SCIENTIFIC DISCUSSION

1. Introduction

Imatinib is a protein-tyrosine kinase inhibitor, which inhibits the Abl tyrosine kinase at the in vitro, cellular and in vivo level. The compound specifically inhibits proliferation of v-ABL and BCR-ABL expressing cells. In addition, imatinib inhibits the activity of the platelet-derived growth factor receptors (PDGFR) α and β, c-kit, the receptor for stem cell factors (SCF), c-Fms, the receptor for macrophage-stimulatin factors (M-CSF), as well as the ABL and Arg PTK. Imitanib also inhibits the cell signalling events mediated by activation of BCR-ABL, c-Kit and the PDGF receptors.

This is an extension of the indications for Glivec, to include:

"Adult patients with myelodysplastic syndrom/myeloproliferative diseases (MDS/MPD) associated with PDGFR gene rearrangements"

The proposed posology would be 400 mg daily, the recommended dose for patients in chronic phase CML and GIST. Dose escalations up to 800 mg/day are foreseen in the indications currently authorised, but are not considered for the proposed new indication.

The COMP granted Glivec the orphan status for MDS/MPD on 10 November 2005. A Commission Decision was issued on 23 December 2005.

3.2. 2. Toxico-pharmacological aspects

A detailed knowledge of imatinib is available, and a plausible and well characterised biological mechanism is available. The growth inhibition potency of Imatinib in cell lines expressing ETV6-PDGFRB is equivalent to those expressing ABL (Carroll M, Ohno-Jones S, Tamura S, et al. CGP 57148 a tyrosine kinase inhibitor, inhibits the growth of cell expressing BCR-ABL, TEL-ABL and TEL-PDGFR fusion proteins. Blood 1997; 90:4947-52). There are also positive data on animal models with the specific molecular abnormality, which fit with the proposed mechanism of the drug action (Tomasson MH, Williams IR, Hasserjian R, et al. TEL/PDGFbR induces hematologic malignacies in mice that respond to a specific tyrosine kinase inhibitor. Blood 1999; 93:1707-14).

3. Clinical aspects

The new WHO classification includes myeloid disorders that have both dysplastic and proliferative features at the time of initial presentation and that are difficult to assign to either the myelodysplastic or myeloproliferative group of diseases. The 3 major disorders that constitute this group are chronic myelomonocytic leukaemia (CMML), atypical chronic myeloid leukaemia (aCML) and juvenile myelomonocytic leukaemia (JMML). Myeloid disease that shows features of both MDS and MPD but does not meet the criteria for any of the 3 major MDS/MPD entities is designated as myelodysplastic/myeloproliferative disease, unclassifiable (MD/MPD-U). The FAB classification system for acute myeloid leukaemias (AML) and the myelodysplastic syndromes (MDS) was replaced by the WHO classification for leukaemias and lymphomas during the main study submitted. A new category, MDS/MPD, emerged. CMML was previously classified as a myelodysplastic syndrome under the FAB scheme; however the WHO classification removed CMML from MDS, placing it in the new category MDS/MPD. JMML is not discussed in this report, as the applicant only claims the indication in adults.

Although they are rare, several translocations have been identified in CMML and aCML patients. t(5;12) (q31;p12) and t(5;10)(q33;q22), which result in fusion proteins that enhance the tyrosine kinase activity of the receptor, PDGFRβ, and may lead to abnormal activation of the RAS pathway, as well as abnormal regulation of other signal transduction pathway. The most common abnormality is the t(5;12)(q31-33;p13), which fuses the ETV6/TEL gene to the PDGFRβ. Other reported cytogenetic abnormalities involve the locus of PDGFRα.

Even though myelodysplastic/myeloproliferative disorder associated with t (5;12) (q31;p12), has been claimed to be a unique entity by some, it has not been recognised as such, and most patients are reported to have CMML. It is usually accompanied by marked eosinophilia. Cases with eosinophilia associated with other rearrangements of the TEL gene have also been reported.

Survival times vary markedly for patients with MDS/MPD, and can range from months to years, depending on the individual disease. The survival of patients with CMML is reported to vary from 1 to more than 100 months, but the median survival time in most series is 12-40 months. Progression to acute leukaemia occurs in approximately 15-30 % of cases. Median survival times reported for aCML are less than 20 months. The prognosis for MDS/MPD U is not known. Several prognostic factors for both aCML and CMML have been identified. The percentage of blood and bone marrow blasts are the most important factors in determining survival. The specific course of haematological diseases associated to PDGFR rearrangements is even harder to predict. In a series of 34 cases associated to PDGFR rearrangements with a myeloproliferative disorder that, according to the authors, could be classified in the category of MP/MDS, only a minority of patients transformed to acute leukaemia with a variable latency.

The incidence of MDS/MPD is not well known either, and it varies regarding the specific subgroup. There are no reliable incidence data for CMML, because in some epidemiologic surveys, CMML is grouped with CML and in others as a MDS. It can range from as many as 3/100,000 individuals over the age of 60 annually for the most common disorder, CMML, to as few as 0.13/100,000 children from 0-14 years of age annually for JMML. aCML is a recently defined entity, and reliable data concerning its incidence are not available. However, in some series, it is reported to be only 1-2 cases for every 100 cases of Ph+, BCR/ABL+ CML. The incidence of MDS/MPD U is unknown. Regarding the incidence of MDS/MPD associated with PDGFR rearrangement, data are even scarcer, probably because cytogenetics or FISH are not always determined. The translocation with t(5;12) (q31;p12) seems to occur in fewer than 1-2 % patients with CMML. Cytogenetics abnormalities, including +8, +13, del (20q), i(17q) and del (12p), are found in up to 80% of patients with aCML, but none is specific. The incidence of PDGFR rearrangements in aCML is unknown, although sporadic cases have been reported in the literature.

The median age at diagnosis of CMML is 65 to 75 years, with a male predominance of 1.5 to 3.1. In the few series reported to date, the median age at diagnosis for aCML is in the seventh or eight decade of life.

Due to the recent creation of the WHO classification, no chemotherapy is yet authorised for the MDS/MPD indication or for MDS/MPD associated with PDGFR rearrangements. Treatments are usually tailored depending on patient's characteristics. Bone marrow transplantation appears to be the only current treatment that alters the natural course of CMML. Various chemotherapy regimens for CMML have been used with only modest success. Hydroxyurea is used in CMML to control hematopoietic proliferation, especially when a rapid decline in leucocytes is required. Median actuarial survival for hydroxiurea (major endpoint) was 20 months in a randomized controlled trial against etoposide (versus 9 months). Response to treatment was seen in 60% of the patients in the hydroxiurea arm. Several clinical trials with 5-azacitidine, etoposide, topotecan, idarubicin, in particular indications such as CMML or aCML have been or are being performed (including an ongoing phase II study with imatinib currently enrolling patients with CMML). In a clinical trial, 25 patients with CMML were treated with topotecan. Complete haematological remissions were induced in 28% of patients. Toxic effects were significant, and the median duration of remission was 8 months. In a follow-up study, where topotecan was used in combination with cytarabine, the combination regimen induced complete remission in 44% of patients with CMML; median duration of complete response was 50 weeks, and patients required monthly maintenance therapy. The optimal treatment for aCML is uncertain because of its rare incidence. Treatment with hydroxyurea may lead to short-lived partial remissions, and it only responds poorly to interferon-α.

3. 1. Clinical pharmacology

A pharmacokinetic study report related to the correlation between clinical response and plasma exposure was provided. Due to the limited sample size per indication the correlation between clinical response and plasma exposure was carried out by using the clinical responses pooled together from patients in different indications and the plasma AUC or trough exposure following the first dose and at steady state. Unfortunately, due to the amount of missing data no clear correlation between clinical response and imatinib plasma exposure was observed in the present study.

3. 2. Clinical efficacy

The extension of indication is mainly based on a subset of the results of study B2225, which included 185 patients with various malignancies possibly associated with imatinib-sensitive kinases, out of which 7 patients were classified as presenting a "Myeloproliferative disorder" and the information collected from 24 patients obtained from the literature (13 published case reports and a clinical study). An ongoing phase II study (AUS19) is currently enrolling patients with CMML.

Study B2225 was an open-label, non-randomized, uncontrolled, single arm study evaluating the efficacy and safety in patients suffering from different life-threatening diseases associated with Abl, Kit or PDGFR PTK and refractory to standard therapeutic options or for which no conventional therapies of definitive benefit existed.

Methods

Patients were eligible to receive imatinib treatment in this study, provided they had a malignant, life-threatening disease (solid or haematological malignancies) and the disease was refractory to standard therapeutic options or no conventional therapies of definitive benefit existed. No specific target groups are further described in the inclusion criteria obtained from the clinical study report or study protocol.

As stated in the clinical study report, this trial was intended to establish proof of concept of activity of imatinib to support hypotheses for future clinical trials. Small cohorts of patients were initially treated and then expanded if clinical benefit was observed. Five to ten patients per indication, condition, or disease were to be initially enrolled. If evaluation of the results of the first five patients suggested a positive effect of imatinib, additional patients with the same disease could be enrolled into the study in order to enable adequate evaluation of imatinib effects.

Patients with myeloproliferative diseases became a target group. The FAB classification system for acute myeloid leukaemias (AML) and the myelodysplastic syndromes (MDS) was replaced during the study for the WHO classification for leukaemias and lymphomas. The category, to which the indication pursued by the MAH belongs (MD/MPD), emerged from this revision.

As stated in the clinical study report, experimental confirmation of imatinib-sensitive target expression was planned to be confirmed before study entry when possible.

Table 1. Patient distribution of study B2225 by malignancy type and diagnosis

Malignancy type	Diagnosis	n (%)
Solid Tumors	Adenoid cystic carcinoma	12 (6.5)
	Aggressive fibromatosis	20 (10.8)
	Chondrosarcoma	7 (3.8)
	Chordoma	4 (2.2)
	Dermatofibrosarcoma protuberans	12 (6.5)
	Leiomyosarcoma	11 (5.9)
	Liposarcoma	11 (5.9)
	Mesothelioma	6 (3.2)
	Synovial sarcoma	16 (8.6)
	Other	41 (22.2)
Hematological malignancies	Hypereosinophilic syndrome	14 (7.6)
	Mastocytosis	5 (2.7)
	Myelofibrosis	8 (4.3)
	Myeloproliferative disorder	**7 (3.8)**
	Other	11 (5.9)

All safety and efficacy evaluations were performed on patients who received at least one dose of study medication.

Due to the exploratory design of the study, the analysis is only descriptive.

The primary objective of the study was the preliminary assessment of imatinib activity. Primary evidence of activity was recorded as the investigator's assessment of a patient's tumour response. The clinical trial did not specifically distinguish between haematological (blood count and bone marrow assessments) and cytogenetic response as primary or secondary efficacy end-point, but haematological response was always used as primary end-point. Specific criteria to determine the efficacy of imatinib on MDS/MPD patients were not prospectively defined. The response to treatment was assessed as normalization of the blood count and of bone marrow appearance – a classical definition -, as well as cytogenetic analysis, but no definition of efficacy assessment parameters is provided.
Still regarding the primary objectives, according to the study report, all evaluations for an individual patient were made according to planned criteria and preferably by the same technique and radiologist.

Secondary objectives included assessing the safety and tolerability of imatinib in these populations, and to evaluate pharmacokinetic profile of imatinib in selected patients. Where feasible, it was planned to assess the functional significance of relevant signal-transduction components. The defined secondary endpoint in study B2225 was the ECOG status.

Results

Demographics and Baseline characteristics

Out of 185 patients, 7 with Myeloproliferative disorders were included.

Demographic details for the population of patients with MDS/MPD are presented in Table 2.

Table 2. Demographics characteristics – Study B2225

Country/Center/Subject	Age (years)	Sex	Race	Karyotype	No. of previous therapies
GBR/201/004*	20	M	Caucasian	t(5:12) (q33:p13)	1
GBR/201/005*	51	M	Caucasian	t(5:12) (q33:p13)	0
GBR/201/073	56	M	Caucasian	NA	0
AUS/901/177	57	F	Caucasian	t(5:12)	1
CHE/801/045	42	F	Caucasian	Normal	2
AUS/901/139	86	F	Caucasian	Normal	1
GBR/201/089	72	F	Caucasian	t(1:3:5)	8

* published as patient 2 (201/004) and patient 4 (201/005) in Apperley, et al 2002

Details of the history of patients with myeloproliferative diseases are limited due to missing data. Information regarding initial stage of the disease at diagnosis is lacking in 6 out of the 7 patients, while there is information lacking in 5 out of the 7 patients regarding time since first recurrence or progression and time since most recent recurrence or progression.

No prior surgical procedure (including biopsy), was performed on patients with myeloproliferative symptoms.

Prior antineoplastic medications are reported in 5 patients (5 patients had received hydroxicarbamide-adjuvant or therapeutic setting-, one patient had received busulfan and one patient had received alpha-interferon). Prior antineoplastic radiotherapy is reported in a single patient.

Dosing and exposure.

Patients with myeloproliferative symptoms received an initial dose of 400 mg daily and treatment was continued for as long as, in the opinion of the investigator, the patient derived benefit from therapy and in the absence of any safety concern. The mean dose in the myeloproliferative disorder group was 433.1 ± 275.36 (median 395.7, ranging 50.8-880.5). One patient started treatment at 800 mg daily and required a dose reduction to 200 mg. The dose was escalated to 1000 mg from 400 mg in 200 mg increases in one patient and to 800 mg in another patient. The recommended starting dose was changed in amendment 01 from 400 mg to 800 mg/daily, with no specific mention to malignancy.

The duration of exposure was under 5 months in 2 patients; between 5-15 months in 2 patients; between 20-25 months is 2 patients and over 25 months in one patient.

Regarding the whole population of the study, dosing errors affected 37 patients (20%), including one patient belonging to the myeloproliferative disease group.

Efficacy results

Activity was assessed by evaluating changes in blood counts (haematological response).The best overall responses for patients with MDS/MPD and best haematological response and duration of response are summarised in tables 3 and 4.

As it has been already mentioned, complete response was not prospectively defined.

Table 3. Best overall response

Best response	N	%
Complete response (CR)	3	42.9
Partial response (PR)	1	14.3
Progressive disease (PD)	1	14.3
Unknown	2	28.6

Best response	N	%

Table 4. Best haematological response and duration of response – Study B2225, MD/MPD patients

Country/Center/ Subject	Karyotype	Best response	Response duration (days)
GBR/201/004*	t(5:12) (q33:p13)	CR	379
GBR/201/005*	t(5:12) (q33:p13)	CR	457
GBR/201/073	NA	CR	421
AUS/901/177	t(5:12)	PR	141
CHE/801/045	Normal	PD	-
AUS/901/139	Normal	UNK	-
GBR/201/089	t(1:3:5)	UNK	-

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disase; UNK=unknown
* patients 201/004 and 201/005 also achieved a complete cytogenetic response according to Apperley, et al (2002)

In the group of seven patients with MDS/MPD, response was not assessable in 2 patients. The peripheral blood count of patient 201/089 never normalized throughout the treatment and the patient was finally withdrawn from the study because of pancytopenia. Patient 901/139 was withdrawn because of unsatisfactory therapeutic effect. Of the other patients, one experienced PD, one patient had PR and the remaining 3 patients achieved a CR, for an overall response rate of 57% (95% C.I. 18 – 90).

Three patients had PDGFR rearrangements, all of which had a haematological response (2CR and 1 PR).

The median duration of therapy was 12.9 months with a range of 24 days to 812 days. All responding patients were still on treatment and in response at the last visit.

In the MDS/MPD population of patients, the ECOG performance status did not change substantially, with two patients having worsened ECOG at the end of the study and two patients improving their ECOG at the end of study from 1 and 3 respectively to ECOG 0.
Cytogenetic response was not evaluated in study B2225.

Clinical studies in special populations

The new indication application only includes the treatment of adults. No children were included in study B2225.

The case of a two 2-year old girl with a MD/MPD with t(1:5)(q23:q33) refractory to etoposide, cytarabine and interferon is reported. Complete haematological and cytogenetic response are reported.

The case of another 2-year old girl with aCML is reported. A translocation t(5:12)(q33:p13) was reported. Only partial responses had been obtained by other treatments (hydroxiurea). Complete haematological response is reported and bone marrow transplant was performed. The girl died of transplant-related complications.

OTHER SOURCES OF EFFICACY DATA

In addition to the clinical study described, the MAH has submitted 13 published case reports and a clinical study including a total of 24 patients (6 classified as MDS/MPD, 4 classified as CMML and 11 classified as aCML).

The published case reports, as well as the clinical study, did not specifically distinguish between haematological and cytogenetic response as primary or secondary efficacy end-point, but haematological response was always used as primary end-point.

The response to treatment was not only assessed as normalization of the blood count and of bone marrow appearance, but also as cytogenetic analysis, FISH analysis for detection of PDGFR rearrangement and PCR analysis for its characterization.
(The case reports and clinical studies are summarised in table 5.)

Table 5. Summarised results for case reports and clinical studies.

N° of patients	Sex	Age (years)	Karyotype	Fusion partners	Daily Dose (mg)	Hematological response	Cytogenetic response
MDS/MPD							
Apperley, et al (2002)							
2	M	36	t(5:12)(q33:p13)	ETV6-PDGFRβ	400	Complete	Complete
	M	69	t(5:12)(q33:p13)	ETV6-PDGFRβ	400	Complete	Complete
Wilkinson, et al (2003)							
1	F	2	t(1:5)(q23:q33)	PDE4DIP-PDGFRβ	NA	Complete	Major
Vizmanos, et al (2004)							
1	M	35	t(5:14)(q33:24)	NIN-PDGFRβ	200–400	Complete	Complete
Pardanani, et al (2003a)							
2	M	45	Normal	NA	100	Complete	Major
	M	58	Trisomy 8	NA	400	None	None
Grand, et al (2004)							
1	M	79	t(5:15)(q33:q22)	TP53BP1-PDGFRβ	300–400	Partial	NA
Levine, et al (2005)							
1	M	42	t(5:14)(q33:q32)	KIAA1509-PDGFRβ	400	Complete	Complete
CMML							
Magnusson, et al (2002)							
1	M	29	t(5:17)(q33:p13.3)	RAB5EP-PDGFRβ	400	NA	NA
Pitini, et al (2003a)							
1	M	68	t(5:12)(q33:p13)	NA	400	Complete	Complete
Cortes, et al (2003)							
3	NA	65*	Diploid (2 cases) Trisomy 21 (1 case)	None	400	None	None
aCML							
Wittman, et al (2004)							
1	F	2	t(5:12)(q33:p13)	ETV6-PDGFRβ	200	Complete	Complete
Garcia, et al (2003)							
1	M	44	t(5:10)(q33:q22)	H4-PDGFRβ	400	Complete	Complete
Cortes, et al (2003)							
7	NA	67*	No t5q33	None	400	None	None
Trempat, et al (2003)							
1	M	47	t(4:22)(q12:q11)	BCR-PDGFRα	400	Complete	Partial
Safley, et al (2004)							
1	M	57	t(4:22)(q12:q11)	BCR-PDGFRα	100	Complete	NA

* Median age for the group of patients; NA = Not Available.

Apperley et al. (2002) provide information about four patients; two of these patients (number 2 and 4 of the publication) are presented in study B2225.

The specific diagnosis of the patients included under the category MDS/MPD by the applicant are chronic myelodysplastic syndromes or chronic myeloproliferative disease, which are not specified in accordance with the current WHO classification.

The durability of response is not fully characterized in all case reports, and it is not described in others. It seems to range between 18 months (Levine et. Al.) and 5 months (Grand et al.). The available data do not seem different among different case reports.

Complete haematological response was achieved by 11 out of 24 patients. Eleven patients presented PDGFR rearrangements, 9 of them achieved a complete haematological response, 1 achieved a partial haematological response and results are unavailable by one of them.

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

The results obtained from the pooled population including the patients from study B2225 and from the published evidence, are a complete haematological response rate of 45% (95% CI 27-64), 14 out of 31 patients; (52% including partial responses) and a complete cytogenetic response of 29% (39% including major and partial responses). Of note, two out of these 14 patients were children, however, a paediatric indication has not been applied for.

If the evaluation is limited to patients with known PDGFR gene re-arrangement or with a translocation known to be linked to a PDGFR gene re-arrangement, the benefit is higher: all 13 patients (100%) with known PDGFR gene re-arrangement achieved a haematological response either complete (11 patients) or partial (2 patients) and 11 out of the 11 patients (100%) who had a cytogenetic evaluation show a response, complete in 9, major in one and partial in another patient, a rarely if ever observed response rate. Again, two of these patients need to be excluded from the analysis (the two children).

Cytogenetic response was not evaluated in the company's study, but a complete cytogenetic response is reported in the two cases published by Apperley et al (2002). Considering the 31 patients treated, 12 (39%) achieved a cytogenetic response (two of them were children), which was complete in nine patients (29%).

To address the risk of a publication bias, a Meta-analysis Report of published papers and Study B2225 efficacy data was performed, as recommended by the EMEA at the pre-submission meeting on scientific advice (2004). Different descriptive analyses as well as statistical models were provided with data for study B2225 and pooled data for published results up to October 2005 on rare malignant diseases treated with imatinib. Results from trial B2225 were not pooled with the published data. The pooled assessments (obtained via the adoption of Bayesian meta-analysis models) were presented side by side with the data collected from the trial. The results from trial B2225 in Myeloproliferative disease group, although slightly lower, could be considered consistent with the published results. However, according to the funnel plot provided, the possible effect of a publication bias can not be discharged. The upper limit of the 95 % CI for overall efficacy rate of the study B2225 (best scenario for the sponsor's trial) is below the point estimate of the overall globally pooled estimate for the published data, indicating that any conclusion with regard to the similitude of the results could not be supported from the results of the report.

Supplementary published data

Further prospective clinical data from published studies were provided to confirm the preliminary results from the phase II, exploratory study B2225.

The following new data has been supplied in this response document:

- A manuscript recently published in Blood (David et al. Blood. 2006 Sep 7; [Epub ahead of print]), which provides information from 7 new patients with Philadelphia negative CMPDs and reciprocal translocations involving PDGFR. Additionally, updates on 5 of their patients and on 8 other patients treated at different institutions, all of which had been included in the original submission, are included in this manuscript.

David's patients had been treated with imatinib for a median of 47 months (range 0.1-60 months). Eleven out of these 12 patients presented a normalization of blood count and ten had a cytogenetic response with a decrease or disappearance of fusion transcripts as measured by RT-PCR. According to the authors, haematological responses have been sustained for a median of 49 months (range 19-60) and cytogenetical responses are reported to last for a median of 47 months (range 16-59). The median OS from diagnosis was 65 months (range 25-234).
Seven out of the 8 patients treated at other institutions, were reported to achieve haematological remissions or complete responses, which last in 6 of them (follow-up ranging from 6 to 38 months). One of these patients died after bone marrow transplant after achieving a complete cytogenetic response and another failed to respond to imatinib but achieved a durable complete haematological response while on hydroxiurea.

- Results from 4 patients with CMML with PDGFR rearrangements from ongoing study CSTI571AUS19 have also been reported. Of these four patients, two of them responded to imatinib, one responded for only two months and had his CMML progress to acute leukaemia and the fourth patient never responded.

Due to the rarity of the disease, the MAH proposes to set up a global registry in order to monitor the efficacy, long term impact and safety of imatinib in this subset of patients. Responses would be characterised by peripheral blood count normalisation, bone marrow evaluation, cytogenetic abnormalities and RNA transcripts by RT-PCR.
The MAH commits to submit longer term follow-up data on all patients to the CHMP, as it becomes available.

Clinical safety

The application for this new indication is based on study B2225, which included 185 patients with various malignancies possibly associated with imatinib-sensitive kinases (45 of them suffered an haematological malignancy, out of which 7 patients were classified as presenting a "Myeloproliferative disorder",). Additional evidence, a clinical study and 13 published case reports (24 patients more), have been presented for this indication.

Due to the few patients with myeloproliferative disease and the well established safety profile of a drug approved since 2001 in myeloid hematological malignancies and solid tumours; the safety of the whole population enrolled will be considered, as well as the safety of the 7 patients with myeloproliferative disease enrolled. Regardless of the possibility of bias in the case reports, the available information was taken into account.

Safety was assessed by collecting reports of deaths, SAEs and AEs, laboratory data (standard hematology, biochemistry and urinalysis) and data on vital signs, weight, ECG and physical examinations. Safety variables consisted of AEs related or not to study drugs and of laboratory parameters, classified according to NCI common toxicity criteria.

Patient exposure

A total of 185 patients suffering from different diseases associated with ABL, Kit or PDGFR PTK were treated with imatinib in study B2225 at doses between 200 and 1000 mg daily. Twenty-five patients were treated for more than 1 year and seven patients for more than 2 years. Patient exposure is summarised in the following table.

Table 6. Patient exposure, study B2225.

Absolute Dose Intensity (mg/day) [1]	**All N = 185**	**Solid tumor group N = 140**	**Hematology group N = 45**	**MDS/MPD patients N = 7**
Mean ±SD	608.1 ±215.46	651.4 ±191.0	473.3 ±233.06	433.1 ±275.36
Median	683.3	739.1	400	395.7
Min – Max	19.6 – 915.2	85.7 – 915.2	19.6 – 880.5	50.8 – 880.5
Duration of Exposure	**All N = 185**	**Tumor group N = 140**	**Hematology group N = 45**	**MDS/MPD N = 7**
Mean ±SD	6 ±7.65	5.1 ±6.86	9 ±9.17	13.7 ±11.45
Median	2.7	2.6	5.1	12.9
Min – Max	0 – 42.7	0 – 42.7	0.3 – 26.7	0.8 – 26.7

[1] Total dose over the course of the trial/total number of days in trial

Demographic characteristics regarding exposure:

Sex ratio: 56.8% male, 43.2% female; Race: Caucasian 94.6 %, Other: 5.4 %; Age: <65: 82.2 %, ≥65: 17.8 % (range: 15-86).

Withdrawals and dose reductions

Out of 7 patients with MDS/MPD, treatment was completed in three patients, was discontinued in three patients and was still ongoing at cut-off date in one of them. The reasons for discontinuing

treatment were unsatisfactory response in one patient and drug-related AEs in two of them. One of these patients presented a grade 1 pancytopenia. This patient also developed a grade 3 neutropenia. The other patient developed a grade 4 arthralgia and grade 2 cramps suspected to be related to the study drug.

Considering all patients from study B2225, out of the 40 patients (21.6%) who discontinued the drug due to AEs, 21 (11.4%) did so because of drug-related events, of CTC grade 3 or 4 in severity in 11 cases (6%).

The most frequent AEs leading to dose adjustment were gastrointestinal AEs, both in the solid tumor and hematological malignancies (nausea in 21.4% and 15.6% of cases, vomiting in 17.1% and 8.9%, diarrhea in 7.1% and 4.4%, respectively). Rash also induced dose reductions in 7.9% of the patients with solid tumors while neutropenia (8.9%) and anemia (6.7%) were the other two leading causes of dose adjustment in patients with hematological malignancies.

Adverse events

Pooling of data was not performed with results of other studies. All patients exposed to more than 1 dose of study treatment were pooled to examine the incidence rate of deaths and SAEs, the affected body systems, type of underlying event and suspected drug relatedness.

All patients, both in the haematology and in the solid tumour group, experienced at least one AE.

All patients in the haematology group and 91.5 % (128 patients) in the solid tumour group experienced an "AE suspected to be drug related".

Table 7. AE classified according to NCI common toxicity criteria.

Primary system organ class	**Maximum Grade**	**Solid tumour group N = 140, n (%)**	**Hematology group N = 45 , n (%)**
Any primary system organ class	1	42 (30.0)	10 (22.2)
	2	41 (29.3)	19 (42.2)
	3	40 (28.6)	14 (31.1)
	4	5 (3.6)	2 (4.4)

Cardiovascular system

In the overall population of 185, four patients experienced drug-related vascular events (2.2%), all CTC grade 1 in severity. Cardiac disorders were considered SAEs in four cases (2.2%). No cardiovascular disorder was reported in patients with myeloproliferative disease.

Renal and urogenital system

A total of three patients (1.6%) experienced AEs that were considered drug-related, and in two cases (1.0%) were of CTC grade 3 or 4 severity. In one case treatment was withdrawn because of drug-related grade 3 creatinine increase.

One MDS/MPD patient presented a grade 2 renal tubular disorder, which was considered unrelated to the study drug but was classified as an SAE.

Hepatic system

Three patients (1.6%) were withdrawn from treatment because of elevated liver enzymes, considered drug-related in two cases. No SAE affecting the hepatobiliary system was reported. No hepatic system disorders were observed in patients belonging to the myeloproliferative group.

Blood and lymphatic system

The frequency of AEs was higher in the haematological malignancies group than in the solid tumour group. A total of 35 AEs were considered drug-related, most of them grade 1 or 2. The most frequent grade 3 haematological AE was lymphocytopenia (11.9%) and the most frequent grade 4 haematological AE was neutropenia (2.7%). Neutropenia (grade 3 or 4) was more common in

haematological malignancies (8.8% vs. 3.5% in solid tumours), while grade 3 lymphopenia was more evenly distributed (15.6% vs. 10.7% in solid tumours).

Haematological AEs led to drug discontinuation in four cases, in one case for grade 3 drug-related granulocytopenia, in one case for grade 3 drug-related anaemias and in one patient for grade 1 drug-related pancytopenia. Blood and lymphatic disorders were considered SAEs in 11 patients.

Four MDS/MPD patients presented six haematological AEs; of those, two were SAEs: one patient presented a grade 2 anaemia and another patient presented a grade 3 febrile neutropenia, although both were considered unrelated to the study drug.

Gastrointestinal system

A total 136 patients (73.5%) experienced gastrointestinal system disorders of any cause, the most frequently observed being nausea, diarrhoea and vomiting. Of those, 13 patients (7.0%) experienced grade 3 AEs and one patient grade 4 severity. A total of 27 patients experienced SAEs involving this system organ class.

Six patients with myeloproliferative disease presented gastrointestinal AE. All of them were grade 1 or 2 and none led to drug discontinuation.

Nervous system

A total of 37 patients (20.0%) experienced AEs that were considered drug-related; all grade 1 or 2 in severity.
Serious adverse events and deaths

There were 23 deaths (12.4%) reported in the overall population enrolled in study B2225 during treatment or up to 28 days after the last dose of study medication. None of these deaths were considered to be related to study drug.

No patient with MDS/MPD died on study. A patient died of pseudomona aeruginosa infection approximately 3 months later.

A total of 79 patients (42.7%) experienced at least one SAE, the most frequent being gastrointestinal (27 patients – 14.6%) or respiratory (26 patients – 14.1%).

No treatment related SAEs were reported in the seven MDS/MPD patients enrolled in Study B2225. Four patients experienced non related, non fatal SAEs. Patient 201/004 had a pseudomonas wound infection, patient 201/089 had fever, skin rash, fungal infection and renal tubular damage, patient 801/45 had a gluteal abscess and febrile neutropenia and patient 901/139 had a left pre-tibial laceration and anemia, as seen in Study B2225.

As expected from a short-term follow up, no second malignancies were reported.

Laboratory findings

Clinical chemistry

Most of the chemistry abnormalities were CTC grade 3 with four instances of CTC grade 4 events in the overall population: two cases for creatinine (1%), one for alkaline phosphatase (0.5%) and one for AST (0.5%). There was no difference between the two main populations of patients in frequency of events regardless of CTC grade, with the exception of creatinine increase, which was more severe in patients with solid tumors (two CTC grade 4 instances) than in patients with hematological malignancies (two CTC grade 3 instances).

In MD/MPD patients, there was only one instance of CTC grade 3 ALT increase.

Five patients (2.7%) were withdrawn from study because of laboratory abnormalities or because of events related to laboratory abnormalities. One patient was prematurely withdrawn from treatment following grade 3 elevation of creatinine which was suspected to be drug induced; another patient presented anemia and recurrence of hypoalbuminemia, which the investigator suspected to be drug related; and three patients were prematurely withdrawn because of elevated liver function tests, in two of these cases it was considered to be drug related.

Safety in special populations

Women of child-bearing potential were advised to avoid becoming pregnant and to use effective contraception during treatment (study B2225). No cases of pregnancies were reported, nor were there cases of partners of male patients becoming pregnant.

Among the published case reports submitted as evidence for the indication of MDS/MPD, two case reports describe the use of imatinib in two 2-year old girls. In both case reports, information is focused on efficacy and further patient safety data are not provided.

Other sources of data

The applicant provided a summary of Periodic Safety Update Reports (PSUR). On the basis of the CHMP assessment on the PSUR 6, received in September 2005, the following signals should continue to be monitored: myocardial infarction, angina pectoris, peripheral ischemia, Raynaud's phenomenon, pulmonary hypertension, inflammatory bowel disease, worsening of ulcerative colitis and Chron's disease, deafness, hypoacusia, thrombocythemia, hemolytic anemia, disseminated intravascular coagulation, Parkinson's disease, suicide attempt, nephrolithiasis/renal colic, scleroderma, glucose metabolism disorders, and arthritis. In addition, a culmulative review of the cases of cardiomegaly/cardiomyopathy, hepatic necrosis/cirrhosis, rhabdomyolysis/myopathy/ myositis, nephritic syndrome, hydronephrosis, proteinuria, cataracts, blindness and allergic reactions should be included in the next PSUR.
Results from a preclinical rat carcinogenicity study have been included in a preclinical safety update of the SPC. The analysis of clinical safety data from clinical trials and spontaneous adverse event reports have not provided evidence for an increased overall incidence of malignancies or in the incidence of bladder, kidney or prostate tumors in patients treated with imatinib compared to that of the general population.
Out of the 14 cases of MDS/MPD reported in the literature, three patients (21%) experienced AEs, with one patient described by Vizmanos et al (2004) not tolerating the 400 mg/day dose (AE not specified), one patient described by Pardanani et al (2003a) as experiencing profound fatigue and weight loss when treated with 400 mg/day imatinib and one patient described by Grand et al (2004) developing CTC grade 4 neutropenia after 36 days of treatment while receiving 400 mg/day imatinib. This event evolved in four episodes of transient cytopenia despite dose reduction to 300 mg/day. Imatinib might have played a role in the neutropenia and transient cytopenia in the later case. No further safety observations were reported in the other published cases. An overview of the safety of imatinib in 48 patients with a variety of hematological malignancies expressing either Kit or PDGFR including ten patients with MDS/MPD is given in Cortes et al (2003). The authors report that the most common side effect was fatigue (n = 30, 63%), CTC grade 3 in one case (2%). Other toxicities (≥ CTC grade 3) included bone pain, fluid retention (two cases each, 4%), nausea and dyspepsia in 1 case each (2%). The overall rate of adverse event is not provided.
Three cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib therapy in patients with hypereosinophilic syndrome (HES) and cardiac involvement (Pardanani et al, 2003a, Pitini et al 2003b). This is particularly important since MDS/MPD associated with PDGFR rearrangements frequently associates with eosinophilia. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily holding of imatinib. No cases as such were reported in study B2225 MDS/MPD patients.

Overall discussion and Benefit-risk assessment

The proposed indication affects a malignant disease with limited therapeutic options. Bone marrow transplant is the only treatment that can change the natural course of the disease. Median survival times in most series are 20-40 months. In this context, imatinib might be useful in patients that cannot benefit from a bone marrow transplant in the short term (e.g. induce remissions that could allow for a subsequent transplant with an acceptable safety profile).

The initial dossier presented for the indication of imatinib in this population was only supported by study B2225, a phase II, exploratory, open label study (which included 4 patients with a myeloproliferative disease and a PDGFR rearrangement). The applicant provided 11 publications,

including data from 12 patients as supportive evidence. The CHMP was particularly concerned by the extremely low quality of data from study B2225, the possibility of publication bias, the lack of long-term follow up and the absence of control data in a disease with an extremely variable prognosis (survival has been reported to range from 1 to more than a 150 months, although median survival times are 20-40 months).
The clinical trial and the rest of the evidence presented are interesting, and the results obtained are quite promising. As expected from such a small sample size, there is a marked heterogeneity among patients (i.e. age 20-86). The overall response rate is very good, 57%, but, as expected from such a sample size, the CI are too wide (95% C.I. 18 – 90). Even though the primary specifications and definitions were vague in the clinical trial, there is certain uniformity across the studies and case reports. The same subrogate primary endpoint is used in the publications and in the clinical trial B2225, and there is a secondary endpoint (cytogenetic response), which is present in some publications. In them, the patients are as heterogeneous as those of the clinical trial and for the most part, they were refractory to first line treatments. The results obtained are also very positive, particularly regarding cytogenetic response, seem in line with the clinical trial findings and are consistent with the biological rationale of imatinib. Nevertheless, whether these results are accompanied by survival benefit will need to be proved and the durability of the response remains also to be determined.
Usual concerns intrinsic to this kind of evidence are present. A metanalysis performed by the applicant could not exclude the possibility of publication bias.
The initial data provided did not allow to firmly establishing the effect of imatinib in the treatment of MDS/MPD associated with PDGFR rearrangements in terms of meaningful variables for the patient. In addition, due to the new WHO classification to which this indication applies, the comparison with historical controls might be misleading.

The MAH acknowledged the exploratory nature of study B2225 and supplemented the dossier with a publication which includes data from 8 new patients and longer follow ups from patients already included in the original submission. Response rates in these patients are compelling and similar to those, which had been previously reported. Results from 4 patients with CMML with PDGFR rearrangements from ongoing study CSTI571AUS19 are also provided in this document.

The MAH proposed to set up a global registry in order to monitor the efficacy, long term impact and safety of imatinib in this subset of patients and compromises to submit longer term follow-up data on all patients, as they become available. Responses would be characterised by peripheral blood count normalisation, bone marrow evaluation, cytogenetic abnormalities and RNA transcripts by RT-PCR.

It is acknowledged that a registry might be the only way for data collection in a prospectively planned and standardised manner. Imatinib's well-known safety profile, the strong biological basis, the observed high response rates, the apparent durability of the response, the limited therapeutic options and the sometimes aggressive course of the disease are recognised and may outweigh the uncertainty about the true effect size.

No new AE were identified that had not been previously described and imatinib can generally be considered well tolerated. However, cardiogenic shock and left ventricular dysfunction is a potential adverse event in patients with MDS/MPD associated with PDGFR rearrangements, which is frequently accompanied by eosinophilia. These events in patients with MDS/MPD associated with PDGFR and eosinophilia will be specifically monitored.

Even though MDS/MPD is a heterogeneous group of diseases with differential characteristics and diverse prognosis, PDGFR is an interesting potential target for those patients with MDS/MPD associated with PDGR rearrangements. This possibility is especially appealing due to the limited number of treatments (especially when bone marrow transplant is not an option), the observed high response rates, the apparent durability of response, the sometimes aggressive course of the disease and Glivec's well-known and well-tolerated safety profile.

Although no robust data are available for MDS/MPD associated with PDGFR rearrangements, it seems clear that it is an extremely infrequent disease in which a traditional approach of randomised controlled trials is not feasible.
In the context of a widely available medication, a registry, as proposed by the applicant, might be the only way to obtain data collection in a prospectively and standardised manner.

Despite the limited data available, imatinib in the treatment of MDS/MPS with PDGFR rearrangements provides an acceptable benefit-risk profile. The MAH commits to provide additional clinical data as follow measures.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Area[1]	**Description**	**Due date**[2]
Clinical	Follow-up data from patients in study B2225	Dec. 2007 and Yearly thereafter
Clinical	Results and follow-up data from patients in study CSTI571AUS19	Dec. 2007 and Yearly thereafter.
Clinical	Results from MDS/MPD patients treated in a global registry as proposed by the applicant in order to monitor the efficacy, safety and long term impact of imatinib in this subset of patients	Dec. 2007 and Yearly thereafter