events by age

No paediatric patients were exposed to begelomab in the clinical trials.

Pregnancy and lactation

No pregnancies were reported during either of the 2 clinical studies and begelomab was not administered to pregnant or lactating women as they were excluded from entering the trial. The patients for whom begelomab is indicated are in general infertile, due to prior or concomitant treatments, and therefore in-utero exposure to begelomab is unlikely.

Immunological events

Eight out of 28 patients (28%) developed detectable human anti-mouse antibody (HAMA) levels, when transient antibody development isalso taken into consideration this number raised to 13 (46%) patients. However, there is a significant amount of missing data. In the majority of patients the follow-up data is incomplete and in some cases there is no follow-up data. Consequently, it is not possible to make an overall evaluation of the development of HAMA antibodies in the first 8 weeks after the 1st day of therapy. However, taking into consideration the significant number of missing samples and that the majority of patients received lower and/or shorter duration of treatment that proposed for licensing, and that the patients are immunocompromised, it can be concluded that treatment appears highly immunogenic which is to be expected for a murine antibody. An analysis of any potential association between the presence of antibodies and the development of adverse events is required.

The further investigations of the immunogenicity of begelomab in the Phase II/III confirmatory study is supported.

Safety related to drug-drug interactions and other interactions

Antibodies have a low potential for pharmacokinetic drug interactions. Therefore no in vitro and in vivo drug interaction studies are considered necessary at this moment.

The patients treated with begelomab received a large number of concomitant medications typically utilized in patients with aGvHD. In particular, additional treatments including 6-methylprednisolone, 2 mg/kg/day, and prophylactic antibacterial and antifungal therapies were administered to a majority of the patients.

Even though the pharmacological target of the product (CD26, i.e. DPPIV) overlaps with that of DPPIV inhibitors, no analysis of potential pharmacodynamics drug-drug interaction with DPPIV inhibitors was performed.

Discontinuation due to AES

There were no adverse events leading to study withdrawal in both studies. One patient did not complete intended dosing, because of death due to acute respiratory failure following pulmonary oedema.

3.3.9. Discussion on clinical safety

The currently available safety database for begelomab is extremely limited, even when taking into consideration the rarity of the disease. The clinical safety of BEGEDINA was evaluated in a total of 29 patients, but only a very limited number of patients (n=6) patients received the proposed extended dose schedule of 5 days consecutive treatment + 6 biweekly administrations. The low number of patients and the variability in the exposure due to the use of various dose levels provide a major level of uncertainty to the safety evaluation of the proposed begelomab treatment regimen. Furthermore, because of the low number of patients in each dose level, conclusions on any-dose effect relationship cannot be made.

In addition, the safety database is comprised of a highly compromised patient population due to their background disease, prior and concomitant treatments. The absence of a control group for comparison, makes it difficult to determine whether individual adverse reactions are treatment-related and whether begelomab treatment affected the overall frequency and type of AEs. This provides an additional level of uncertainty on the safety profile.

A pooled analysis of the safety data from the 2 clinical studies has been provided. It is stated that this represents data collected up to 180 days, however it is questioned whether the data from the pilot study actually represents up to 365 days and this needs to be clarified, together with the timings and methods of adverse event data collection.

Treatment compliance was very good. All but one patient received the scheduled dose of begelomab (or more). This one patient died of respiratory failure associated with pulmonary oedema. The death of this patient should be considered treatment-related according to the investigator. Based on the narrative of this patient, it is agreed with the Applicant that it is more likely that this death was due to the underlying condition (aGvHD) and not begelomab treatment. However, a relationship with treatment cannot be excluded.

Currently adverse events have been analysed as a whole by the planned dose cohorts, and by looking at those AEs that were present before treatment, during treatment and after treatment. Particularly given the uncontrolled open label nature of the trials, this is of limited value in trying to assess any potential causality and dose dependency of begelomab. A re-analysis of the adverse event data is required by cumulative dose (e.g. 2 groups 'high' and 'low') and presenting this by month.

The high frequency of AEs noted at baseline indeed indicates that the population at hand is very sick. Of the many reported AEs (total of 867) only a small fraction AEs (n=14) reported from six patients (20.7%) were judged as related to study medication by investigator, but no AE reported required treatment discontinuation.

Fourteen adverse events have been identified by the applicant as possibly related to begelomab and proposed for inclusion in section 4.8 of the SmPC. However, no explanation of how causality has been assessed has been provided. Notably, the most commonly reported AE SOC was Infections and infestation. However, without an adequate control group it is not possible to determine whether begelomab had any role in the aetiology of these infections as the population being treated is already immunocompromised and thus at risk for such infections.

Based on the type of product, begelomab treatment can cause infusion-related reactions. While some AEs were noted that may be related to infusion, a conclusion on their relation to treatment is not possible. It is reassuring that no anaphylactoid reaction or other serious AEs indicative of infusion reaction was noted. However, patient's numbers are low, and the analysis of infusion reactionslacks sufficient detail so a firm conclusion cannot be drawn.

Malignancy and autoimmunity are indicated as important potential risks in the RMP, autoimmunity is even mentioned in section 4.4 of the SmPC. However, apparently, the AEs profile does not appear to have been analysed for signals of these potential risks.

It is known that the target of begelomab, CD26 is involved in multiple processes. In principle, non-clinical studies could provide clues on which types of effects can be expected in humans. However, no support is currently present from those studies, as it was concluded that the toxicity studies are inconclusive on the safety risks of begelomab use (see non-clinical section). Based on the knowledge of the function of CD26, more AEs of special interest can be envisioned than were discussed by the Applicant, such as interference with the cardiovascular system and/or the regulation of glucose levels. In this respect, it is important to note that to a relatively large number of patients insulin was given as concomitant treatment. While there may be other causes for insulin use (pre-existing diabetes or steroid-induced diabetes), a relationship with begelomab treatment cannot be excluded, so further evaluation is needed.

Overall the number of patients that had died by D180 in both studies was similar (38.5% in the pilot study and 37.5% in the dose-finding study) and no deaths were attributed to begelomab by the

investigator. However, the overall survival in days for the patients that died was lower for the patients in the dose-finding study, despite the fact that the patients in the pilot study had a higher overall baseline GvHD grade and this needs further discussion. One patient in the extended dose group of the dose-finding study died due to worsening GvHD before completing all 11 doses of the study medication and any potential causative role of begelomab in this patient's death has not been discussed.

As may be expected for a murine antibody, treatment with begelomab is therefore highly immunogenic. Due to the high intra-subject variability observed and the unknown drug tolerability of the HAMA assay, no conclusions can be drawn if the HAMAs affected pharmacokinetics of begelomab. It is agreed to determine immunogenicity of begelomab in the Phase II/III confirmatory study.

In addition to the uncertainties in the analysis of the safety profile mentioned above, multiple inconsistencies were noted in the documentation of safety (frequencies of AEs) (examples can be found in the AR). Together, these results point toward a lack of accuracy in data collection within the studies and inconsistencies in choice of reporting between studies. This all further adds to the uncertainty on the reliability of the data/dossier as presented by the Applicant.

3.3.10. Conclusions on clinical safety

The clinical evaluation of the safety of begelomab is hampered by a large number of factors, such as the low number of patients, the variability in treatment schedules, the heterogeneity of the patient population, the absence of a control group and the severity of the underlying condition that is accompanied by a high morbidity and mortality. As a consequence the safety profile of begelomab cannot be adequately described. It is, however, important to note that all but 1 patient completed the intended dosing schedule, which suggests that safety should not be an obstacle for the use of this product in this population of high unmet medical need. A number of further analyses of the limited safety data available are requested, as a better description of the safety profile should aid the treating physician in choosing the adequate support during treatment of his/her patient .

3.4. Risk management plan

Safety concerns

The Applicant provided the following tabulated summary of the safety concern in the RMP:

Table 26 Summary of safety concerns

Important identified risks	Development of neutralizing human anti-mouse antibodies Infusion-related reactions
Important potential risks	Severe infections Autoimmune disorders Malignancies
Missing information	Long-term outcome Use during pregnancy or lactation Use in elderly Use in paediatric population Use in patients with renal impairment Use in patients with hepatic impairment

Having considered the data, the CHMP consider that the following issue should be addressed with regard to the safety concerns:

- The Applicant should reword the proposed identified risk 'infusion-related reactions' into severe hypersensitivity reactions including anaphylactic responses and cytokine release syndrome'. In the search criteria the MedDRA SMQ of Anaphylactic reaction should be added:
- The Applicant should reword the proposed potential risk 'malignancies' into 'malignancies, including progress of underlying disease';
- Regarding the potential risk 'severe infections' the Applicant should broaden the PTs used as search criteria to retrieve applicable case reports;
- The Applicant should omit 'autoimmune disorders' as important potential risk;
- The Applicant should amend 'use in paediatric population' as a topic for missing information into 'off label use in paediatric population (< 18 year)' as important potential risk;
- The Applicant should re-consider the need for inclusion of 'use during pregnancy and lactation' and the 'use in elderly' in the list of missing information. This because the use of begelomab in pregnant or lactating women or elderly subjects is highly unlikely given the fact that HSCT is unlikely to be performed in these patient populations and it is therefore unlikely that including these populations in this list will increase the likelihood of gaining information on treatment experiences in these patient populations.

It should be noted that most likely the safety specifications need to be further updated following assessment of Applicant's response to the questions raised on the submitted quality, non-clinical and clinical data. Topics that may further affect the RMP include among others:

- Virus inactivation;
- Interactions during co-medication with CD26 targeted medicinal products;
- Product's precise effect on CD26 and as such among other the effects on the glucose metabolism and other related possible adverse events.

In the submitted RMP the Applicant did not address the following topics:

- 'patients with other relevant co-morbidity';
- 'patients with different racial and/or ethnic origin'.

In the updated RMP, the Applicant should address these issues and include available information in line with the assessment following submission of the requested (non)clinical data.

Pharmacovigilance plan

Table 4 Safety concerns and overview of planned pharmacovigilance actions

Development of neutralizing human anti-mouse antibodies		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
Changes in the profile and frequency together with the outcomes and impact on the treatment of this safety concern	- Routine pharmacovigilance - A prospective, Phase II/III, randomized study to compare BEGEDINA versus "conventional treatment" for steroid-resistant aGvHD	To further characterize the risk in terms of frequency, symptoms in a real life use, potential risk factors, and consequences.

Infusion-related reactions		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
Changes in the profile and frequency of this safety concern	- Routine pharmacovigilance - A prospective, Phase II/III, randomized study to compare BEGEDINA versus "conventional treatment" for steroid-resistant aGvHD	To further characterize the risk in terms of frequency, symptoms in a real life use, potential risk factors, and consequences.

Severe infections		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
Changes in the profile and frequency of this safety concern	- Routine pharmacovigilance - A prospective, Phase II/III, randomized study to compare BEGEDINA versus "conventional treatment" for steroid-resistant aGvHD	To further characterize the risk in terms of frequency, symptoms in a real life use, potential risk factors, and consequences.

Autoimmune disorders		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
The relevance of this safety concern to BEGEDINA therapy	- Routine pharmacovigilance - A prospective, Phase II/III, randomized study to compare BEGEDINA versus "conventional treatment" for steroid-resistant aGvHD	To further characterize the risk in terms of frequency, symptoms in a real life use, potential risk factors, and consequences.

Malignancies		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
The relevance of this safety concern to BEGEDINA therapy	- Routine pharmacovigilance - A prospective, Phase II/III, randomized study to compare BEGEDINA versus "conventional treatment" for steroid-resistant aGvHD	To further characterize the risk in terms of frequency, symptoms in a real life use, potential risk factors, and consequences.

Long-term outcome		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
The long-term effects of BEGEDINA therapy	- Routine pharmacovigilance - A prospective, Phase II/III, randomized study to compare BEGEDINA versus "conventional treatment" for steroid-resistant aGvHD	To investigate and further characterize the possibility of long-term risks associated with BEGEDINA therapy

Use during pregnancy or lactation		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
Safety of BEGEDINA therapy during pregnancy and/o lactation	- Routine pharmacovigilance	To monitor for adverse events, detect, and evaluate signals in this special population.

Use in elderly		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
Efficacy and safety of BEGEDINA therapy in this special population	- Routine pharmacovigilance	To monitor for adverse events, detect, and evaluate signals in this special population.

Use in paediatric population		
Areas requiring confirmation or futher investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
Efficacy and safety of BEGEDINA therapy in this special population	-Routine pharmacovigilance	To invesitgate possibility of risks associated with use of begelomab in this special population

Use in patients with renal impairment		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
Efficacy and safety of BEGEDINA therapy in this special population	- Routine pharmacovigilance - A prospective, Phase II/III, randomized study to compare BEGEDINA versus "conventional treatment" for steroid-resistant aGvHD	To monitor for adverse events, detect, and evaluate signals in this special population.

Use in patients with hepatic impairment		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities**	**Objectives**
Efficacy and safety of BEGEDINA therapy in this special population	- Routine pharmacovigilance - A prospective, Phase II/III, randomized study to compare BEGEDINA versus "conventional treatment" for steroid-resistant aGvHD	To monitor for adverse events, detect, and evaluate signals in this special population.

The PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC consider that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

The planned studies in the Post-authorisation Pharmacovigilance Development Plan are sufficient to address the safety concerns identified in the safety specification. The Applicant is asked to submit the protocols for the three studies or at least the synopsis.

Risk minimisation measures

Proposal from applicant for risk minimisation measures is shown in Table 5.

Table 5 Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Development of neutralizing human antimouse antibodies (HAMA)	Prescription only medicine - Warning about the possibility of development of neutralizing human anti-mouse antibodies in the target population is presented in section 4.4. Similar information is included in the PL in language more appropriate for the lay audience.	Not applicable
Infusion-related reactions	Prescription only medicine - Warning about the possibility and proposed management of infusion-related reactions in the target population is presented in section 4.4. Similar information is included in the PL in language more appropriate for the lay audience.	Not applicable
Severe infections	Text included in the SmPC: - Warning about the possibility of severe infections in the target population is presented in section 4.4. Similar information is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Autoimmune disorders	Prescription only medicine - Warning about the possibility of autoimmune disorders in the target population is presented in section 4.4. Similar information is included in the PL in language more appropriate for the lay audience.	Not applicable
Malignancies	No specific risk minimisation measures are felt necessary at this point of knowledge. Prescription only medicine	Not applicable
Long-term outcome	No specific risk minimisation measures are felt necessary at this point of knowledge. Prescription only medicine	Not applicable
Use during pregnancy or lactation	Text included in the SmPC: - Listed in section 4.3 as contraindication of BEGEDINA use. - All relevant information is	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	summarized in section 4.6. - The information about missing pre-clinical developmental or reproductive studies is included in section 5.3. Similar information is included in the PL in language more appropriate for the lay audience. Prescription only medicine	
Use in elderly	Text included in the SmPC: - Section 4.2 informs about the no data on efficacy and safety of BEGEDINA use in this special population. Similar information is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Use in paediatric population	Text included in the SmPC: - Section 4.2 informs about the no data on efficacy and safety of BEGEDINA use in this special population. - Information relevant to the clinical development of BEGEDINA in paediatric population is summarized in section 5.1. Similar information is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Use in patients with renal impairment	Text included in the SmPC: - Section 4.2 informs about the lack of experience with BEGEDINA in this special population. Similar information is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable
Use in patients with hepatic impairment	Text included in the SmPC: - Section 4.2 informs about the lack of experience with BEGEDINA in this special population. Similar information is included in the PL in language more appropriate for the lay audience. Prescription only medicine	Not applicable

The PRAC, having considered the data submitted, was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s). The applicant should also take into account, where necessary, additional PhV activities for the safety concerns to be added.

In general the elements for a public summary are acceptable. However, this section in the RMP should be amended as detailed in the list of questions.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 (DLP 2 February 2015) could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

3.5. Pharmacovigilance system

The CHMP consider that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

4. Orphan medicinal products

According to the conclusion of the COMP (Opinion dated 26.11.2010), at the time of designation the prevalence of the "condition" graft-versus-host disease was less than 0.4 per 10000 individuals in the EU. This was equivalent to a total of fewer than 20,000 people, and is below the threshold for orphan designation, which are 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

5. Benefit risk assessment

The overall purpose of begelomab treatment is blocking the expansion CD3+CD26+ T lymphocytes by binding to CD26 and consequently mediating a reduction of the immune response occurring during steroid-resistant aGvHD.

This application is based on 2 uncontrolled studies:

- a Phase I/II open-label pilot study in patients who received prior HSCT and with grade II-IV Graft versus Host Disease (GvHD) (Study EUDRACT 2007-005809-21). In this study 14 patients were included and 13 were treated with begelomab, of which 12 had steroid-refractory acute GvHD.
- a Phase II open-label dose-finding study for treating steroid-resistant aGvHD patients who previously underwent hematopoietic stem cell transplantation (HSCT) (Study EUDRACT 2012-001353-19). In this study 16 patients were included and treated with begelomab.

Overall 5 dose levels have been tested in a total of 29 patients, each in only a limited set of patients using schedules of 5 days consecutive treatment that were sometimes repeated. Only one schedule was followed by 6 biweekly administrations, as currently recommended in the SmPC. This was tested in 7 patients in the dose-finding study and will be further studied in the planned phase II/III study.

Benefits

Beneficial effects

Endpoints in both studies included frequency of responders at day +28 or 30, and day +56 or 60, where response was defined as reduction of aGvHD to a less severe grading. Furthermore, data on survival, Karnofsky index, relapses and chronic GvHD were collected. The primary endpoint of the pilot study was evaluation of the response rate at day 10. The primary endpoint of the dose-finding study was to determine the Minimum Effective Dose (MED) of begelomab treatment in steroid resistant acute GvHD treatment by means of determining the number of begelomab positive cells shortly after begelomab treatment. In acute GvHD key clinical endpoints are transplant related mortality and overall survival data. Whilst responder rates, unlike survival data are not a measure of long-term benefit, there is some evidence from the literature that response rates at D+28 may be reasonably likely to predict a clinical benefit.

In the pilot study, 7 of 12 (58%) patients were alive at day 180, for 4 patients (33%) death was considered related to HSCT. At 1 year, 4 (33%) patients were still alive. In the dose-finding study, 10 of 16 patients were still alive (63%) at day 180, for 4 patients (25%) death was considered related to HSCT.

In the pilot study, the frequency of responders was 58% at day 10, 83% at day 30 and 92% at day 60. In the dose-finding study the frequency of responders was 69% at day 28 and 75% at day 56, with no clear difference in responder rates between the various dose levels.

The pooled begelomab population (n=28) was compared to a historical control population from the same institution matched to those of the dose-finding study (n=36). Results showed that the day 28 frequency of responders was significantly higher in the begelomab-treated populations (75% vs 31%), as was overall survival (61% vs 22% at day 180, and 46% vs 19% at 1 year).

Uncertainty in the knowledge about the beneficial effects

There are a number of significant limitations and uncertainties surrounding these provisionally promising beneficial effects. These include the low number of aGvHD patients that were treated, the large diversity in the used dosing schedules with only 7 subjects treated with the proposed dosing schedule and 4 patients receiving additional administrations without knowing the impact, the lack of information on baseline characteristics, in particular on the disease to be treated, and sparse information on co-medication and the (possibility to) initiate next-line therapy that may have impacted outcome.

Both clinical trials were uncontrolled, open-label and undertaken in the same single centre in Italy with the same principal investigator. Consequently this does not allow for a proper assessment of any potential treatment effect and the external validity of the data is unknown.

The provided comparison with the historical control group is accompanied with many uncertainties, including the pooling of data of the begelomab study populations and groups with differences in in- and exclusion criteria and dosing schedules, and similarity of the historical control group in baseline characteristics and prognosis. Also, it is questioned whether the documentation of the events in the control group was sufficiently accurate and complete to allow for evaluation of responses.

Also, there are major uncertainties regarding the conduct of the two studies. These include the accuracy of the data with a high level of missing data, re-review of the major outcome data without justification, and several unexplained protocol deviations/violations. A critical evaluation on the conduct of the study and protocol adherence, and discussion of the impact of the identified protocol

deviations/violations on the validity of the data are lacking. Because of these multiple concerns, the planned GCP inspection should be considered to be a triggered GCP inspection and the outcome of this inspection and the satisfactory responses to its findings are considered to be an integral part of this procedure and will be needed by Day 121.

These major uncertainties are accompanied by numerous other causes for concern on validity and interpretation of the data. These include, but are not limited to, the following aspects:

- insufficient description of the manufacturing process and validation of the production process;
- comparability between the batches;
- near absence of pharmacodynamic endpoints;
- lack of support for the selected dose;
- descriptive character of the statistical methods;
- assessment of response in terms of stable disease;
- lack of information on the diagnosis of aGvHD vs *chronic* GvHD and the cut-off of 100 days;
- differences in in- and exclusion criteria for the two studies;
- determination of response in several subjects;
- difference in frequency of early mortality (before day 90) between the studies;
- lack of supportive endpoints (incidence of chronic GvHD, Karnofsky index, relapse) as data was generally limited to very few patients.

Risks

Unfavourable effects

The safety assessment of begelomab is based on clinical and laboratory evaluations from the 29 patients of the 2 uncontrolled studies also submitted in support of efficacy. The evaluation of safety included the collection of adverse events (AEs), serious AEs (SAEs) and treatment-related AEs as well as clinical laboratory evaluation, vital signs, physical findings, and immunogenicity. These variables were collected up to 180 days from the start of treatment. For the analysis of the safety the Applicant has pooled the adverse events from the two clinical trials.

A total of 867 adverse events, irrespective of relationship to study treatment, were reported during the 2 studies. All subjects were reported as having experienced at least 1 grade ≥ 3 AE. The most common reported AEs occurred in the system organ classes Infections and infestations (93.1%), Gastrointestinal disorders (86.2%), General disorders and administration site conditions (82.8%), Investigations (79.3%), Skin and subcutaneous tissue disorders (75.9%), Blood and lymphatic system disorders (62.1%), and Musculoskeletal and Connective Tissue Disorders (55.2%). A relatively large proportion of the adverse events were classified as severe (CTC grade ≥ 3), with all patients experiencing at least one severe AE. This adverse event profile is not unexpected in this patient population and no adverse events reported required discontinuation of treatment.

A relative small fraction of all AEs was considered to be possibly treatment-related by the investigator (total of 14 AEs in 7 subjects). Sixteen (16) subjects (55.2%) were reported with at least one serious adverse event. Of these, 11 (37.9%) were subjects with fatal adverse events by day 180 from start of therapy with begelomab. Importantly, there were no adverse events leading to study withdrawal in both studies. No deaths were attributed to begelomab by the investigator. One patient did not complete intended dosing, because of death due to acute respiratory failure following pulmonary oedema most likely because of worsening GvHD before completing all 11 doses of the study medication.

As a murine monoclonal antibody it would be expected to see the occurrence of severe infusion reactions and hypersensitivity reactions, particularly with repeated exposure. However, the patient population exposed to begelomab are immunocompromised and patients received premedication with intravenous steroids and antihistamines. There were no reports of anaphylactic/anaphylactoid reactions during the clinical trials.

Based on the very limited immunogenicity data available, 12 patients (46%) developed transient or persistent antibodies during treatment suggesting begelomab is highly immunogenic which is to be expected for a murine antibody.

In the comparison with the historical control group there were more than twice as many deaths due to GvHD (44% vs 14%) and more multi-organ failure (17% vs 7%) at day 180 in the control group when compared to the pooled begelomab group. Deaths due to relapse were 11% in the begelomab group and 6% in the control group.

From a quality point of view, sterility and viral safety of the product is currently not sufficientlydemonstrated, and potential contamination with adventitious agents is of major concern for this immunocompromised population.

Uncertainty in the knowledge about the unfavourable effects

The currently available safety database for begelomab is extremely limited, even when taking into consideration the rarity of the disease. Overall, a total of 29 patients have received at least 5 doses of begelomab in clinical trials of who only 6 have received the dose and duration of treatment proposed for licensing. A further concern is that the comparability of the begelomab batches that will be used in the confirmatory trial and for marketing to those used in the clinical trials has not yet sufficiently demonstrated.

In addition to being very limited, the safety database is comprised of a highly compromised patient population due to their background disease, prior and concomitant treatments. Furthermore both trials were open label with no comparator arm. Consequently, this makes it very difficult to define any clear correlation between adverse events and the study medication and to characterise the safety profile of begelomab. A number of re-analyses of the very limited safety database are requested and a description of how potential causality was assessed.

The data on exposure to begelomab is currently too limited to draw any conclusions on the safety of begelomab in special populations and no data is available on potential drug-drug interactions.

Immunogenicity data are currently very limited and the impact of antibodies on PK, PD, efficacy and safety is largely unknown. It is reassuring that no anaphylactoid reaction or other serious AEs indicative of infusion reaction was noted. However, patient's numbers are low, so a firm conclusion cannot be drawn.

The Applicant did not analyse the observed AE profile for AEs that could be anticipated based on the pharmacological target of CD26, more AEs of special interest can be envisioned, such as interference with the cardiovascular system and/or the regulation of glucose levels. Furthermore, the non-clinical toxicity studies are inconclusive on the safety risks of begelomab use, and thus do not provide any clue on which types of adverse effects are to be expected in the clinic. Also it should be clarified whether begelomab treatment could potentially interfere with DPPIV inhibitors at a pharmacological level.

Malignancy and autoimmunity are indicated as important potential risks in the RMP, autoimmunity is even mentioned in section 4.4 of the SmPC. However, apparently, the AEs profile does not appear to have been analysed for signals of these potential risks.

Because of the limited evaluation of safety the clinical impact of the concern regarding contamination with adventitious agents cannot be assessed.

On several occasions a discrepancy was observed between the frequencies in the AE tables provided by the Applicant in the overview or summary of clinical safety and the patient listings in the study reports. As the order of magnitude of the frequencies is generally similar, this does not really affect the overall impression of the safety profile of begelomab, it does point towards inaccuracy of documentation. Furthermore, there appears to be a lack of accuracy in AE collection within the studies and inconsistencies in choice of AE reporting between studies.

Effects Table

Effects Table for begelomab treatment in steroid-resistant aGvHD (based on data available from the pilot study (study 2007-005809-21) and the dose-finding study (2012-001353-19)).

Effect	Short Description	Unit	Treatment with begelomab	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Response	Defined as reduction of aGvHD to a less severe grading*	Frequency at day 28 or 30	75% (21 of28)^	n/a[$]	Data obtained in too few patients to allow for definitive conclusions. Data are not reliable because of lack of accuracy in reporting, large amount of missing data and unexplained re-reviewing. Lack of adequate control group. Relationship to treatment unclear.	
Survival	Defined from date of informed consent	Percentage patients alive at day 180	61% (17 of 28) ^	n/a[$]	Data in too few patients to allow for conclusions. Lack of adequate control group. Relationship to treatment unclear.	
secondary endpoints	Incidence of chronic GvHD, Karnofsky index, relapse	various	-	n/a[$]	Data in too few patients to allow for conclusions.	
Unfavourable Effects						
General profile	AE frequency and type	various	-	n/a[$]	Data in too few patients to allow for definitive conclusions. Lack of control arm. Inaccuracy of reporting.	

*Notes: * in initial definition, on initiative of the sponsor the statistical analysis plan was adapted so that stable disease should be considered a response to treatment. It is however not clear whether this change was indeed implemented; ^patients pooled from 2 studies; $: no control group in the study;*

Benefit-risk balance

Importance of favourable and unfavourable effects

There is a high unmet medical need in the treatment of steroid-resistant acute graft versus host disease (aGvHD), as also shown by the high morbidity and mortality seen in the studied population and which is further supported by literature. Currently there are no registered treatment modalities for steroid-resistant aGvHD. Begelomab could be of interest for patients affected by steroid-resistant aGvHD based on its intended mechanism of action blocking the expansion CD3+CD26+ T lymphocytes. However, the *in vitro* and *in vivo* data in support of its mechanism of action is extremely limited. Furthermore, major quality issues regarding the product have been identified.

The clinical data is based on only 28 subjects with steroid-resistant aGvHD that were treated with begelomab who were treated with 5 different treatment schedules with only 6 patients exposed to the proposed extended dose schedule. It is not clear whether the effects of the other dose regimens are in line with the efficacy of the proposed dose regimen and whether pooling of data across these dosing regiments, as has been performed by the Applicant, is justified.

Two main parameters were used to assess efficacy, i.e. response rate (reduction in aGvHD to a less severe grading) and survival. The frequency of responders was assessed as high. However, due to the many uncertainties regarding the interpretation of the response, there is no confidence in the use of this parameter as outcome measure. This leaves survival as the only potentially reliable endpoint for estimation of the effect of begelomab treatment. A difference in survival was noted between the pooled begelomab population and the historical control group in favour of the begelomab treated population. However, the interpretation of this difference in survival is hampered for several reasons as indicated above. Also, any assessment of the importance of the effects is hampered by uncertainties on the conduct of the two studies.

Considering the safety, the pattern of the most reported AEs is as expected considering the population at hand. Any impact of identified or potential risks is therefore difficult to make, in particular as the studied population is very small in numbers and adequate comparative data lacking. It may be reassuring that all but 1 patient completed the intended dosing schedule, but any conclusions on safety warrant further confirmation by additional clinical data.

Benefit-risk balance

As the efficacy of begelomab treatment cannot be determined due to major uncertainties in its interpretation and assessment on safety is premature and inaccurate, the benefit-risk balance cannot be established. Furthermore, major issues exist on quality, non-clinical studies and conduct of the two clinical trials.

Discussion on the benefit-risk assessment

Overall, the current data do not support any definite conclusion on the efficacy of begelomab treatment at the chosen dose level and schedule for patients with acute steroid-resistant GvHD. For this not only additional data of the submitted studies plus additional analyses would be required, but also more clinical data. In general, the dossier is considered premature. In this respect, the proposed controlled

confirmatory efficacy and safety phase II/III study in adults with steroid-resistant aGvHD is considered pivotal.

Since a conclusion on the efficacy of treatment cannot be drawn and safety assessment is limited and inaccurate, the benefit-risk can not be assigned as positive and therefore, it cannot be determined whether the unmet medical need for patients with steroid-resistant aGvHD can be fulfilled by begelomab. Thus, this requirement for a conditional approval is not met.

A GCP inspection is required and planned to meet existing questions regarding the conduct of the clinical trials.

5.1. Conclusions

The overall B/R of begelomab is inconclusive and thus current application not approvable.

6. Recommended conditions for marketing authorisation and product information

6.1. Conditions for the marketing authorisation

6.2. Product Information

The CHMP comments on the SmPC, Labelling and Package leaflet (PL) are included in the product-information, attached as separate file. Please note that due to the major objections raised, only a limited assessment of the PI is possible at this stage.

The Package leaflet will be fully assessed after it has been updated according to the comments regarding the SmPC.

User consultation

User consultation of the Package Leaflet has not yet been performed. The applicant committed to submit the results of the readability testing on Day 121 of the procedure.