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-stimulating factors (M-CSF), as well as the ABL and Arg PTK. Imatinib also inhibits the cell signalling events mediated by activation of BCR-ABL, c-Kit and the PDGF receptors.

The MAH submitted a type II variation for Glivec, proposing to include "Treatment of adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL)"

Folowing the assessment the indication has been specified for HES/CEL patients with demonstrated FIP1L1-PDGFRα fusion kinase. A starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

The COMP granted Glivec the orphan status for HES on 19 August 2005. A Commission Decision was issued on 28 October 2005.

Clinical aspects

Chronic myeloproliferative diseases (CMPD) can be classified as either being Bcr-Abl positive or negative. Classic Chronic Myelogenous Leukemia (CML) is defined by the presence of the Bcr-Abl fusion kinase RNA transcripts in the blood and bone marrow. Bcr-Abl negative CMPD can be further classified into "classic" forms of CMPD, which include polycythemia vera, essential thrombocythemia, and myelofibrosis with myeloid metaplasia. Other disorders that are Bcr-Abl negative share certain phenotypic characteristics of the "classic" forms of CMPD, but are considered "atypical" as they have other unique features. Clinicopathologically these disorders include mastocytosis, varying forms of eosinophilic disorders (including HES, CEL), chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia, chronic neutrophilic leukemia, and an unclassified category of mixed or hybrid CMPD (Pardanani & Tefferi 2004).

Idiopathic hypereosinophilic disorder is a rare hematological disorder characterized by chronic overproduction of eosinophils, tissue infiltration and organ damage. Diagnostic criteria include sustained eosinophilia (>1500 eosinophils/mm^3) for more than six months, exclusion of reactive causes of hypereosinophilia, such as parasitic infections or allergic reactions, and evidence of end organ involvement. Following original classification, other classification schemes developed that required HES remain a disorder of exclusion of all other causes, including eosinophilia of clonal origin, such as the atypical chronic myeloproliferative disorders mentioned in the first paragraph of this section. In this instance, the clonal disorders would be classified as chronic eosinophilic leukemia (CEL). In the most current WHO classification, a diagnosis of HES or CEL requires exclusion of reactive causes, of malignancies in which eosinophilia is reactive or part of the neoplastic clone, and of T-cell disorders with immunophenotype and cytokine production abnormalities, with or without evidence of lymphocyte clonality, as reported by Bain, et al (2001) . The authors further commented on the separation of HES and CEL, following the report by Cools, et al (2003) demonstrating that many patients with HES had a clonal molecular abnormality, the FIP1L1-PDGFRα fusion gene (Bain 2004b) .

Criteria for the diagnosis of chronic eosinophilic leukemia

Criteria
Eosinophil count at least 1500/mm^3
Peripheral blood and bone marrow blast cells <20%
Criteria for atypical CML, CMML and Ph+ CML not met
Myeloid cells demonstrated to be clonal, e.g. by detection of a clonal cytogenetic or molecular genetic abnormality or by demonstration of very skewed expression of X chromosome genes

If no such evidence was found, Bain (2004a) still felt a diagnosis of CEL could be based on clinical features (i.e. elevated blasts, etc.). Although the WHO classification of eosinophilic disorders recommends a diagnosis of CEL when clonality is proven and maintains that the idiopathic hypereosinophilic syndrome (IHES) remains a diagnosis of exclusion, several authors have pointed out the problems of sorting these patients in clinical practice (Vandenberghe, et al 2004, Martinelli, et al 2006) . Elevated blasts in blood and marrow are often not present in patients with CEL defined by detecting a cytogenetic abnormality, other surrogate clinical/laboratory markers for CEL are often also present in IHES, and organ infiltration/damage can occur in both disorders. For this reason, the sponsor will broadly define HES as including both CEL and IHES in his description of the role of imatinib in the treatment of these disorders in the dossier.

Eosinophils derive in the bone marrow from CD34+ myeloid progenitor stem cells and differentiate in response to a number of T-cell derived eosinophilic cytokines and growth factors including IL-3, GM-CSF and IL-5 (Ackerman & Butterfield 2005) . Eosinophils participate broadly in a variety of functional roles, including host defense, allergic responses, and inflammatory reactions (including tissue injury and fibrosis). Clinically, these multiple functions lead to the protean manifestations of eosinophilic disorders. The clinical manifestations of organ infiltration and subsequent dysfunction often dominate the clinical picture. Patients with HES have a predilection for organ infiltration of the heart, the central and peripheral nervous system, the lungs and the skin.

The illness most often develops in patients 20 to 50 years of age and has a strong male to female predilection (9:1 ratio) (Fauci, et al 1982) . End organ manifestations are multiple.

End organ damage produced by hypereosinophilia

System Organ Class	Damage
Cardiac disorders	Constrictive pericarditis, endomyocardial fibrosis, myocarditis, intramural thrombi, valve regurgitation, cardiomyopathy
Nervous system disorders	CNS thromboemboli, peripheral neuropathy, CNS dysfunction, epilepsy, dementia, eosinophilic meningitis
Skin and subcutaneous tissue disorders	Angioedema, urticaria, papulonodular lesions, mucosal ulcers, vesicobullous lesions, microthrombi
Respiratory, thoracic and mediastinal disorders	Pulmonary infiltrates, lung fibrosis, pleural effusions, pulmonary emboli
Eye disorders	Microthrombi, vasculitis, retinal arteritis
Musculoskeletal and connective tissue disorders and/or vascular disorders	Arthralgia, joint effusions, polyarthritis syndromes, Raynaud's phenomenon, digital necrosis
Gastrointestinal disorders	Ascites, diarrhea, gastritis, colitis, pancreatitis, cholangitis, Budd-Chiari syndrome

In addition to the system specific abnormalities, patients may also have unexplained constitutional symptoms of anorexia, weight loss, fever, excessive sweating and psychiatric disturbances

The most commonly encountered clinical events, and often the most serious, are the cardiovascular complications that occur in 50-75% of all patients. These are often life threatening and life limiting in patients with HES. In the early phases of cardiac involvement, eosinophilic infiltration can cause inflammatory disorders of the heart and intramural thrombi to form on the endocardial surfaces. In time, inflammation leads to fibrosis leading to valvular disorders and constrictive pericarditis. Once fibrosis occurs, the cardiac conditions are irreversible by medical therapy alone and often require cardiac surgical procedures for control.

Treatment for HES, once appropriate diagnostic and extent of disease evaluations have been performed, employ algorithms for treatment based on the presence or absence of the FIP1L1-PDGFRα

fusion gene (see discussion below "The role of genetics in HES"). If the patient does not have the FIP1L1-PDGFRα fusion gene, no extreme eosinophilia in the peripheral blood, and no evidence of organ dysfunction, following the patient quarterly with re-evaluations is the currently accepted approach.

If the disease is more extreme, then systemic corticosteroid therapies are generally administered using various regimens. If control is not achieved, other agents are added or used, including hydroxyurea, interferon-α, vincristine and alkylating agents. Pheresis, anticoagulation, cardiac surgery, splenectomy, stem cell transplantation, and investigational agents are included under specialized circumstances (Ackerman & Butterfield, 2005) .

Hypereosinophilic syndrome remains a serious disease in many patients with continued unmet medical needs for therapy, especially if the patient's condition is not easily improved with systemic corticosteroids or if the patient develops serious signs of organ dysfunction. Traditional cytotoxic chemotherapies are difficult to take and not very effective. Plasmapheresis and major surgical procedures are not easy for the patient to tolerate and do not treat the underlying cause of the disorder. Thus, newer approaches to the treatment of HES in patients with aggressive forms of the disease need to be developed. Early reports, prior to recognition and treatment techniques for the cardiovascular complications, gave a dismal prognosis for patients with HES. Improvements in therapies and patient support generally led to survival rates in the late 1980s reported as 80% at 5 years and 40% at 10 and 15 years (Ackerman & Butterfield 2005) .

The role of genetics in HES

The clonal nature of some patients with HES was first described utilizing X-inactivation assays in the 1990s, however it was the description of a fusion gene on chromosome 4 (FIP1L1-PDGFRα) that first described a clonal genetic abnormality related to the HES phenotype and a rationale for its treatment with imatinib (Cools, et al 2003) . FIP1L1-PDGFRα is a unique fusion gene caused by the fusion of the FIP1L1 gene to the PDGFRα gene. The fusion results from an interstitial deletion of approximately 800-kb on chromosome 4q12 that includes the cysteine-rich hydrophobic domain 2 (CHIC2) locus. This small deletion is not readily seen in routine karyotyping, hence it has been described as a "silent deletion". The resulting fusion kinase, FIP1L1-PDGFRα, is constitutively active and drives the phenotype of HES in patients who have it. It is also a target for imatinib.

Other clonal and molecular genetic abnormalities have been identified in patients with HES. These may or may not be associated with easily identified karyotypic abnormalities, but have added further weight to arguments and classification schemes driving attempts to separate CEL from IHES. There have been multiple molecular genetic abnormalities detected in patients with eosinophilic disorders and recent reviews are available that describe them (Bain 2004a, Gotlib, et al 2004) . Some of these reports describe clonal abnormalities of PDGFRβ, another known target for imatinib (Apperley, et al 2002) . Other as yet undescribed cytogenetic abnormalities and fusion kinases sensitive to imatinib may be found in patients with HES and myeloproliferative disorders associated with eosinophilia (Cools, et al 2003) .

A proportion of patients with HES demonstrate a clonal expansion of abnormal lymphocyte populations. The abnormal T-cell populations may overexpress the cytokine IL-5, leading to the expansion of the eosinophil mass causing manifestations of HES. Clonal rearrangements of T-cell genes have been described and this T-cell stimulated mechanism may explain other cases of HES. It is currently unknown whether subsets of T-cell associated HES also express the FIP1L1-PDGFRα fusion gene. Additionally, the sensitivity of HES patients with this T-cell driven pathogenesis to imatinib is unknown. Recent reviews comment on this aspect of HES (Gotlib, et al 2004) .

Imatinib specifically inhibits Abl, PDGFRs, and c-Kit kinases and displays impressive clinical efficacy in Bcr-Abl-positive CML. (Cools, et al 2003) were the first to describe the relationship between FIP1L1-PDGFRα, patients with HES, and the response of the target to imatinib. They showed that the proliferation of Ba/F3 cells expressing FIP1L1-PDGFRα was inhibited by imatinib (IC50) at 3.2 nM, whereas the same measure for cells expressing Bcr-Abl was 582 nM. The publication described responses in 9 of 11 patients treated with imatinib and the presence of FIP1L1-PDGFRα in 5 of the 9 patients whose illness responded for more than 3 months. The subsequent detection of a T647I mutation in PDGFRα, a mutation known to confer resistance to imatinib, in a patient who relapsed

gave further proof that FIP1L1-PDGFRα was causally related to the disorder in some patients. Cools, et al (2003) .

2 Clinical studies

This application is supported by:

- A phase II open label [Study B2225] in patients with life threatening diseases, including HES, known to be associated with one or more imatinib-sensitive tyrosine kinases and
- 34 publications and one manuscript submitted for publication (Martinelli, et al 2006) .

The total number of HES and CEL patients included is 176 (14 from [Study B2225] and 162 from the publications).
At least three investigator-led studies, CSTI571ADE31, CSTI571AIT12 and CSTI571AUS19, are enrolling patients with HES. These studies are ongoing.

Study B2225 was an open-label, multicenter, 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.

2. 1. 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. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, adequate end organ function, life expectancy of more than 3 months, adequate contraception and written, informed consent.

The **primary objective** of the study was to assess the efficacy of imatinib in patients suffering from different malignancies known to be associated with one or more imatinib-sensitive PTKs following failure of standard therapeutic options or without therapeutic options of definitive benefit.

The ***primary efficacy variable*** was the frequency of response to treatment, although no formal definition of response was included in the protocol for haematologic malignancies. The activity of imatinib was assessed primarily by evaluating normalization of blood counts, and/or relevant bone marrow or radiologic assessments (e.g. radionuclide scanning). The response for either of these was captured in the same way and categorized as complete response, partial response; stable disease/no response, progressive disease or unknown. The best response status was classified as unknown for any category of response (except progressive disease) if not confirmed by a subsequent evaluation after at least 4 weeks. Tumor status was assessed at baseline, at Visits 6, 9, 12, 15, 18, 21 and at End of Study. The planned duration of the study was 2 years.

The main clinical ***secondary efficacy variable*** was the evolution of the ECOG performance status. It was assessed at baseline and at Visits 6, 9, 12, 15, 18, 21 and End of Study. Similarly, periodic weight assessments were summarized by visit looking at changes over time.

The **secondary objectives** were to assess the safety and tolerability of imatinib, to evaluate the pharmacokinetic (PK) profile of imatinib in selected patients and to assess, if feasible, the functional significance of relevant signal-transduction components in target tissues by evaluating the expression and activation status of the relevant tyrosine kinase molecules or associated signaling molecules, by measuring indices of cellular proliferation and by correlating the changes in the above findings with clinical outcomes.

Safety assessments consisted of evaluating adverse events (AE) and serious adverse events (SAE), laboratory parameters including hematology, biochemistry, vital signs, physical examinations, and documentation of all concomitant medications and therapies. All safety and efficacy evaluations were performed on patients who received at least one dose of study medication.

2.2 Results

Demographics and Baseline characteristics

Among the 185 patients included in the study, there were only 14 with a HES diagnosis.

Demographics by malignancy group – Study B2225, all patients

Demographic variables		Hematology group N = 45	All N = 185	HES patients N = 14
Sex – n (%)	Male	35 (77.8)	105 (56.8)	**11 (78.6)**
	Female	10 (22.2)	80 (43.2)	**3 (21.4)**
Race – n (%)	Caucasian	43 (95.6)	175 (94.6)	**12 (85.7)**
	Black	1 (2.2)	3 (1.6)	**1 (8.3)**
	Oriental	1 (2.2)	3 (1.6)	**1 (8.3)**
	Other	0	4 (2.2)	**0**
Age Groups	< 65	32 (71.8)	152 (82.2)	**14 (100)**
	≥ 65	13 (28.9)	33 (17.8)	**0**
Age (years)	N	45	185	**14**
	Mean ±SD	52.2 ±17.34	47.8 ±16.4	**48.6 ±13.46**
	Median	51.0	49.0	**51**
	Range	15.0 – 86.0	15.0 – 86.0	**16.0 – 64.0**
Weight at baseline (kg)	N	43	178	**14**
	Mean ±SD	74.75 ±13.96	73.78 ±16.34	**74.86 ±12.11**
	Median	71.80	71.70	**71.55**
	Range	45.0 – 105.4	36.6 – 135.0	**60.5 – 98.2**

No further details of the history of patient with HES, such as cytogenetic abnormalities, are provided in the clinical study report, due to missing data.

Dosing and exposure

No dose finding studies have been performed. The dose of imatinib for this study was chosen on the basis of demonstrated efficacy and safety in other malignant diseases, suggesting that a similar dose could be employed to explore the efficacy of imatinib in the new indication. Patients with haematologic malignancies were initiated on imatinib therapy at a dose level of 400 mg/day.

In the published literature listed in this submission, patients received doses ranging from 100 mg to 800 mg daily. From the reports, the dose selection rationale used by investigators included the recognition of FIP1L1-PDGFRα inhibition by low concentration exposures to imatinib, empiricism, the clinical status of the patients, known efficacy and safety profile of imatinib at the 400 mg dose.

None of these studies were large enough to provide a dose selection rationale and were not designed for this purpose. In the first case series report, the investigator made an empiric decision to begin treatment with 100 mg daily, which was reduced to 200 mg weekly in responders (Gleich, et al 2002) . In the largest case series, patients were begun at a dose of 100 mg and then increased in 100 mg increments weekly to a dose of 400 mg (Martinelli, et al 2006) . Clearly patients with FIP1L1-PDGFRα can develop responses on doses of imatinib as low as 100 mg per day, but other investigators have administered imatinib at 400 mg per day to such patients. The median dose intensity was as planned in the protocol, approximately 400 mg daily for hematological malignancies, indicating a good compliance by the patients. The mean dose intensity HES patient was slightly higher than planned dose in patients with hematological malignancies (473 mg, 118%), similar to the median dose intensity in the whole population with hematological malignancies. Of note, the frequency of dose variation (dose escalation) due to lack of efficacy is very similar in the two populations (11.4% in solid tumors and 11.1% in hematological malignancies).

The median duration of therapy was 8.8 months with a range of 16 to 709 days.

Efficacy results

In patients with HES, efficacy was assessed by evaluating the frequency of haematological response.

Best hematological response, time to progression and duration of response Study B2225, HES patients

Country/Center/Subject	Dose (mg/day)	Best response	Time to progression (days)	Duration of response (days)
GBR/201/093	**400→300→400→100**	**PR**	**349+**	**131+**
GBR/201/144	400→200→300→400	UNK	114	
GBR/201/145	400	SD	561+	
GBR/201/146	400	UNK	177+	
GBR/201/147	400→300→400→200	UNK	76	
GBR/201/163	400→600→400	SD	400	
GBR/201/178	400	UNK	99	
CND/701/111	800→1000→600	PD	30	
CND/701/169	400→300→400	PD	71	
CND/701/171	**400→500→400**	**PR**	**210+**	**183+**
AUS/901/120	400→200	UNK	16	
AUS/901/152	**400→600→800**	**PR**	**429+**	**348+**
AUS/901/168	400	UNK	51	
AUS/901/173	**400**	**PR**	**421+**	**394+**

PR = Partial response, SD = Stable disease, PD = Progressive disease, UNK = unknown
The + sign indicates that the Time to Progression was censored on that day.

In the group of 14 patients with HES, four patients experienced a partial response (PR) with durations of response of at least 348, 394, 131 and 183 days and time to progression censored on Days 429, 421, 349 and 210, respectively. The duration of this partial response was longer than 4 months. Another two patients had SD, one kept on treatment for 678 days while the other progressed after 400 days. Two patients had "Unknown" as best response due to missing data; one with time to progression censored on Day 177, the other progressing after 114 days.

The ECOG performance status for the HES population is better at baseline than in the overall population (no worse than 2). In these patients, the overall ECOG performance status did not change substantially, with two patients having worsened ECOG at the end of the study (but only one with ECOG 2) and two patients improving their ECOG at the end of study from ECOG 1 to ECOG 0.
The results in ECOG status do not provide relevant efficacy information. The results of cytogenetic response have not been provided and seem to have not been collected. There is not any information about improvement of symptoms or organ damage related to HES either.

As there is no description of the presence and type of any mutation or disease status in these 4 patients, it is not possible to analyse if these aspects were correlated with response.

Only patients aged 15 years old or older were included in study B2225. As HES/CEL is usually diagnosed in adults, the age group investigated is adequate.

3.3 Published Case Series and Case Reports

In addition to the clinical study described, the MAH has submitted 34 publications and one manuscript submitted for publication (Martinelli, et al 2006) including a total of 162 patients.

Clinical experience with imatinib in the treatment of HES/CEL

Diagnosis	FIP1L1-PDGFRα fusion gene	Daily Dose (mg/day)	Hematological response	Duration of response	Cytogenetic response
Single case reports from the published literature[†]					
19 HES 1 CEL	8 Positive 2 Negative 10 NA	75 to 600	**19 Complete** 1 Transient*	6 weeks to 18+ months	**10 Complete** 9 NA
Case series from the published literature					
Gleich, et al (2002): 5 cases [a]					
HES	NA	100	**3 Complete** 1 None	97+, 105+, 127+ days	NA
Gotlib, et al (2002): 5 cases					
HES	NA	100 to 400	**5 Complete**	NA	NA
Cools, et al (2003): 11 cases					
HES	5 Positive 5 Negative 1 NA	NA	**9 Complete** 1 Transient** 1 None	3 (died while in complete remission), 5 (relapse), 3+ (n=2), 7+, 8+, 9+, 11+, 16+ months	NA
Cortes, et al (2003): 9 cases					
HES	NA	100	**4 Complete** 1 Transient*** 1 Unknown 3 None	49+ days (n=2)	
Klion, et al (2004): 7 cases					
MP-HES	7 positive	400	**7 Complete**	1 month (died from unrelated cytomegalovirus infection), 1+ (n=4), 3+ (n=2) months	**6 Complete** 1 Partial
Pardanani, et al (2003): 5 cases					
HES	NA	100 (n=4) 400 (n=1)	**2 Complete** 3 Partial [b]	10+, 14+, 17+, 21+, 33+ weeks	NA
Salem, et al (2003): 6 cases					
HES	NA	100	**6 Complete**	6+, 12+ (n=2), 19+ (n=2), 22+ weeks	NA
Musto, et al (2004): 4 cases					
HES	1 Positive 3 NA	100 (n=1) 400 (n=3)	**3 Complete** [c, d] 1 None	2, 5 (relapse), 9+ months	**1 Complete** 3 NA
Payne, et al (2004): 2 cases					
HES	NA	100	**1 Complete** 1 None	12+ months	NA
Smith, et al (2004): 3 cases					
HES	2 Positive 1 Negative	400 (n=2) 600 (n=1)	**3 Complete** [e]	4 (relapse), 7+, 8+ months	NA
Vandenberghe, et al (2004): 5 cases					
CEL	4 Positive 1 Negative	100	**4 Complete** 1 None	4+ (n=3) months, NA (died of brain hemorrhage)	**2 Complete** 2 None 1 NA
La Starza, et al (2005): 12 cases [f]					
6 CEL 5 HES	6 Positive 5 Negative	100 to 600	**8 Complete** 3 None	2+, 7+, 9+ (n=2), 10+, 11+, 19+, 25+ months	**2 Complete** 4 None 5 NA

Diagnosis	FIP1L1-PDGFRα fusion gene	Daily Dose (mg/day)	Hematological response	Duration of response	Cytogenetic response
Roche-Lestienne, et al (2005): 9 cases					
6 MP-HES	4 Positive	NA	**5 Complete**	2+ (n=4) months	NA
3 HES	5 Negative		4 None		
Müller, et al (2005): 2 cases					
HES	1 Positive	100	**2 Complete**	16+, 21+ months	NA
	1 Negative	400			
Martinelli, et al (2006): 59 cases					
HES	23 Positive	100 to 400	**26 Complete**	1 to 44 months	**20 Complete**
	36 Negative		9 Partial		2 NA
			22 None		
			2 NA		

† Schaller & Burkland (2001), Ault, et al (2002), Nolasco, et al (2002), Ishhii, et al (2003), Koury, et al (2003), Ascione, et al (2004), Frickhofen, et al (2004), Malagola, et al (2004), Martinelli, et al (2004), Pottier, et al (2003), Rose, et al (2004), Rotoli, et al (2004), Tan, et al (2004), Wolf, et al (2004), Anghel, et al (2005), Cervetti, et al (2005), Imashuku, et al (2005), Musial, et al (2005), Onitilo, et al (2005), Chung, et al (2006)

NA = Not Available; CEL = Chronic Eosinophilic Leukemia; MP = Myeloproliferative

* The publication states that the patient presented with a reduction in eosinophils to 10.3% associated with a marked decrease in mast cells after 4 weeks with 100 mg/day imatinib. However, at 8 weeks, the Eo count increased again in the peripheral blood; an increased dose of 200 mg/day was temporarily effective up to 30 weeks of treatment, after which the disease became refractory to the increased dose.

** The publication states that a complete hematological remission was achieved, although this patient had only a transient response to 100 mg/day imatinib, which lasted several weeks, and had no response to an increased dose of imatinib

*** The publication states that the patient experienced transient normalization of peripheral Eo counts within 1 week of the start of 100 mg/day imatinib. Two weeks later, the symptoms recurred and the Eo count increased without further improvement despite dose increase to 400 mg.

[a] Including one patient reported by Schaller & Burkland (2001) already counted in the single case reports

[b] Treatment discontinued in one patient due to CTC grade 3 fatigue

[c] Duration of response in one patient of 5 months, then relapse

[d] Treatment discontinued in one patient due to AEs (fatigue, diarrhea, muscle cramps)

[e] Relapse in one patient with blast crisis

[f] Including one patient already reported by Rotoli, et al (2003) already counted in the single case reports

Haematological response

107 out of 162 patients (66%) reported in the literature experienced a complete hematological response. Cytogenetic abnormalities were evaluated in 117 of the 176 patients treated in the published reports and [Study B2225]. Sixty-one out of these 117 patients had FIP1L1-PDGFRα fusion kinase. All these FIP1L1-PDGFRα fusion kinase positive patients achieved a complete hematological response.

The FIP1L1-PDGFRα fusion kinase was either negative or unknown in 115 patients, of which 62 (54%) achieved either a complete (n=46) or partial (n=16) hematological response.

Cytogenetic and molecular response

There are several reports of complete cytogenetic response and a few of molecular response.

Analysis of response by HES type and cytogenetic abnormality

FIP1L1-PDGFRα fusion kinase	Number of Patients	Hematological Response	Duration* (at time of reports)
Positive for FIP1L1-PDGFRα fusion kinase			
Cools, et al (2003)	5	**5 Complete**	9+, 7+, 5 (relapse), 8+, 3 months
Klion, et al (2004)	7	**7 Complete**	1+ (n=4), 3+ (n=2), 1 month
Frickhofen, et al (2004)	1	**1 Complete**	248+ days
Malagola, et al (2004)	1	**1 Complete**	120+ days
Martinelli, et al (2004)	1	**1 Complete**	17+ months
Musto, et al (2004)	1	**1 Complete**	9+ months
Rose, et al (2004)	1	**1 Complete**	12+ months
Rotoli, et al (2004)	1	**1 Complete**	17+ months
Smith, et al (2004)	2	**2 Complete**	8+, 7+ months
Vandenberghe, et al (2004)	4	**4 Complete**	NA, 4+ (n=3) months
Cervetti, et al (2005)	1	**1 Complete**	12+ months
La Starza, et al (2005)**	6	**6 Complete**	9+ (n=2), 10+, 11+, 2+, 7+ months
Musial, et al (2005)	1	**1 Complete**	6+ months
Roche-Lestienne, et al (2005)	4	**4 Complete**	2+ (n=4), NA months
Chung, et al (2006)	1	**1 Complete**	2+ months
Müller, et al (2006)	1	**1 Complete**	21+ months
Martinelli, et al (2006)	23	**23 Complete**	1 to 44 months
Total	**61**	**61 CR**	
Negative for FIP1L1-PDGFRα fusion kinase			
Cools, et al (2003)	5	**3 Complete** 1 Transient [a] 1 None	16+, 11+, 3+ months
Smith, et al (2004)	1	**1 Complete**	4 months (relapse)
Vandenberghe, et al (2004)	1	1 None	
Wolf, et al (2004)	1	**1 Complete**	24+ months
Imashuku, et al (2005)	1	1 Transient [b]	30 weeks
La Starza, et al (2005)	5	**2 Complete** 3 None	25+, 19+ months
Roche-Lestienne, et al (2005)	5	**1 Complete** 4 None	
Müller, et al (2006)	1	**1 Complete**	16+ months
Martinelli, et al (2006)	36	**3 Complete** 9 Partial 22 None 2 NA	1 to 44 months
Total	**56**	**12 CR, 9 PR, 2 Transient, 31 None, 2 Not available**	

FIP1L1-PDGFRα fusion kinase	Number of Patients	Hematological Response	Duration* (at time of reports)
Unknown cytogenetic abnormality			
Schaller & Burkland (2001)	1	**1 Complete**	6+ weeks
Ault, et al (2002)	1	**1 Complete**	3 months (died from unrelated pneumococcal sepsis)
Gleich, et al (2002)***	4	**3 Complete** 1 None	97+, 105+, 127+ days
Gotlib, et al (2002)	5	**5 Complete**	NA
Nolasco, et al (2002)	1	**1 Complete**	NA
Cools, et al (2003)	1	**1 Complete**	3+ months
Cortes, et al (2003)	9	**4 Complete** 1 Transient [c] 1 Unknown 3 None	49+ days (n=2)
Ishhii, et al (2003)	1	**1 Complete**	3+ months
Koury, et al (2003)	1	**1 Complete**	18+ months
Pardanani, et al (2003)	5	**2 Complete** 3 Partial	10+, 33+, 21+, 14+, 17+ weeks
Salem, et al (2003)	6	**6 Complete**	12+ (n=2), 6+, 19+ (n=2), 22+ weeks
Ascione, et al (2004)	1	**1 Complete**	4+ months
Musto, et al (2004)	3	**2 Complete** 1 None	5 (relapse), 2 months
Payne, et al (2004)	2	**1 Complete** 1 None	12+ months
Pottier, et al (2003)	1	**1 Complete**	6+ months
Tan, et al (2004)	1	**1 Complete**	7+ months
Anghel, et al (2005)	1	**1 Complete**	8 months
Onitilo, et al (2005)	1	**1 Complete**	18+ months
Novartis [Study B2225]	14	4 Partial 2 Stable disease 2 Progressive disease 6 Unknown[†]	131, 183, 348, 394 days
Total	**59**	**34 CR, 7 PR, 2 SD, 2 PD, 1 Transient, 6 None, 7 Unknown**	
Overall Total	**176**	**107 CR, 16 PR, 3 Transient, 2 SD, 2 PD, 37 None, 7 Unknown**	

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

* The ultimate duration for each ongoing patient in the publications is unknown. The durations presented in this table are those reported in the publications at the time of each report.

** One patient is already reported by Rotoli, et al (2003) and counted with that publication.

*** One patient is already reported by Schaller & Burkland (2001) and counted with that publication.

[a] The publication states that a complete hematological remission was achieved, although this patient had only a transient response to 100 mg/day imatinib, which lasted several weeks, and had no response to an increased dose of imatinib

[b] The publication states that the patient presented with a reduction in eosinophils to 10.3% associated with a marked decrease in mast cells after 4 weeks with 100 mg/day imatinib. However, at 8 weeks, the Eo count increased again; a dose increase to 200 mg/day was temporarily effective up to 30 weeks of treatment, after which the disease became refractory to the increased dose.

[c] The publication states that the patient experienced transient normalization of peripheral Eo counts within 1 week of the start of 100 mg/day imatinib. Two weeks later, the Eo count increased without further improvement despite dose increase to 400 mg.

[†] Best response by Novartis criteria required that responses be accurately coded on two successful visits for confirmation. Otherwise it is listed officially as "Unknown".

Additionally, although the evaluation of hematological responses as defined by improvement in hematologic and bone marrow abnormalities was the primary basis for determining response in these patients, improvements in symptomatology and other organ dysfunction abnormalities were reported by the investigators.

In the largest case series in this application, 28 out of 59 patients (47%) presented with organ involvement (Martinelli, et al 2006) . The most common organ involvement was with lung, skin or heart, and less common with liver, spleen or soft tissue. Organ involvement regression was recorded in all the patients that reached CR. La Starza, et al (2005) published the second largest case series in which lung, heart, skin, CNS, or gastrointestinal involvement were reported in 10 of 12 patients. Improvements were observed in heart and CNS involvement. Klion, et al (2004) treated seven patients who presented with lung, heart, skin, and spleen involvement. Organ involvement resolved or normalized in all but the heart. Although the patients' constitutional symptoms improved, the signs and symptoms of congestive heart failure in three patients with endomyocardial fibrosis remained unaffected. End organ damage caused by eosinophilic infiltration is reversible to a point, but once organ fibrosis occurs in response to the infiltration the disorder is unlikely to be reversible with therapy.

Published reports of improvement in end organ damage

System organ class	Case reports of organ damage improvement
Cardiac disorders	Ault, et al (2002); Koury, et al (2003); Ascione, et al (2004); Payne, et al (2004); Rotoli, et al (2004); Anghel, et al (2005); La Starza, et al (2005); Musial, et al (2005); Onitilo, et al (2005); Martinelli, et al (2006)
Nervous system disorders	Frickhofen, et al (2004); Wolf, et al (2004); La Starza, et al (2005)
Skin and subcutaneous tissue disorders	Ault, et al (2002); Klion, et al (2004); Koury, et al (2003); Pardanani, et al (2003); Musto, et al (2004); Smith, et al (2004); Müller, et al (2006); Martinelli, et al (2006)
Respiratory, thoracic and mediastinal disorders	Ishhii, et al (2003); Klion, et al (2004); Koury, et al (2003); Pardanani, et al (2003); Chung, et al (2006); Müller, et al (2006); Martinelli, et al (2006)
Eye disorders	NA
Musculoskeletal and connective tissue disorders and/or vascular disorders	Ault, et al (2002); Payne, et al (2004)
Gastrointestinal disorders	Chung, et al (2006)

Summary of Published Case Series and Case Reports

Schaller and Burkland (2001) were the first to report that treatment with imatinib at a dose of 100 mg/day caused rapid and complete hematological remission (CHR) in a 41-year-old male patient with HES who suffered from severe, intractable side effects of long-term hydroxyurea and interferon-α therapy.

Ault, et al (2002) reported on a 54-year-old male patient with HES resistant to steroids and chemotherapy, with persistent hip pain. Upon administration of imatinib at 100 mg/day, the patient had a rapid and significant reduction of hip pains, as well as rapid improvement of the hemoglobin and platelet counts and disappearance of eosinophilia. He experienced no side effect from the therapy, but developed fulminant pneumococcal sepsis and died three months after initiation of imatinib treatment.

Gleich, et al (2002) reported positive response to imatinib 100 mg/day in 4 of 5 patients with HES. One of these patients had previously been reported by Schaller and Burkland (2001) . Responding patients were all males with normal serum interleukin-5 levels. Analysis for c-Kit activation loop mutation (D816V) in the responding patients was negative, suggesting that c-Kit was not the target of imatinib.

Gotlib, et al (2002) described imatinib treatment of 5 male patients with HES unresponsive to prior therapies including corticosteroids and/or hydroxyurea. Four patients had a normal karyotype and one patient had a t(1:4) translocation. A complete hematologic remission was rapidly achieved in all patients, which was still ongoing at the time of the publication.

Nolasco, et al (2002) reported on a 46-year-old male with normal karyotype and Bcr-Abl negative by PCR analysis. After treatment with interferon-α associated to glucocoticosteroids and hydroxyurea was discontinued due to GI intolerance, hydroxyurea was stopped and imatinib at 100 mg/day was started. Within one week, Eo count decreased rapidly and reached normal levels at the end of the second week of treatment. Glucocorticosteroids were progressively discontinued and imatinib was tapered to 100 mg twice weekly by the end of the fourth week. A bone marrow biopsy at the time showed only rare eosinophils and slight fibrosis. Since then, the patient remains asymptomatic and is off any other type of treatment.

Cools, et al (2003) enrolled 16 patients with HES. All patients had received prior therapy with no or limited success including, but not limited to, prednisone, hydroxyurea and/or interferon-α. Eleven patients (9 men and 2 women) with symptomatic disease (e.g. endomyocardial fibrosis, gastrointestinal Eo infiltrates, cranial nerve palsies, rash, hepatosplenomegaly) were treated with imatinib. Treatment with imatinib (100-400 mg/day) resulted in CHR in 10 of 11 patients after a median of 4 weeks (range 1-12 weeks). One of the ten patients had a transient response that lasted several weeks and did not respond to increasing doses of imatinib. The median duration of response in the remaining nine patients was 7 months (range 3-15 months). Analysis of patient DNA for activating mutations in known targets of imatinib (PDGFRα, PDGFβ, c-Kit) indicated the presence of a deletion on 4q12 with a breakpoint near PDGFRα. This deletion left behind fragments of two genes, FIP1L1 and PDGFRα, which fused to form a novel gene, FIP1L1-PDGFRα, which has constitutively active tyrosine kinase analogous to the imatinib sensitive Bcr-Abl enzyme.

Cortes, et al (2003) reported the results of imatinib treatment in 9 patients with HES. All patients had received prior therapy with no or limited success including, but not limited to, steroids, hydroxyurea, interferon-α and/or chemotherapy. All patients were symptomatic at the start of imatinib therapy. All patients had normal karyotypes, and no patient had the Bcr-Abl rearrangement. Four patients achieved CR. All 4 responders were men. All patients in the series were treated with imatinib at 100 mg/day, although in one patient the dose was increased to 400 mg/day before the response could be confirmed.

Ishii, et al (2003) reported one 41-year-old male patient diagnosed with HES and myelofibrosis based on bone marrow biopsy and bronchoalveolar lavage (32% eosinophils). He was treated with prednisolone, interferon-α, hydroxyurea and cyclosporine A without significant efficacy for his eosinophilia and complained of asthma-like respiratory symptoms. He was started on imatinib at 100 mg/day; after 7 days, absolute Eo count fell to within the normal range and asthma-like symptoms disappeared completely. Imatinib was administered for 7 days at 100 mg/day and then maintained at 100 mg twice weekly. At the time of the publication, no eosinophilia was noted, and there were no notable adverse events.

Klion, et al (2004) analyzed responses in seven HES patients treated with imatinib at 300 to 400 mg/day. All seven patients had elevated serum tryptase levels and the FIP1L1-PDGFRα mutation in RNA from peripheral blood cells. All seven patients responded to imatinib. 1 mo of imatinib administration, a rapid and dramatic decrease in Eo was found as well as complete resolution of Eo-related signs, except for cardiac involvement. The lack of reversal of cardiac abnormalities and persistence of the FIP1L1-PDGFRα mutation in one patient suggests that early intervention with higher doses than the administered (300-400 mg/day) of imatinib may be desirable in the treatment of patients with MP-HES. Abnormalities in laboratory test results, including anemia, thrombocytopenia, and elevated serum tryptase and B12 levels resolved in all seven patients. There was also a reversal of BM abnormalities as well as a reduction in aberrant and activated mast cells and activated Eo. The authors concluded that elevated serum tryptase is a sensitive marker of a myeloproliferative variant of HES characterized by tissue fibrosis, poor prognosis, and imatinib responsiveness.

Koury, et al (2003) reported a case where HES was coexisting with a rare skin disease, lymphomatoid papulosis, characterized by multiple transient papular eruptions due to focal dermal T-cell infiltration who had failed treatment with hydroxyurea for HES and methotrexate, psoralen-ultraviolet A light for the skin disorder, presented with severe dyspnea and biventricular heart failure. Serum IL-5 levels were markedly elevated. Imatinib was given at the dose of 400 mg/day for 2 weeks, 200 mg/day for 7 months, and 100 mg/day for 11 months. Eo counts and skin lesions disappeared within a week, serum IL-5 rapidly declined and normalized in 5 weeks; hydroxyurea was discontinued

in 2 weeks and prednisone reduced in the course of 6 months. At 6 months, cardiac status improved dramatically and at 18 months the patient was active. The authors concluded that an unidentified TK in the intracellular pathways of IL-5 production or IL-5 receptor signaling is the target for imatinib and that imatinib should be considered for all patients with HES or lymphomatoid papulosis.

Pardanani, et al (2003) treated five HES patients (all male, median age 46 years) and 2 with the very rare eosinophilia-associated chronic myeloid disorder (Eos-CMD) (both male, aged 45 and 58). All patients had failed previous treatments including but not limited to prednisone. At a median follow-up of 17 weeks (range 10-33 weeks), two HES and one eos-CMD patient achieved CHR and one HES achieved PR.

Pottier, et al (2003) published a case report of a 32-year-old male who had hypereosinophilia associated with cutaneous mastocytosis. The patient failed interferon-α and hydroxyurea therapy, but responded completely to imatinib 400 mg/day within three weeks of initiation. The urticaria pigmentosa lesions persisted. The patient was still on therapy after six months.

Salem, et al (2003) reported six patients with idiopathic HES. All patients had received prior therapies including but not limited to corticosteroids alone (n=2) or in association with hydroxyurea (n=2) or with hydroxyurea, interferon-α and cytarabine (n=2). All patients achieved partial response with these initial therapies. Five patients had normal karyotypes and one showed trisomy 8. RT-PCR was negative for ETV6-PDGFRB and Bcr-Abl fusion mRNAs. All patients rapidly achieved CHR when treated daily with imatinib at 100 mg.

Ascione, et al (2004) reported the case of a 33-year-old man with HES and with cardiac involvement (acute coronary syndrome). A treatment with imatinib at 400 mg/day and warfarin was initiated. After four months, the WBC showed Eo count decreased to normal levels and an ECG revealed normal sinus rhythm without ST segment modifications.

Frickhofen, et al (2004) reported a 33-year-old man in whom a diagnosis of hypereosinophilic syndrome was made. Treatment with azathioprine and prednisone was started, the patient's condition improved. However, laboratory evaluations confirmed eosinophilia with counts varying between 1.5x109/L (during treatment with azathioprine) and 8.4x109/L (after discontinuation of azathioprine). Cytogenetic analysis revealed a normal karyotype. The patient was started on imatinib at 200 mg/day. Within two weeks, Eo count decreased to normal levels and remained there with continued imatinib treatment. At the time of the report, the patient was feeling well without any adverse events.

Malagola, et al (2004) reported the case of a 47-year-old male diagnosed with chronic eosinophilic leukemia (CEL). His karyotype was normal. No Bcr-Abl rearrangement was found, but FIP1L1-PDGFRα rearrangement was detected. Treatment with imatinib was begun on a dose-escalation regimen: 100 mg/day for the first week with weekly dose increases of 100 mg/day up to a maximum dose of 400 mg/day. Seven days after start of treatment, the WBC and eosinophil counts were dramatically reduced and maintained constantly within normal ranges over 120 days of observation. Molecular response was documented 80 days after the start of the treatment.

Martinelli, et al (2004) reported the case of a 65-year-old man presenting with idiopathic HES. RT-PCR analysis detected the FIP1L1-PDGFRα fusion gene but no Bcr-Abl, FGFR1-Bcr or PDGFRα-Tel rearrangement. The patient was started on imatinib at 600 mg/day; after 21 days, the white cell and eosinophils counts fell dramatically and have remained normal over 17 months of continuing treatment.

Musto, et al (2004) observed a t(2:4)(p24:q12) reciprocal translocation in a 64-year-old male affected by HES with complete clinical response, CHR and CCR to imatinib (100 mg/day) sustained for 10 months of follow-up. Cytogenic and FISH analyses suggested a different molecular abnormality than the FIP1L1-PDGFRα rearrangement. The authors described that while the patient with t(2:4) achieved impressive durable response with 100 mg/day imatinib, for the other three patients 400 to 800 mg/day imatinib was necessary to achieve response..

Payne, et al (2004) reported 2 clinical cases of HES refractory to standard therapy in two male patients with organ involvement. Both were treated with imatinib. In one patient, a 29-year-old man with normal cytogenetics, treatment with imatinib at 1400 mg/day produced resolution of symptoms and peripheral blood count within 6 days. The patient had maintained normal blood count s and was

symptom free more than one year after start of treatment. The second patient, a 20-year-old man also with normal cytogenetics, failed to respond to imatinib even at a maximum dose of 400 mg/day.

Rose, et al (2004) reported the case of a leukemic form of HES refractory to intensive treatment (including hydroxyurea, prednisone, interferon-α, cytarabine, thiotepa, etoposide and allograft) in whom sustained clinical and molecular response was induced by 200 mg/day imatinib. The 29-year-old male patient in poor clinical status achieved CCR after only 15 days of treatment with imatinib and the response persisted 1 year later.

Rotoli, et al (2004) treated a 37-year-old male affected by Loeffler's endocarditis with imatinib. Cytogenetics, FISH and molecular analyses showed the presence of the FIP1L1-PDGFRα fusion gene. Standard echocardiography revealed a large infiltration of the apical region, with apparently pedunculate corpora floating in the LV chamber. Treatment with low dose imatinib (initially 200 mg/day reduced to 100 mg/day after 2 weeks) caused rapid regression of both eosinophilic proliferation and endomyocardiopathy. The CHR and reversion of the cardiac damage were sustained for 17 months at the time of the report. The FIP1L1-PDGFRα fusion gene was found significantly decreased after a few months of treatment. Using a contrast echocardiographic approach, we demonstrated the non-thrombotic origin of the "in-plus" image in our patient and its rapid resolution following imatinib treatment.

Smith, et al (2004) describe 3 patients with HES with cytogenetic abnormalities (FIP1L1-PDGFRA fusion in two patients, t(5:12)(q33:p13) translocation in a third patient). The two first patients (46- and 52-year-old men) were given imatinib at 400 mg/day and both presented rapid normalization of eosinophils counts; at the time of the publication, they had remained clear for 8 months with no apparent adverse effects from the drug. The third patient, a 56-year-old man, was given imatinib at 600 mg/day; initial rapid resolution of eosinophilia was observed; however, after 4 months of imatinib therapy the patient experienced blast crisis.

Tan, et al (2004) describe a 32-year-old male with HES and significant end organ damage who remained refractory to conventional therapy (hydroxyurea). No clonal karyotypic abnormalities were observed. The patient was started on imatinib 100 mg/day. The patient achieved CHR without any side effects reported.

Vandenberghe, et al (2004) retrospectively characterized 17 patients fulfilling WHO criteria for IHES or CEL, using RT-PCR and FISH. Eight patients had FIP1L1-PDGFRα positive CEL, three had FIP1L1-PDGFRα negative CEL and six had IHES. Four FIP1L1-PDGFRα positive patients were treated at an initial dose of 100 mg/day of imatinib. In all four treated patients, including one female, imatinib induced rapid and complete hematological response with normalization of the peripheral Eo count. Nevertheless, no clear improvement of the eosinophilic endomyocardial disease was observed in the three patients presenting with cardiac involvement, and one of these patients died from cardiac failure a few weeks later. The presence of FIP1L1-PDGFRα mRNA was analyzed in the blood of the three surviving patients under treatment: the fusion became undetectable by nested PCR in two patients and remained so during 4 months of follow-up. The third sample from the female patient remained positive. In the IHES group of patients, only one patient was treated with imatinib, which was rapidly abandoned for intolerance without evidence of response.

Wolf, et al (2004) describe a 47-year-old man with a HES, diagnosed 20 years ago. The patient was admitted due to insufficient therapeutic response to hydroxyurea: in general, he felt well, but reported increasing neurological problems, such as ataxia, memory deficits and dysarthria. No insertional deletion 4q12 with concomitant fusion of the FIP1L1 to the PDGFRα locus was detected. Magnetic resonance imaging (MRI) indicated a granulomatous vasculitis, most likely due to the hematologic malignancy. Despite negativity for the FIP1L1-PDGFRα fusion gene, therapy was started with 100 mg/day imatinib. This led to a rapid normalization of eosinophilic granulocytes in the peripheral blood as well as in the bone marrow. Partial cytogenic remission was achieved at 6 months; CR at 17 months, confirmed at 21 months. Due to the good response at 9 months the dose of imatinib was reduced to 100 mg once weekly, which was subsequently increased at 18 months to 100 mg/day. This led to a rapid normalization of eosinophilic granulocytes in the peripheral blood as well as in the bone marrow. In addition, the neurological symptoms substantially improved.

Anghel, et al (2005) describe the case of a young male patient with a six year history of HES and severe heart involvement who, after unsuccessful treatment attempts with steroids, hydroxyurea and interferon-α, had a prompt, clinical and hematological complete remission following administration of imatinib. As his cardiac function also markedly improved, he was considered for heart transplant. However, seven years after the onset of the disease and four months after the termination of imatinib treatment the patient died of a cerebral hemorrhage that occurred during an episode of acute respiratory sepsis.

Cervetti, et al (2005) reported on one case of HES treated with imatinib. The case concerned a 61-year-old male presenting HES and hepatomegaly who was treated with interferon-α for 5 years, obtaining normalization of peripheral blood count with unmodified hepatomegaly. Due to neutropenia, thrombocytopenia, and massive liver and spleen enlargement with appearance of ascites, the treatment was stopped and imatinib at 100 mg/day was initiated. Three months after beginning the treatment, hematological toxicity resolved and the patient showed significant improvement of hepatomegaly with complete resolution of ascites. The presence of FIP1L1-PDGFRα rearrangement was retrospectively tested on bone marrow samples harvested from the patient at diagnosis and after 12 months of imatinib therapy. The first sample tested positive, whilst the second did not show the FIP1L1-PDGFRα fusion gene.

Imashuku, et al (2005) A 26-year-old man with HES was treated with imatinib following a 5 year history of prednisolone therapy. The patient had hypereosinophilia (absolute eosinophil count >1500/μL) occurring in cyclic oscillations as well as histologically diagnosed eosinophilic vasculitis, bursitis, and periodic soft-tissue swellings. Laboratory data revealed high levels of serum tryptase and increased numbers of mast cells in the bone marrow, but serum interleukin-5 levels were within the normal range. The disease initially responded well to 100 mg/day of imatinib but recurred 8 weeks later. Thereafter, a 200 mg/day dose was temporarily effective. Despite the response to imatinib, the FIP1L1-PDGFRα fusion gene was not detected by fluorescence in situ hybridization (FISH) analysis. Additional molecular and cytogenetic studies showed neither translocations of PDGFR genes nor mutations in the c-KIT or the PDGFR genes.

La Starza, et al (2005) reported on a multicentric study that included 20 patients fulfilling the WHO criteria for HES and 6 patients without signs or symptoms of end-organ involvement. Ten of the 26 patients presented the FIP1L1-PDGFRα gene. Seven of these 10 patients received imatinib therapy with the peripheral Eo count normalizing within 2-4 weeks. In three patients, interphase FISH and RT-PCR demonstrated cytogenetic and molecular remission during therapy. Five of the FIP1L1-PDGFRα negative patients also received imatinib therapy. Two of these patients achieved hematologic remission with peripheral Eo count normalization.

Musial, et al (2005) reported a 41-year-old man diagnosed with HES with cardiac involvement. Genetic analysis revealed a FIP1L1-PDGFRA fusion gene. The patient was unresponsive to interferon-α therapy. He was started on imatinib at 100 mg/day for the first 3 months and then continued treatment at 100 mg every second day. Full hematological and molecular remission was accompanied by spectacular improvement in cardiac function.

Onitilo, et al (2005) reported a 50-year-old male patient with HES with trisomy 8 who experienced a complete and durable hematological and cytogenetic remission with low-dose imatinib therapy (100 mg/day). He also had a significant reversal of cardiac dysfunction with a reduction in cardiac hypertrophy, resolution of pericardial effusion and mitral and tricuspid regurgitation. He remained in remission 3 years after therapy.

Roche-Lestienne, et al (2005) performed molecular characterization of HES in 35 patients with normal karyotypes by conventional cytogenetic analysis. TCRγ gene rearrangements suggesting T clonality were seen in 11 patients (31%), and FIP1L1-PDGFRα by RT-PCR in six of 35 patients (17%), who showed no evidence of T-cell clonality. An elevated serum tryptase level was observed in FIP1L1-PDGFRα-positive patients responding to imatinib, whereas serum IL-5 levels were not elevated in T-cell associated hypereosinophilia. Sequencing FIP1L1-PDGFRα revealed scattered breakpoints in FIP1L1-exons (10-13), whereas breakpoints were restricted to exon 12 of PDGFRα. In the 29 patients without FIP1L1-PDGFRα, no activating mutation of PDGFRα/PDGFRβ was detected; however; one patient responded to imatinib. FISH analysis of the 4q12 deletion was concordant with

FIP1L1-PDGFRα RT-PCR data. Further investigation of the nature of FIP1L1-PDGFRα affected cells will improve the classification of HES. Nine patients were treated with imatinib (100-200 mg/day), seven males, two females, and five of the male HES patients achieved sustained CR.

Chung, et al (2006) reported a case of persistent cough associated with gastro-esophageal reflux and hypereosinophilia. Treatment with proton pump inhibitors and fundoplication did not control the cough. However, high dose prednisolone, but not inhaled corticosteroids, did. The presence of the FIP1L1-PDGFRA fusion gene in myeloid cells was confirmed by fluorescence in situ hybridization analysis using CHIC2 deletion as a surrogate marker. The cough and other disease features were subsequently suppressed by imatinib at the dose of 100 mg/day. This 54 year old male scientist is the first case of persistent cough caused by HES characterized by FIP1L1-PDGFRA fusion gene and aberrant tyrosine kinase activity.

Mueller, et al (2006) The authors summarize recent knowledge of clinical features, pathophysiology and novel treatment aspects of HES by performing a comprehensive search of the available literature and report on 94 patients. The Authors particularly address the issue of organ involvement and specific characteristics of the variable clinical pictures. In addition, two cases are presented, which illustrate typical clinical scenarios and treatment outcome.

Martinelli, et al (2006) treated **59 HES patients** (age range 18-78) with imatinib. Fifty patients received 100 mg/day increasing by 100 mg/day at weekly intervals to reach the planned dose of 400 mg/day; the imatinib dose was subsequently reduced to 200-300 mg/day in 5 of these patients and maintained at that level due to AEs. Of the remaining nine patients, one patient discontinued before reaching the full dose due to rapid progression and one patient discontinued during dose escalation due to renal failure. One HIV positive patient remained on low dose to prevent possible pharmacological interaction with antiviral therapies. Four patients remained at 100 mg/day per investigator's decision due to concomitant morbidity. The two remaining patients received an unknown dose of imatinib. All patients were studied by molecular analysis for expression of FIP1L1-PDGFRα, Tel-PDGFRβ, FGFR1-Bcr and Bcr-Abl chimerical transcripts.

Rapid, hematological CR was recorded after one month of therapy in all 23 (39%) FIP1L1-PDGFRα positive patients. In 36 patients negative for FIP1L1-PDGFRα rearrangement, 9 (25%) experienced PR and 3 CR (PR+CR 33%). Furthermore, a molecular complete remission (defined as the disappearance of FIP1L1-PDGFRα at qualitative RT-PCR evaluation) was also recorded in 20 FIP1L1-PDGFRα positive patients after 3 months of therapy. The median follow up was 4 months (range 2-39). The authors concluded this study supports the use of imatinib as first line therapy in FIP1L1-PDGFRα positive HES patients.

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

A Bayesian [Meta-analysis Report] of efficacy data from published papers was performed and compared with the [Study B2225] efficacy data to examine the effect of potential publication bias in the published reports.

This report cannot rule out the existence of publication bias, as the observed response rate (i.e. complete plus partial responses) in [Study B2225] of 28.6% does not fall within the pooled posterior response rate confidence interval for literature reported patients with HES treated with imatinib, which is [74.2%,94.3%]. The posterior median response rate in the meta-analysis for the published literature is of 83.5%. The discrepancy between the two could be explained by the small sample size of the [Study B2225] HES patient population compared to the pooled sample size of the published literature (0.14 ratio between the two). Furthermore, this discrepancy could also be attributed to the fact that six out of 14 patients within the [Study B2225] HES population had a best overall response of Unknown, as they did not have a sufficient number of meaningful tumor assessments in order to be assigned a best overall response different from Unknown according to the SWOG criteria. Of note, the publication cut-off date for the literature in the [Meta-analysis Report] was 14-Oct-2005 and only patients with HES were included, which explains the difference in the number of published cases included in the [Meta-analysis Report] compared to the present application.

Discussion on clinical efficacy

The reported benefit of reported responses in the whole population from [Study B2225] and published literature, can be summarized as follow:

- A complete reported response rate of 107/176 or 61%
- An overall reported response rate of 123/176 or 70% (complete and partial responses)
- A reported response to imatinib that was often durable

If the evaluation is categorized by patients demonstrating known cytogenetic abnormalities associated with imatinib sensitivity, the benefit is higher:

- All 61 patients (100%) with known FIP1L1-PDGFRα fusion kinase achieved a hematological complete response.
- Sixty-two of 115 patients (54%) with no or unknown cytogenetic abnormality achieved a hematological response, either complete (46 patients) or partial (16 patients).

Many patients reported improvement in HES related organ dysfunction with imatinib therapy.

The MAH has provided additional evidence from publications concerning 162 HES/CES patients. Although these case reports and case series are a source of heterogeneous and incomplete information, they are a very relevant part of the evidence.

In accordance with the description, the population treated with imatinib seems to have an advanced stage of HES-CEL, as many of the patients suffered organ damage and had received previous treatments without satisfactory results.

Regarding efficacy, there is a high rate of haematological response (83.5%), mainly complete (66%). The responses were rapid and more convincing in FIP1L1-PDGFRa positive patients (100% complete remissions). The duration of the responses is heterogeneous with median durations of about 7-8 months but wide ranges (3-more than 15 months). Some of the patients have responses lasting more than 1 year. Of relevance, a consistent number of patients obtained cytogenetic and molecular response, mainly in FIP1L1-PDGFRa patients. There are also some reports of improvements in symptoms and organ dysfunction. So, in accordance to these findings, imatinib has convincing activity in certain HES-CES patients who carry the FIP1L1-PDGFRa gene.

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 a haematological malignancy, out of which 14 patients were classified as presenting HES-CEL). Additional evidence in 35 published articles with 162 additional patients, have been presented to support this indication.

Because of the nature of the reports (clinical study involving multiple diseases vs. case reports) and the well established safety profile of imatinib in myeloid haematological malignancies and solid tumours, for Study B2225 the safety of the whole population of 185 patients enrolled is considered, as well as the safety of the 14 patients with HES enrolled in the study. The case reports are discussed with special attention to any event not consistent with the known imatinib safety profile.
Safety was assessed by collecting reports of deaths, SAEs and AEs, laboratory data (standard haematology, 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.

Duration of exposure – Study B2225, all patients

Duration of Exposure (months)	All N = 185 n (%)	Hematology group N = 45 n (%)	HES patients N = 14 n (%)
0 – < 5	124 (67.0)	22 (48.9)	**6 (42.9)**
5 – < 10	22 (11.9)	5 (11.1)	**1 (7.1)**
10 – < 15	13 (7.0)	6 (13.3)	**1 (7.1)**
15 – < 20	6 (3.2)	2 (4.4)	**2 (14.3)**
20 – < 25	16 (8.6)	8 (17.8)	**4 (28.6)**
25+	4 (2.2)	2 (4.4)	**0**
Mean ±SD	6 ±7.65	9 ±9.17	**10.9 ±9.55**
Median	2.7	5.1	**8.8**
Min – Max	0 – 42.7	0.3 – 26.7	**0.5 – 23.3**

Demographic characteristics regarding exposure:

In the overall study population, according to gender there were 56.8% male and 43.2% female; 94.6 %, of patient were Caucasian, and they were mainly aged <65 years. (82.2 %), and only 17.8 % were over 65 years (range: 15-86). Most patients with haematological malignancies had been diagnosed within the preceding 12 months whereas most of the patients with solid tumours had been diagnosed more than 1 year before being recruited into the study.

In the HES patients, 11 out of 14 were males, 12 of them were Caucasian and there were no patients aged 65 years old or more, while all of them were between 16 and 64 years. There is no individualized information about history of malignancy in the HES group.

The applicant highlights that most of the information related to disease characteristics is missing for the haematology group, and therefore no conclusions can be reached.

Participation, withdrawals and dose reductions

Patient disposition – Study B2225, all patients

	All N = 185		Solid tumor group N = 140		Hematology group N = 45		HES patients N = 14	
	n	(%)	n	(%)	n	(%)	n	(%)
Ongoing at cut-off date	15	(8.1)	12	(8.6)	3	(6.7)	**2**	**(14.3)**
Completed	11	(5.9)	2	(1.4)	9	(20.0)	**3**	**(21.4)**
Discontinued	159	(85.9)	126	(90.0)	33	(73.3)	**9**	**(64.3)**
Unsatisfactory therapeutic effect	108	(58.4)	86	(61.4)	22	(48.9)	**8**	**(57.1)**
Adverse events	29	(15.7)	22	(15.7)	7	(15.6)	**0**	
Subject withdrew consent	9	(4.9)	7	(5.0)	2	(4.4)	**1**	**(7.1)**
Death	7	(3.8)	6	(4.3)	1	(2.2)	**0**	
Condition no longer required study drug	5	(2.7)	4	(2.9)	1	(2.2)	**0**	
Abnormal laboratory values	1	(0.5)	1	(0.7)	0		**0**	

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. Overall, the most frequently reported AEs in both tumor groups affected the gastrointestinal system, general and administration site disorders or skin, musculoskeletal, respiratory or nervous system disorders. Patients with haematological malignancies had a higher frequency of skin disorders (68.9% vs. 57.1%), blood disorders (48.9% vs. 24.3%) and cardiac disorders (11.1% vs. 6.4%) than patients

with solid tumours and a lower frequency of general disorders (62.2% vs. 80.7%), of metabolic and nutrition disorders (24.4% vs. 42.1%) and of eye disorders (13.3% vs. 26.4%).

All HES patients experienced at least one AE, the AE profile was consistent with the one of the overall group, the most commonly affected system organ classes being the gastrointestinal system, cutaneous disorders, and musculoskeletal disorders.

The most frequently occurring adverse events in patients with HES were nausea in 9 cases, followed by diarrhea and muscle cramps in 7 cases each and then by periorbital edema and vomiting (4 cases each). All other AEs occurred in three patients or less.

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 HES died on study.

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%). Although many of the AEs were mild to moderate in severity, a total of 82 patients (44.3%), 61 in the solid tumor group and 21 in the hematology group, experienced CTC grade 3 AEs by any cause and a total of 33 patients (17.8%), 27 with solid tumours and 6 with haematological malignancies, experienced CTC grade 4 AEs by any cause. The majority of these AEs were related to the underlying conditions; drug-related CTC grade 3 AEs were reported in a total of 54 patients (29.2%), 40 patients with solid tumours and 14 with haematological malignancies, and drug-related CTC grade 4 AEs were reported in 7 patients (3.8%), 5 with solid tumours and 2 with haematological malignancies.

Two HES patients experienced three drug-related SAEs: patient [701/111] presented a CTC grade 3 acute renal insufficiency from Day 14 to Day 22 and a CTC grade 3 edema from Day 28 to Day 33, both of which resulted in hospitalization as seen in [Study B2225−PTL 10.2-1]. Patient [901/152] experienced CTC grade 3 decreased sperm count on Day 362 which did not lead to further action.

Three additional HES patients experienced non-related, non-fatal SAEs: patient [201/093] had CTC grade 3 ascites which resolved in two days with non-drug therapy; patient [201/147] had a CTC grade 3 chest infection from Day 7 to Day 20 which led to hospitalization and administration of concomitant medication; he was again hospitalized on Day 24 due to the following SAEs: CTC grade 2 sweating which resolved after one day, CTC grade 2 endomyocardial fibrosis, ischemic lesions in cerebral hemispheres, diarrhea and dizziness and CTC grade 1 nausea, which led to permanent discontinuation of the study treatment. Patient [701/171] had a CTC grade 2 cerebral ischemia from Day 89 to Day 93 which led to hospitalization and the use of concomitant medication.

Analysis by organ system or syndrome

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%).

Two HES patients presented two cardiovascular SAEs which were not considered study drug-related: patient [201/147] presented a CTC grade 2 restrictive cardiomyopathy which led to study drug discontinuation, and patient [701/171] presented transient CTC grade 3 peripheral ischemia which led to hospitalization and administration of concomitant medication.

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 CTC grade 3 creatinine increase.

HES patient [701/111] presented an SAE of CTC grade 3 acute renal failure which was suspected of being study drug-related and led to hospitalization, study drug interruption and administration of concomitant medication. This SAE resolved after 9 days.

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 patient with HES presented hepatobiliary system disorders.

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.

Twelve patients with HES presented gastrointestinal system disorders, of which three were SAEs: patient 201/093 presented a CTC grade 3 ascites, while patient 201/147 presented CTC grade 1 nausea and CTC grade 2 diarrhea, none of which were considered study drug-related.

Nervous system

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

Six HES patients presented nervous system disorders, two of which were non drug-related SAEs: patient [201/147] presented a CTC grade 2 cerebral ischemia that led to study drug discontinuation; it was accompanied by CTC grade 2 dizziness which resolved after one day.

Laboratory findings

Haematology

Most of the haematological abnormalities were CTC grade 3, with only eight instances of CTC grade 4 events in the overall population: five cases of neutropenia, two of leukopenia and one of thrombocytopenia. As expected, most of these CTC grade 4 events occurred in patients with haematological malignancies (two instances of neutropenia and one each of thrombocytopenia and leukopenia), with a frequency at least double of that seen in solid tumor patients, although the absolute frequency never exceeded 4.4% in the overall population.

In HES patients, the worst hematological abnormalities were CTC grade 3 in severity. Four HES patients presented one blood and lymphatic system disorder AE each (two cases of anemia and one case each of neutropenia and thrombocytopenia), none of which were SAEs and none of which led to study drug discontinuation.

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 tumours (two CTC grade 4 instances) than in patients with haematological malignancies (two CTC grade 3 instances).

In HES patients, there was one instance of CTC grade 3 albumin decrease and one instance of CTC grade 3 creatinine increase. No HES patient was withdrawn from the study due to abnormal laboratory values.

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.

Postmarketing safety and other sources of data

Since the international lauch date (May 2001), the Post marketing experience with imatinib has been reviewed on an ongoing basis in the Periodic Safety Update Reports (PSUR) and the US Periodic Reports (USPR).

Based upon cumulative reviews in the most recent PSUR version 6 (period 11 May 2004 to 10 May 2005), it was recommended to continue to monitor the following events: myocardial infarction, cardiomegaly/ cardiomyopathy, angina pectoris, thrombosis/embolism, pulmonary hypertension, hepatic necrosis/cirrhosis, disseminated intravascular coagulation, glucose metabolism disorders, rhabdomyolysis, hemolytic anemia, suicide attempt, ideation and suicide.

There are no new events reported from Post marketing experience which have not already been observed during clinical trials. No important targeted safety studies were identified. The safety profile of imatinib remains consistent with the information provided in the CDS of the product.

In the ongoing trials recruiting patients with HES, six SAEs have been reported to Novartis to date. Most were related to preexisting conditions or concomitant medications, and none was suspected of being related to the study drug.
Case reports

Out of 162 cases of HES/CEL in the literature, few AEs were reported by the authors. Schaller, et al (2001) reported that the patient they treated reported transient mild nausea on 100 mg daily imatinib, relieved with ondansetron. The patient then developed a constant mild headache, which disappeared with a dose reduction to 75 mg daily.

Cortes, et al (2003) reported one patient with a rash consistent with exacerbation of preexisting psoriasis and who was taken off therapy after 10 days. Abdominal cramps and nausea developed in one patient, necessitating a dose reduction from 100 mg o.d. to 100 mg every other day; all other adverse events were grade 1 and consistent with previously reported toxicity with imatinib, including fluid retention (n = 2), diarrhea (n = 1), muscle cramps (n = 1), and nausea (n = 1).

Pardanani, et al (2003) reported a patient who developed mild fatigue when imatinib dose was increased from 100 mg o.d. to 400 mg o.d. and another patient who experienced grade 3 fatigue on 100 mg o.d. imatinib and elected to stop imatinib after 4 weeks of treatment.

Another of their patients developed progressive dyspnea and orthopnea from acute left ventricular dysfunction with cardiogenic shock, which required intravenous pressor support following 8 days of imatinib therapy. An echocardiogram revealed new-onset severe generalized left ventricular (LV) hypokinesis (LV ejection fraction decreased from 71% to 10%) and the endomyocardial biopsy confirmed eosinophilic infiltration of the myocardium. Placement of an intraaortic balloon pump became necessary for hemodynamic support. The patient was started on high dose steroids with rapid improvement of hemodynamic parameters and was weaned of the pressors after 72 hours. After LV function recovery (LV ejection fraction 55-60% at 4 weeks after imatinib discontinuation), the patient was rechallenged with imatinib at 100 mg/day. The patient tolerated imatinib retreatment well without recurrence of cardiac toxicity.

Klion, et al (2004) reported one case of transient grade 3 neutropenia leading to interruption of the study drug followed by a dose reduction from 400 mg to 300 mg o.d., one case of grade 1 pedal and facial edema requiring no additional therapy, and one case of transient grade 2 myalgia resolved with ibuprofen.

Musto, et al (2004) reported the appearance of fatigue, muscle cramps, and diarrhea in a patient treated with 400 mg/day imatinib; a dose reduction to 200 mg/day led to the return of symptoms as well as that of the eosinophils count to baseline levels. The patient refused to be further treated. No further safety observations were reported for the other published case reports.

Martinelli, et al (2006) reported common adverse events including neutropenia, gastrointestinal disorder, thrombocytopenia, muscle cramps, edema and anemia.

Grade 3 or 4 events were infrequent. Grade 3 or 4 neutropenia was noted in two (3.4%) patients, and grade 3 thrombocytopenia in one patient only (1.7%). Drug-related adverse events led to discontinuation of therapy in two patients.

Out of 162 cases of HES/CEL reported in the literature, five deaths were reported on treatment with imatinib. Taking into consideration the level of detail provided, none appears attributable to imatinib.

Ault, et al (2002) reported that their patient developed a fulminant pneumococcal sepsis and expired three months after initiation of treatment with imatinib at 100 mg/day.

Cools, et al (2003) reported that one patient died after 3 months of imatinib treatment while in complete remission, without further detail.

Klion, et al (2004) reported that a patient with endomyocardial fibrosis in whom symptoms and signs of congestive heart failure remained unaffected by imatinib therapy died 1 month after beginning imatinib at 400 mg/day from disseminated cytomegalovirus infection thought to be a result of prolonged high-dose steroid use. At autopsy, extensive endomyocardial fibrosis was evident throughout the ventricular walls and interventricular septum.

Vandenberghe, et al (2004) reported that one patient presenting with cardiac failure and thrombotic events early in his disease course died from cardiac failure a few weeks after starting imatinib at 100 mg/day.

Anghel et al (2005) reported that four months after the withdrawal of imatinib, while in good clinical and hematological remission, the patient died of a brain hemorrhage that occurred during an episode of acute respiratory sepsis.

Discussion on safety

In the original submission, it was reported that caution must be exercised because of the occurrence of severe thrombopenias and/or neutropenias and the rare occurrence of a fluid retention syndrome. Transaminitis is also a known risk with imatinib. The data from this application confirm these risks, although they are manageable by either reducing the dose or temporarily suspending treatment with imatinib. No new risk questions were identified. Isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib therapy in patients with HES and cardiac involvement (Pardanani, et al 2003 , Pitini, et al 2003) . The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily holding of imatinib. Screening with echocardiograms and serum troponin levels should be considered in patients with HES. If either is abnormal, then the prophylactic use of systemic steroids (1-2 mg/kg) for 1 to 2 weeks concomitant with imatinib should be considered. Therefore, the CDS Section 4.4 “Special warning and special precautions for use” has been updated accordingly.

Benefit-Risk assessment

The initially claimed indication was HES-CEL, which include a very heterogeneous range of diseases, with a wide spectrum of biological and clinical situations, including, in one extreme, patients with moderate eosinophilia without organ dysfunction who do not need treatment and, in the other extreme, patients with cytogenetic aberrations and aggressive forms of the disease with massive organ infiltration and a dismal prognosis. For some of these subgroups, there are limited treatment options and systemic therapies, mainly corticosteroids, are not satisfactory, therefore, new treatments are required.

The molecular mechanism underlying the FIP1L1-PDGFRa fusion gene giving rise to a new constitutively active fusion tyrosine kinase that can be targeted by imatinib makes plausible the biological and molecular basis for this treatment. However, this is not the case when such a molecular mechanism is not found or it is already unknown.
The dossier presented to support the indication of Glivec for the treatment of adult patients with HES-CEL is limited to a phase II, uncontrolled, open label study (which includes 14 patients with HES-CEL) and 35 publications, including a total of 176 patients.

The main clinical study (B2225) was designed as a proof of concept trial, so, it is not specifically designed for the investigation of imatinib in HES-CEL. It has several major problems of design and efficacy results are unclear. None of the 14 patients with HES-CEL had a complete response, and only 4 of them showed a partial response. Due to the missing information, neither the adequacy of treatment nor the low response rate can be assessed adequately.

In contrast to the clinical study B2225, the efficacy results found in case-reports and case series are positive, although this evidence can be influenced by publication bias. In particular, all patients with the FIP1L1-PDGFRa mutation showed complete haematological response. Not unexpectedly, taking into account the biological background, the response was rapid and durable with some reports of cytogenetic and molecular responses that translate in improvement in organ damage. This is consistent with the previous experience with imatinib in other indications with similar biological rationale.

Concerning imatinib safety profile in this disease, it did not differ substantially from that previously described and it can generally be considered well tolerated. There was one case of cardiac adverse event (acute left ventricular dysfunction) related with imatinib, which could suggest additional monitoring in this patient population. Until more information is available, a warning about the use of imatinib in HES/CEL has been included in the SPC.

In accordance with these results, the CHMP requested additional information to clarify some clinical aspects and SPC information. The MAH response document to the day 120 CHMP list of questions mainly consists on further justification that confirm the initial findings.

For efficacy, more detailed information about patient characteristics, study design and results was requested. A new description of the results for FIP1L1-PDGFRa population has also been provided.

A controversial point was the benefit/risk of imatinib therapy in patients without the FIP1L1-PDGFRa mutation. Although some patients have demonstrated a response, in general, these responses have been slower and have required higher imatinib doses than those in patients with FIP1L1-PDGFRa associated disease. The data submitted in this application are clearly insufficient and do not allow an adequate assessment of the effects of imatinib when the presence of the FIP1L1-PDGFRa mutation has not been shown.

Another aspect that was based on limited investigations is the optimum dose of imatinib for this indication, as responses were obtained for various doses, but this has not been discussed relating the intensity and durability of response and the safety profile obtained with them. As the studies submitted used imatinib 100 mg or 400 mg obtaining positive results, the proposal to use imatinib 100 mg initially in the FIP1L1-PDGFRa population is acceptable.

No long term data on the maintenance of the response and survival have been provided either.
As the experience with imatinib is limited, further investigations of the use of imatinib in HES/CEL are recommended to better define its role. The company mentions more studies in this indication. For them, additional results, including molecular response, should be provided, if relevant.
The safety profile of imatinib in HES-CEL patients seems not different from the one in the whole population of Study B2225, which included patients with various diagnoses.

One HES patient suffered cardiogenic shock/left ventricular, which has been associated with the initiation of imatinib therapy. As HES may be associated with cardiac dysfunction, this adverse event could occur more frequently. The Applicant has reflected this in the proposed SPC, which it is reasonable to grant safety.

Case reports are focused on efficacy data and information related to safety is limited. There are few adverse events reported in HES-CEL patients obtained from publications and they seem consistent with previous experience. As the HES-CEL population can have previous cardiac problem, it is very reasonable to monitor cardiac safety at the initiation and during imatinib treatment. A relevant warning has been introduced in the SPC.

In conclusion, imatinib treatment was well tolerated by patients with HES-CEL. Its safety profile does not seem different substantially from the known safety profile of imatinib observed in other larger haematological malignancies populations, such as CML.

To summarize, efficacy and safety clinical results obtained with imatinib in the advanced HES/CEL FIP1L1-PDGFRα mutation population, although limited, can be considered positive. Taking into account the interest of having adequate treatments in this patient group (the current treatment with steroids provides symptomatic improvement associated with a poor safety profile in the long term treatment) and also the mechanism of action, there is a solid rationale to support the interest of this use of imatinib as a therapy that can be more effective to control this disease. The marketing authorization holder in the response document provides additional information, which is acceptable for the Rapporteurs. The evidence presented can be considered sufficient to grant a new labelling.

The changes proposed for the SPC (pending minor amendments) reflect adequately the comments made by the CHMP.
In the light of the above discussion, we consider that an indication "Imatinib is indicated in the treatment of adult patients with advanced HES-CEL with FIP1L1-PDGFRα rearrangement" is acceptable.

CONCLUSION

- On 18 October 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

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	1. The results of the investigations planned or ongoing on the use of imatinib in patients with HES/CEL, including long term data on the maintenance of the response and survival should be submitted to the CHMP	Dec. 2007 and yearly thereafter.
Clinical	2. There are currently no data regarding the RT-PCR number of transcripts in HES/CEL patients. • As this information would be useful to assess the response to imatinib, the collection of these data should be considered in clinical investigations. • The molecular data requested should be submitted	. Dec. 2007 and yearly thereafter.
Clinical	3. The dosage proposals for HES/CEL should be reviewed when more information, i.e. molecular response, duration of response, safety, etc., is available	Dec. 2007 and yearly thereafter.
Clinical	4. The cardiac safety profile of imatinib in HES/CEL patients should be reassessed when more experience in this patient population is available	Dec. 2007 and yearly thereafter.

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.