SCIENTIFIC DISCUSSION

Introduction

Busilvex contains the active substance busulfan in a concentrate for solution for infusion. Busulfan acts as an alkylating agent. On December 29, 2000, busulfan (intravenous use) was designated Orphan Medicinal Product in the indication "Conditioning treatment prior to haematopoietic progenitor cell transplantation". A marketing authorisation was granted in the EU on July 2003 for the indication "Busilvex followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option".

At the time of positive opinion, the Marketing Authorisation Holder committed to perform a clinical study in the paediatric population. As a result, the MAH has submitted a variation application for Busilvex for an indication in the paediatric population "Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients".

The proposed dose of Busilvex is as follows:

Actual body weight (kg)	Busilvex dose (mg/kg)
< 9	1.0
9 to < 16	1.2
16 to 23	1.1
> 23 to 34	0.95
> 34	0.8

followed by 4 cycles of 50 mg/kg body weight (BW) cyclophosphamide (BuCy4) or by one administration of 140 mg/m² melphalan (BuMel).

Busilvex is administered as a two-hour infusion every 6 hours over 4 consecutive days for a total of 16 doses prior to cyclophosphamide or melphalan and conventional haematopoietic progenitor cell transplantation (HPCT).

Clinical aspects

Conditioning regimens used for HSCT must accomplish two goals, depending on the patient's disease and the source of progenitor cells. Since the majority of autologous and allogeneic HSCT are performed for the treatment of malignant disease, the regimen must provide tumour cytoreduction and, ideally, disease eradication. In the case of allogeneic HSCT, the regimen must be sufficiently immunosuppressive to prevent graft rejection of the donor stem cells by residual host haematopoiesis.

Early conditioning regimens were based on total body irradiation (TBI), where high doses of radiation were required to provide adequate myeloablation and immunosuppression. Alkylating agents are the major class of drugs used in conditioning regimens for HSCT because they have many desirable characteristics. Many of these agents have marrow toxicity as the main dose-limiting factor, which allows for dose escalation when HSCT is utilized. Alkylating agents are not cycle specific and therefore capable of killing resting tumour cells, they do not exhibit cross-resistance and have relatively steep log-linear dose-response curves. Although it is impossible to combine these agents at maximum tolerated doses (MTD), between 50-70% of the MTD can be used in two or three drug combinations[1].

Busulfan (Bu) is an alkylating agent with profound myeloablative properties that has been extensively used for decades in the treatment of chronic myeloid leukaemia. The MTD of Bu given alone over four days followed by HSCT is 20mg/kg[2]. Busulfan has a broad spectrum of activity and is active against a variety of malignancies including acute and chronic leukemias, lymphomas, multiple myeloma and solid tumours. Bu in high doses has been used alone or in combination as preparative regimen for HSCT. One of the problems with the optimal utilization of the oral form of Bu has been

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[1] Bensinger WI, Spielberger R. Preparative regimens and modification of regimen-related toxicities. In Blume KG, Forman S, Appelbaum F eds. Thomas´ Hematopoietic cell Transplantation. 3rd ed. Blackwell Publishing. 2004 pg 158-177

[2] Peters WP, Henner WD, Grochow LB. Clinical and pharmacologic effects of high dose single agent busulfan with autologous marrow support in the treatment of solid tumours. Cancer Res 1987; 47:6402-6

the high pharmacokinetic variability between individuals that probably contributes to the significant differences observed in toxicity and clinical response in patients receiving the same dose in mg/kg or mg/m^2. It has been demonstrated a relationship between low Bu steady-state plasma concentrations and graft rejection in children[3]. There are also data suggesting a relationship between the sinusoidal obstruction syndrome of the liver and high Bu plasma levels, and more recently a correlation of steady-state Bu concentration and relapse rates[4].

Cyclophosphamide (Cy) is very immunosuppressive alkylator, its dose-limiting toxicity is hemorrhagic cystitis. As single agent the MTD is approximately 200 mg/kg. Cy has been extensively used in combination con busulfan or TBI in the conditioning regimens for HSCT.

Melphalan (Mel) is a bifunctional alkylating agent that incorporates nitrogen mustard and phenylalanine. Dose-limiting toxicities are gastrointestinal and hepatic. Melphalan 240 mg/m^2 has been used alone in conditioning regimens for patients with hematologic malignancies receiving HSCT. Mel has also been extensively used in HSCT for solid tumours or other malignancies either alone or in combination with busulfan, carmustine or TBI.

In 1983, a conditioning regimen termed By/Cy4 was designed by Santos et al., combining high dose oral busulfan (1 mg/kg every 6 hours, over 4 days -16mg/kg-) and cyclophosphamide (50mg/kg every 24 hours x 4 days -200 mg/kg-). This regimen was profoundly myeloablative and immunosuppressive and was very effective for the treatment of high risk acute leukemias and other malignancies either in the autologous or the allogeneic setting[5]. This combination was subsequently modified by decreasing the dose of Cyclophosphamide to 120mg/kg administered in two days -the Bu/Cy2 regimen- with an apparent decrease in toxicity without an increase in relapses, although not surprisingly Bu/Cy4 was more effective in high risk leukemias. In children receiving allogeneic transplantation, the Bu/Cy regimen is the most commonly used non-TBI-based pre-transplant conditioning treatment. Bu/Cy4 is preferred in high risk leukemias and to prevent rejection in nonHLA identical siblings or unrelated donors. In this preparative regimen, the primary purpose of busulfan is to eradicate malignant cells (myeloablation) and for cyclophosphamide is to induce immunosuppression in the recipient so that rejection is prevented and engraftment of the donor haematopoietic system is permitted.

Two randomised comparison trials between Cy/TBI and Bu/Cy2 have shown no significant differences in long-term survival in patients with chronic myeloid leukaemia in the chronic phase receiving HLA-matched allogeneic transplants. A SWOG study compared Bu/Cy and Cy/TBI/Etoposide in 122 patients with advanced acute leukaemia or CML undergoing allo-HSCT. There were no important differences in toxicity, survival or disease free survival in patients receiving either regimen.

A regimen with busulfan (16 mg/kg) and melphalan (140 mg/m2) (Bu-Mel), followed by autologous or allogeneic HSCT demonstrated efficacy in patients with myeloid malignancies, multiple myeloma and solid tumours. The European Bone Marrow Transplant Group has reported its experience over 6.000 HSCT in the paediatric age, showing that the Bu-Mel conditioning was the most successful combination in the EBMT solid tumour registry data resulting in significantly better survival rates in neuroblastoma and Ewing´s tumours[6]

In patients with thalassemia, busulfan at 14 mg/kg and cyclophosphamide at 120-200 mg/kg was a well-tolerated and effective regimen for allografting. A conditioning regimen including busulfan (12 mg/kg), melphalan (100 mg/m^2) and thiotepa (500 mg/m^2) following by autologous HSCT have shown good results in a variety of haematological malignancies and solid tumours. Regimens involving busulfan, cyclophosphamide and thiotepa or melphalan, or etoposide has been utilised prior to autografting and allografting.

[3] Slattery JT, Sanders JE, Buckner CD et al. Graft rejection and toxicity following bone marrow transplantation in relation to busulfan pharmacokinetics. Bone Marrow Transplant 1995; 16:31-42

[4] Grochow LB. Busulfan disposition. The role of therapeutic monitoring in bone marrow transplantation induction regimens. Semin Oncol 1993; 20:18-25 // Slattery JT, Clift RA, Buckner CD et al. Marrow transplantation for chronic myeloid leukaemia: the influence of plasma busulfan levels on the outcome of transplantation. Blood 1997; 89:3055-60

[5] Santos GW, Tutschka PJ, Brookmeyer R, et al. Marrow transplantation for acute nonlymphocytic leukaemia after treatment with busulfan and cyclophosfamide. N Engl J Med 1983; 309:1347-53

[6]

Since the authorization of the intravenous formulation of busulfan, it has been widely used in the conditioning regimens replacing the use of the oral tablets.

Rationale for intravenous high dose busulfan in children

Busulfan is an alkylating agent with myeloablative properties and activity against non-dividing marrow cells and, possibly, non-dividing malignant cells. Currently, iv busulfan is licensed for adult use. The use of oral busulfan, administered at high doses (*i.e.* 1 mg/kg x 16 doses, administered over 4 days) for the preparative treatment before HSCT in the paediatric population is current practice and there could also be a use "off label" of the intravenous formulation in this patient group.

One of the problems with optimal utilisation of busulfan is the bioavailability of the oral form. The pharmacokinetic variability between patients is high, which can be involved in the significant differences observed in toxicities and clinical responses in patients receiving the same oral dose. The steady-state busulfan concentration has been correlated with graft rejection and disease relapse, as well as with the severity of conditioning regimen toxicities, especially veno-occlusive disease of the liver. Consequently, it should be expected from an I.V. form of busulfan to reduce these issues. It should be taken into account that the use of Busilvex in children would be particularly interesting because of the toxicity associated with total body irradiation, the difficulties related to oral medications and the favourable outcome of transplantation in this group.

The main benefits expected from an I.V. form in paediatric use are:

− To provide a well-controlled dose to the patient through avoiding vomiting or poor compliance with the oral form and to offer a more comfortable way of administering to patients having difficulties in swallowing numerous pills.

− To facilitate the targeting of a defined range of AUC considered to ensure engraftment, reduce the risk of toxicity, and thereby improve the outcome of HSCT.

− To reduce individual variability on blood exposure by administering a 100% bioavailable dose to every patient at every administration. A lower variability would result in a less frequent under-exposure, as the concentration obtained in children is lower than in adults with the same dose.

− To reduce the high hepatic concentration of Bu resulting from hepatic first pass through the liver, which is suspected to be highly involved in risk of hepatic veno-occlusive disease (VOD).

These properties should increase the assurance of a successful HSCT by providing a safer transplant and by reducing early morbidity and mortality.

Development programme for the paediatric indication

It can be considered that, in its main aspects, the clinical programme is in accordance with current recommendations of the Note for Guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99) and the Note for Guidance on evaluation of anticancer medicinal products in man: Addendum on paediatric oncology. In the above documents it is stated that"When a medicinal product is to be used in the paediatric population for the same indication as that studied and approved in adults, the disease process is similar in adult and paediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of paediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of paediatric doses that will produce blood levels similar to those observed in adults".

The CPMP provided protocol assistance on February 2001 concerning the clinical development of Busilvex, including its use in children. At that time, it was considered that an application based on a new (i.v.) formulation of an old drug previously used in oral administration, rather could depend upon a thorough pharmacokinetic and pharmacodynamic comparison and then with a mainly supportive role of the clinical results. Therefore, the development programme in children carried out by the Applicant is basically in accordance with the protocol assistance received.

Pharmacodynamics

Busulfan is a bifunctional alkylating agent used in bone marrow transplantation (BMT). The major issues of Bu pharmacodynamics are:
- The conditioning regimen firstly must promote the engraftment of the haematopoietic stem cell transplant
- Secondly, it must generate as few low-rated regimen-related toxicities as acceptable for HSCT. Higher busulfan exposure than 1500 µM.min has been correlated with an increase frequency of hepatic complications, especially veno-occlusive disease (VOD).

Consequently, a targeted range of Bu concentrations in plasma was defined for an optimal compromise between efficacy and toxicity. A usual "therapeutic window" range is 900-1500 µMol.min, although slight differences exist between authors. However, the high variability in oral Bu disposition is known to affect the safety and efficacy outcomes of Bu-based conditioning regimen. Indeed, therapeutic drug monitoring and dose adjustment are usually necessary during the 16 Bu administrations to shift plasma concentrations into the desired target area.
The "therapeutic window" 900 to 1500 µMol.min is validated in adult and patient populations. So, it can be considered as an adequate surrogate during the studies, which can be confirmed during the efficacy and safety investigations.

Pharmacokinetics

Two trials were conducted with Busilvex in paediatric patients to characterise its pharmacokinetic profile.

Study	Phase	Number of patients	Age	Gender	Patient diagnosis	Study design
OMC BUS 5	II	24	54% < 4y 46% > 4 y	50% male	Allogeneic HSCT	Dose 1 through 16: I.V.
F60002 IN 1 01 G0	II	55	4.0 (0.7–14.9) 7.2 (0.3-17.2)	53% male	Autologous and Allogeneic HSCT	Doses 1 through 16: I.V.

In the first trial (OMC-BUS 5), intravenous busulfan was used in combination with cyclophosphamide in paediatric patients as a conditioning regimen (BuCy4) for allogeneic HSCT for malignant and non-malignant disease.
The paediatric dosing of Busilvex was the equivalent of what is done with oral Bu. For children ≤ 4 years: 1.0 mg/kg IV Bu and for children > 4 years: 0.8 mg/kg IV Bu in a 2 hour infusion every 6 hours for 4 consecutive days. Cyclophosphamide was subsequently administered (24 h later), once daily over four days (50 mg/kg/day).
The main objective of this study was to define an appropriate dosing schedule for Busilvex in children. The therapeutic window was defined at 900 – 1350 µMol.min. Bu dose adjustment was allowed in patients when Bu plasmatic AUCs stand outside the therapeutic window ± 5%.
Up to 24 paediatric patients of either sex could be included in the trial (no detailed sample size estimation performed).

Results
Twenty-four evaluable patients were enrolled (13 patients ≤ 4 years [0.4 – 4] and 11 patients > 4 years [4 – 16.7]). Although the number of patients included is low and heterogeneous regarding age and disease, the population can be considered representative of the target paediatric population for Busilvex.
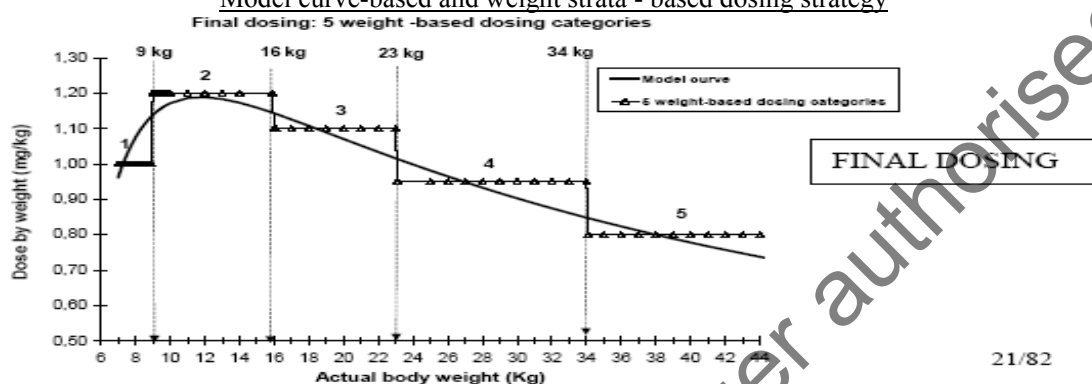The study essentially confirms the findings from the oral experience in this patient population and its good predictability, as the initial doses were adequate to reach the therapeutic levels in 66% of patients for both paediatric age subgroups.
The pharmacokinetic profile has also been characterised more accurately across the paediatric age subgroups, so that dosing can be recommended in a more individualised schedule on the basis of actual body weight for the design of the subsequent studies.

<u>Study F60002 IN 1 01 G0</u>. This prospective phase II trial was carried out in paediatric patients with malignant and non-malignant disease elected for HSCT, receiving IV Bu administered as a standard 16-dose regimen at a fixed dose varying from 0.8 to 1.2 mg/kg in combination with either Mel (140 mg/m²) for autologous transplants or Cy (50 mg/kg/day over 4 days) for allogeneic transplants. No IV Bu dose adjustment was allowed during the full Bu treatment.

The primary objective of the study was the AUC targeting performance of the new fixed Bu dosing (no dose adjustment was allowed during the treatment). To adjust Bu dosing, 5 subgroups of body weight were defined: 0 – 9 kg, 9 – 16 kg, 16 – 23 kg, 23 – 34 kg and >34 kg and thus, resulting in a total of five different Bu dose levels.

<u>Model curve-based and weight strata - based dosing strategy</u>

Final dosing: 5 weight -based dosing categories

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<u>Results</u>
Sixty evaluable patients (12 per group of body weight) were planned and an intermediate report on 55 evaluable patients (27 autologous and 28 allogeneic) is presented (In the first and fourth strata, only 8 and 6 patients, respectively, were included). There were 20 (36%) and 35 (64%) patients ≤ 4 years and > 4 years, respectively, with a median age of 6 years (0.3-17.2). Patient's weight ranged from 5 to 62.5 kg.
The study population, although limited to 55 subjects, is representative of the paediatric age and of the paediatric diseases currently conditioned by Bu-Mel (solid tumours) or BuCy 4 (haematological diseases) regimens followed by HSCT.
In the [900 – 1350 µMol.min] ± 5% AUC range, the targeting performance was ≥ 75 % at doses 1, 9, and 13, and when using the usual [900 – 1500 µMol.min] AUC range, the targeting performance is about 90%.
A slight increase is observed on AUCs between dose 1 and dose 9, which was attributed to misevaluation of AUCinf at dose 1, and this increase is also seen between doses 9 and 13.
Study F60002 IN101G0 confirms the appropriateness of the proposed new IV Bu dosing based on body weight, which resulted in a more efficient targeting performance than previous experiences without invasive TDM and dose adjustment. Its results are consistent with the findings of the preliminary study OMC BUS 5. Therefore, the proposed dosing schedule can be considered adequate. Clinical efficacy and safety results from the two studies will be useful to confirm these pharmacokinetic conclusions.

Clinical efficacy

The two clinical trials using intravenous busulfan (IV Bu) in paediatric patients in the setting of HSCT have also investigated the efficacy and safety aspects.

The pivotal study for efficacy and safety (<u>F00002 IN 101 G0</u>) was performed in 55 paediatric patients, The chemotherapy regimen of intravenous busulfan and cyclophosphamide administered corresponds to the "intravenous version" of BuMel and Bu/Cy4, which are widely used with oral busulfan for HSCT prior conditioning to autologous or allogeneic transplants. A fixed dose based on body weight varying from 0.8 to 1.2 mg/kg of IV Bu was administered over the complete treatment period without

any further dose adjustment. No investigation with Busilvex in other conditioning regimens has been provided.

The protocol considers patients suffering from solid tumours and malignant and non-malignant haematological diseases that are usually candidates for HSCT. Although the indications for transplant are the usual in clinical practice, that is autologous transplants for advanced stage solid tumours, allogeneic transplants for leukemias and congenital haemoglobinopathies and haematological defects, there is a short number of patients in the study and a wide heterogeneity of diagnosis, stage of disease, source of stem cells (peripheral blood in autologous transplant, bone marrow in allogeneic transplants, related and unrelated donors) and GVH. No randomisation or stratification has been considered in this study.

The selected endpoints are appropriate to assess the short-term efficacy and safety of Busilvex in combination treatment with cyclophosphamide or melphalan in the claimed indication.
Patients suffering from solid tumours and haematological diseases (malignant or not) were included in this phase II study. An important proportion is heavily pre-treated. Allogeneic and autologous HSCT is considered an adequate treatment for this population, although there exists a certain degree of disease-specific indication, as can be observed in the final population enrolled in each group. Overall, both groups (autologous and allogeneic) included standard patients for whom HSCT is either the best available option to consolidate remission/best response or the only treatment allowing to eradicate the underlying disease. Therefore the groups are considered relevant and appropriate for the outcome analysis, especially short-term efficacy. The number of patients by type of malignancy is insufficient as to perform a disease-guided approach analysis.

The age of the included population is representative of HSCT paediatric patients, although the number of patients of each age group is limited.

Kinetics of myeloablation was what is commonly expected from myeloablative conditioning regimens such as BuMel or BuCy 4. All patients showed profound pancytopenia after transplantation and all showed engraftment and this occurred at the expected time for neutrophils. [already answered in the response to questions]. The investigation of chimerism in allogeneic transplants revealed that 100% of patients achieved stable chimeras at some time after transplantation (93% complete chimeras). This high rate of successful engraftment, even with unrelated donors, and the absence of rejection are consistent with the rest of endpoints. Transplant related mortality was cero at day +100 post HSCT, both in autologous and allogeneic transplants; that is in accordance with the claimed high degree of safety of Busilvex in the pediatric population. For disease related endpoints, although the follow-up is short, the rate of disease recurrence is low and the results event free survival and overall survival are at least comparable to what is expected with oral Busulfan-based conditionings in this setting.

The intake of concomitant medication, such as methotrexate, directed to prevent and treat graft versus host disease did not show an influence on engraftment and time to engraftment.

Although, it is difficult to relate the outcome of this transplant study exclusively to busulfan therapy, this result can be considered positive and an indirect measure of the myelosuppresive activity of Busilvex.

The open label design does not allow making a comparison of the efficacy and safety of Busilvex with either oral busulfan containing regimens or other conditioning strategies. The quality of clinical data that this type of studies can provide is of limited value and comparative data would have been preferred. However, this study is the main clinical evidence for the efficacy and safety of Busilvex in children, as a III controlled study has not been performed. Nevertheless, it is agreed that Busilvex based regimens should not be essentially different from those based on oral busulfan, and thus, a consistent demonstration of pharmacokinetic comparability can be regarded as pivotal for this application.

In this study, the new dosing of IVBu has been associated with adequate efficacy results in autologous and allogeneic transplant recipients across all the paediatric age, which could be considered as a confirmation that this therapeutic regimen is adequate to reach the established "therapeutic window" for Bu exposure.

There is additional evidence from the preliminary study OMC-BUS 5 in patients receiving allogeneic transplant. In this case, as the two protocols are not identical, they are described separately.

OMC-BUS 5 is a preliminary study in 24 paediatric patients aged from 2 weeks to <18 years intended to receive an allogeneic transplant. An age-based dosing regimen was used to mimic oral Bu: children < 4 years old received an initial dose of 1.0 mg/kg of IV Bu and those > 4 years received an initial dose of 0.8 mg/kg, in combination with cyclophosphamide in a BuCy 4 regimen. Subsequently, IVBu doses were adjusted based on the pharmacokinetic (PK) parameters obtained with the initial dose.

The results are positive and consistent with those obtained in the pivotal study. However this series is very heterogeneous, with a short follow-up. The rate of mixed chimera (19%) as well as the TRM at day +100 (17%) are higher than the pivotal study, although the patients who died had been heavily pre-treated prior to enrolment in this study.

Clinical safety

The use of high-dose oral Bu in the HSCT setting is associated with well-recognized regimen related toxicities involving crucial organs such as lung, CNS (seizures) and liver (liver function abnormalities, VOD). Therefore, the key safety issue with the new IVBu dosing is: 1) whether the new dosing of IVBu influence the safety profile and /or contributes to additional toxicity; 2) whether the use of DMA in this formulation contributes to additional toxicity, particularly in consideration of the reported cardiac, neurologic and hepatic toxicities associated with the human use of DMA (Weiss A.J., 1962).

The results for Busilvex in the paediatric population from studies F00002 IN 101 and OMC-BUS 5 show a similar safety profile to that described with busulfan in children and adults.

The majority of patients presented elevations of liver enzymes during Busilvex treatment, but VOD incidence was comparable to that observed with oral busulfan.
The relationships between IV Bu AUC and the worst NCI/CTC grade achieved during the study period for each of the seven major organs system (i.e. CNS, cardiac, lungs, liver, renal, bladder and GIT including stomatitis) were explored. Given that there were limited severe toxicities (grades 3 and 4) in these major organ systems, no significant correlation could be established. However, for stomatitis a high correlation with AUC was demonstrated for autologous transplant patients. [already answered in the response to questions]

The potential effect of the high amount of DMA in the intravenous formulation of busulfan on neurological, cardiovascular and hepatic safety profiles in children is discussed. In this respect, there does not seem to be an increased toxicity.

Although the review of these data does not raise safety concerns about the use of IV Bu in children; for further reassurance, the safety results in paediatric patients obtained from the studies should be described separately for each paediatric subgroup regarding age or weight.
It should be taken into account that the information provided is limited to 55 and 24 children of ages from 0 to 18 years old. So, post marketing data in paediatric population from those countries where the indication is accepted should also be provided.

Discussion and Benefit- Risk assessment

Busilvex is currently authorised for adult use in the EU. Oral busulfan, administered at high doses is widely used as part of conditioning regimens before HSCT in paediatric population. The pharmacokinetic variability of oral busulfan has been correlated with graft rejection and disease relapse, as well as with the severity of conditioning regimen toxicities, especially veno-occlusive disease of the liver.
The use of Busilvex in children would be particularly interesting because of the toxicity associated with total body irradiation, the difficulties related to oral medications (vomiting, nasogastric tube, treatment compliance) and the favourable outcome of transplantation in this group.

The equivalence of oral and intravenous busulfan was shown in adults and it constituted the main evidence at the time of initial registration of Busilvex, supported by efficacy and safety data.

In the current use of busulfan in paediatric HSCT, the oral formulation is used at the same doses in adults and children older than 4 years. However, in children ≤ 4 years, the use of the same dose would provide a lower plasma concentration; therefore, higher doses are required. This is expectable, taking into account the characteristic differences in elimination rate of drugs across the paediatric age, with clearance often exceeding adult values.

Busilvex in combination with cyclophosphamide or melphalan in a dose schedule that aims to reproduce the use of oral busulfan in the Bu/Cy 4 and BuMel based regimens has been investigated as conditioning therapy prior to HSCT in two phase II uncontrolled, open label studies in paediatric patients (0 to 18 years old) receiving autologous or allogeneic HSCT.

Busilvex at the proposed regimen was adequate to obtain the target plasmatic concentration, which is validated in adult and patient populations. The positive efficacy and safety clinical results supported the performance demonstrated on pharmacokinetics to efficiently target the "therapeutic window" for paediatric patients through the new weight-based dosing regimen. The results were similar to those published with oral busulfan.

The safety profile for Busilvex in the paediatric population was also similar to that described with the oral formulation. It consisted of well-described toxicities commonly encountered in previous studies with busulfan in children and adults.

The potential effect of the high amount of DMA in the intravenous formulation of busulfan on neurological, cardiovascular and hepatic safety profiles in children is discussed. In this respect, there does not seem to be an increased toxicity.

The open label design does not allow making a comparison of the efficacy and safety of Busilvex with either oral busulfan containing regimens or other conditioning strategies. The quality of clinical data that this type of studies can provide is of limited value and comparative data would have been preferred. Nevertheless, it is agreed that Busilvex based regimens should not be essentially different from those based on oral busulfan, and thus, a consistent demonstration of pharmacokinetic comparability can be regarded as pivotal for this application.

The approach of not performing a comparative trial of Busilvex with the oral formulation in children, can be considered acceptable as, although it would have provided useful information, there are previous comparative data on the equivalence of both formulations in adults, a well defined therapeutic concentration range in both populations and the possibility of dose adjustments during the clinical studies. It should also be reminded that the procedure of HSCT, including conditioning treatment, in the paediatric population is similar to that in adults.

In accordance with current recommendations, when a medicinal product is to be used in the paediatric population for the same indication as that studied and approved in adults, the disease process is similar in adult and paediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of paediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of paediatric doses that will produce blood levels similar to those observed in adults.

In the dossier submitted, the number of patients is limited as to allow for a disease-specific analysis. The results observed in the different groups seem to be consistent with the global analysis and similar to those published with oral busulfan.

As the information about the use of Busilvex in non-malignant diseases is very limited, more data has been requested to characterise efficacy and safety and to assess the need for dose adjustments in this patient population.

Although it is agreed that Busulfan is not the usual conditioning regimen in Fanconi anemia, there is recent data on its use in this condition (Maschan AA, et al. Fludarabine, low-dose busulfan and antithymocyte globulin as conditioning for Fanconi anemia patients receiving bone marrow transplantation from HLA-compatible related donors. Bone Marrow Transplant 2004; 34: 305-7). In addition, busulfan is part of many of the reduced-intensity conditioning devised to treat non-malignant

diseases (Satwani P, et al. Reduced-intensity allogeneic stem cell transplantation in adults and children with malignant and non-malignant diseases: end of the beginning and future challenges. Biol Blood Marrow Transplant 2005; 11:403-422).

The safety profile did not show any unexpected or new toxicity not previously reported with Busulfan. A warning in the Summary of Product Characteristics of Busilvex in relation to its eventual use in Fanconi anemia patients was included until more data is acquired.

Due to the lack of data regarding efficacy and safety in these situations, it is highly recommended to gather as much information as possible involving groups as EBMT, if required. The last EBMT 2003 survey reports that out of 7091 allogeneic HSCT, 189 were performed in patients with hemoglobinopathies, meaning 2% of the overall number of allogeneic transplants (BMT 1-16; 2005). The F60001 IN 101 G0 enrolled 7 patients with hemoglobinopathies. Six patients have already been included in the interim report and one additional patient has been further included. This pathology represents 20 % of the studied population. As previously described in the Interim Report, all patients engrafted without any early or late graft rejection. Six out of seven patients are still alive with a median EFS of 28 months (range 18,2-38,2 months).

Based upon the above the MAH commits to supply the following:
1. Long – term follow up of all patients enrolled in the F60001 IN 101 G0 protocol including all the hemoglobinopathy patients;
2. Information on the frequency of the use of Busulfan from the EBMT survey concerning patients with hemoglobinopathies and Fanconi anaemia treated by allo-HSCT;
3. Further information on hemoglobinopathy and Fanconi anaemia patients potentially included in specific trials conducted either by PFM or by Independent Investigators.

In the light of the above discussion, the benefit risk ratio for the indication proposed "Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients" is positive.