European Medicines Agency
Evaluation of Medicines for Human Use

London, 29 April 2009
Doc. Ref No.:EMEA/CHMP/323593/2009

ASSESSMENT REPORT FOR GLIVEC

International non-proprietary name/Common name: imatinib

Procedure No. EMEA/H/C/406/II/0048

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Introduction

Glivec, containing imatinib, was first authorised in the EU in 2001 under the Centralised Procedure and subsequently the license was extended to include the following indications:

• Adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.

• Adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.

• Adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.

• Adult patients with relapsed or refractory Ph+ ALL as monotherapy.

• Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.

• Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

• Adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).

• Adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and

adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In the current application, the MAH is seeking an extension of the imatinib indication, to include the adjuvant treatment of adult patients following resection of Kit (CD117)-positive GIST.

The proposed dose for this indication is 400 mg/day.

Glivec in malignant GIST was issued an orphan drug designation in September 2001.

2 Clinical aspects

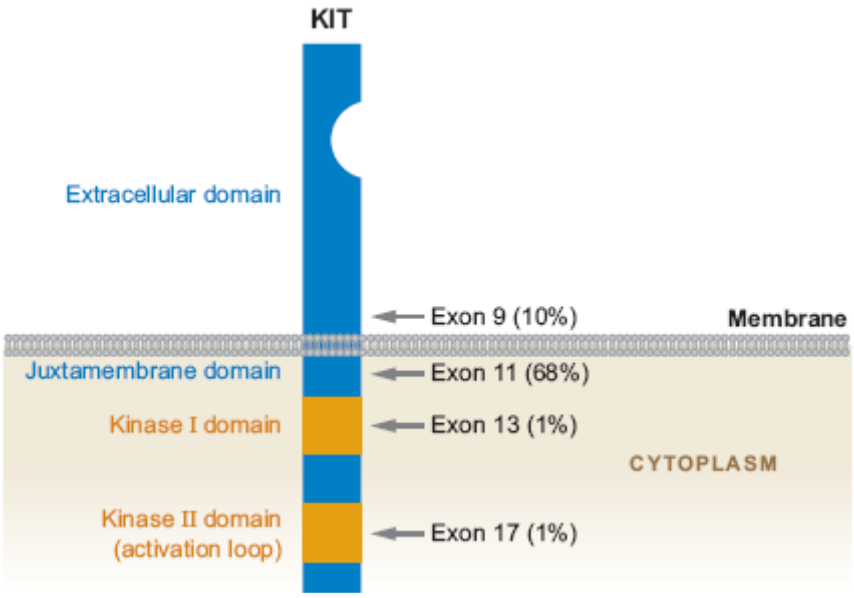
This extension is based on the preliminary analysis of a pivotal randomised phase III trial (Z9001) of Glivec and placebo as adjuvant therapy in adult patients following resection of KIT-positive GIST. Currently there is no approved therapy for this indication.

Based on the review of the data on safety and efficacy, the CHMP considered that the variation application EMEA/H/C/00406/II/0048 for Glivec (Imatinib mesilate) as adjuvant treatment of adult patients following resection of Kit (CD117)-positive GIST was not approvable unless the MAH could provide satisfactory responses to the request for supplementary information.

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract and are thought to arise from the interstitial cells of Cajal or their mesenchymal stem cell precursor. These neoplasms account for 1% to 3% of all malignant GI tumours. The estimated incidence ranges from 11 to 15 cases per million population/year and are consistent across different populations (Iceland 11, Holand 12.7, Sweden 14.5). GIST can occur from infancy to old age, but median age of presentation is 58 years. The incidence is slightly higher in men than in women. This neoplasm can arise in any site within the gastrointestinal tract, but the most frequent site of presentation is the stomach (60-70%), followed by the small intestine (20-30%). Extraintestinal abdominopelvic sites such as omentum, mesentery and retroperitoneum have also been reported. GIST spreads intraabdominaly, to the liver, omentum or peritoneal cavity. Metastatic spread to lymph nodes is very rare.

Approximately 85% of GISTs are driven by oncogenic mutations in either of two receptor tyrosine kinases: KIT or PDGFRα. Activating mutations in KIT are the most common, with exon 11 mutations found in about 68% of cases. Otherwise KIT exon 9 mutations have been found in approximately 10%

of cases, with point mutations in exons 13 and 17 being rare. Among the GISTs without KIT mutations, one subgroup has mutations in the platelet-derived growth factor receptor A (PDGFRα), constituting 5-8% of GISTS overall, and another subgroup lack identified mutations.



Risk of recurrence after surgery

Efforts have been made to identify the individual risk of a patient with a resected primary tumour to develop metastases. The most important prognostic factors are the size and the mitotic count. The site of the primary tumour has been also associated with prognostic significance. The prognostic impact of kinase mutations has been examined in a number of retrospective studies. Many groups have noted that *KIT* exon 11 mutations are a negative prognostic factor. *PDGFRA* mutant GISTs appear to be less aggressive than *KIT* mutant GISTs. Once GISTs become metastatic, kinase genotype does not factor into overall survival.

Unfortunately, knowledge of these additional mutations remains limited, and current recommendations for assessing the risk of progression of a newly diagnosed primary GIST are based on three simple parameters: tumor size, tumor location, and mitotic index (mitoses per 50 high-power fields).

In April 2001 the United States National Institutes of Health (NIH) convened a GIST workshop with the goal of developing a consensus approach to diagnosis and morphologic prognostication. Key elements of the consensus were the defining role of KIT immunopositivity in diagnosis and a proposed scheme for estimating metastatic risk in these lesions, based on tumor size and mitotic count, table 1.

Table 1. Risk groups by the NIH criteria.

Risk Group	Size (cm)	Mitotic count /50 GCA	Risk of recurrence
Very low	**< 2**	<5	0%
Low	**2-5**	**<5**	2.5%
Intermediate	<5 5-10	5-10 <5	19%
High	**>10** Any **5-10**	Any **>10** **5-10**	62.5%

The most complete data currently available have been provided by Miettinen and colleagues at the **United States Armed Forces Institute of Pathology (AFIP)**. They have performed considerable efforts in studying the outcome of patients prior to the advent of modern therapies, and have reported pathological diagnosis and long-term follow up of 1765 gastric, 906 small intestinal, 144 duodenal and

111 rectal GISTs. They have developed a classification based on this parameters to estimate the individual risk of progression after primary GIST diagnosis.

Table 2. Risk groups by the AFIP classification.

Tumor	Parameters	Risk of progressive disease[a] (%)			
Mitotic index	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
≤5 per 50 hpf[b]	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 ≤ 5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
	>5 ≤ 10 cm	Low (3.6%)	Moderate (24%)	(Insufficient data)	(Insufficient data)
	>10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
Mitotic index	≤2 cm	None[b]	High[c]	(Insufficient data)	High (54%)
>5 per 50 hpf	>2 ≤ 5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
	>5 ≤ 10 cm	High (55%)	High (85%)	(Insufficient data)	(Insufficient data)
	>10 cm	High (86%)	High (90%)	High (86%)	High (7%)

A great proportion of cases of limited disease are cured with surgery, all over those with lower mitotic count and size smaller than 5 cm, with an expected recurrence rate lower than 5%. On the other hand tumours higher than 10 cms in their greatest diameter and with high mitotic count (>5 per 50 hpf) are rarely cured with surgery with a recurrence rate higher than 85%. An adequate selection of patients candidates for adjuvant treatment is of importance, and should be based on known prognostic factors and risk stratifications.

At the moment, the gold standard of treatment in primary resectable GIST is surgery with gross margin resection. To date there is no accepted adjuvant treatment.

2. 1. Clinical trials

There are 5 non randomised studies in high risk GIST. The first of these studies was conducted by ACOSOG, the sponsor of the Z9001 study. Two other studies in Japan and korea have been conducted in the same population. Two other studies, with biological endpoints are ongoing in neoadjuvant operable GIST. The next two tables summarises the non randomised studies in GIST.

Sponsors and collaborators	**CTC Number**	**Phase**	**Duration**	**Risk Population**	**Primary Endpoint**	**Status**	**N**	**Start date**
ACOSOG (American College of Surgeons), NCI (National Cancer Institute)	NCT00025246	**II**	1 year	**High** risk	Survival & RFS	Ongoing, not recruiting	89	September 2001
Novartis. Japan	NCT00171977	**IV**	1 year	**High** risk	RFS	Ongoing, not recruiting	60	July 2004
Asan Medical Center. South Korea	NCT00278876	**II**	NA	**High** risk & exon 11 KIT mut	RFS	Completed	47	April 2005
RTOG, NCI, ACR Imaging Network, ECOG	NCT00028002	II **Neoadj** & Adj	2 years	Operable Gist	Biological effect, recurrence rate, RFS.	Ongoing, but not recruiting	63	February 2002
M.D. Anderson Cancer Center Novartis	NCT00500188	II **Neoadj** & Adj	2 years	Operable GIST	Inhibition of angio-genesis and predictors of response.	Recruiting	48	July 2003

In 2008, Dr De Matteo presented the results of the ACOSOG Z9000 phase 2 trial at the 2008 Gastrointestinal Cancers Symposium. The study Z9000 is an open label phase 2 trial of Glivec in 107

patients diagnosed of high risk GIST. The criteria to define high risk were diameter > 10 cms, ruptured tumor or multifocal. The trial was conducted between September 2001 and September 2003, and median follow up at presentation was 4 years. There is a delay in the recurrence of the tumours, with most recurrence beginning after stopping treatment at 1 year. The recurrence rate at 1,2 and 3 years were 94% ,73% and 61%, and the OS rate at 1,2 and 3 years were 99%, 97% and 97% respectively. The comparison with valid historical controls is not possible, since the historical series report patients treated before the GIST era, and to date we know that most patients at recurrence are rescued with Glivec (>80%) and that the median overall survival of metastatic patients exceeds 5 years. At the meeting outcomes according to the mutational status were reported. Interestingly exon 9-mutated tumours have higher relapse rate than the exon 11, wild-type or PDFRA mutated tumours. This is increasingly interesting, since correlative studies could help to identify patients that achieve the maximum benefit form this treatment, and the benefit in exon 9 mutated tumours has yet to be demonstrated.

There are three randomised trials in resected primary GIST. Two of these studies have been conducted comparing Glivec with placebo. One of these studies, conducted in the US is the supportive study in this application while the other conducted in Europe and Australasia has not been reported to date. There are three major differences between these trials: the primary endpoint (RFS vs OS), the population included (All GISTs> 3 cms vs Intermediate or High risk) and the duration of Glivec (1 vs 2 years). The third randomised trial in adjuvant GIST pretends to address the optimal duration of the adjuvant treatment. The Scandinavian Sarcoma Group is conducting a randomised trial comparing 1 and 3 years of adjuvant Glivec.

Sponsors and collaborators	CTC Number	Phase	Treatment Duration	Risk Population	Primary Endpoint	Status	N	Start date
American College of Surgeons (ACOSOG), NCI, CALGB, SWOG.	NCT0004 1197	III Glivec vs Placebo	1 year	All KIT + GIST > 3 cms	RFS	ongoing, not recruiting	732	June 2002
EORTC, Australasian Gastro-Intestinal Trials Group, Italian Sarcoma Group Federation Nationale des Centres de Lutte Contre le Cancer Grupo Espanol de Investigacion en Sarcomas	NCT0010 3168	III, Glivec vs Placebo	2 years	Intermediate and High risk GIST	Overall survival	Ongoing, recruiting	752	December 2004
Scandinavian Sarcoma Group	NCT0011 6935	III Glivec Short vs long	1 vs 3 years	High risk GIST	RFS	recruiting	400	February 2004

Pivotal study

The indication is supported by one pivotal phase III trial, ACOSOG Z9001/ BUS89: "A phase III randomized double-blind study of adjuvant STI571 (GleevecTM) versus placebo in patients following the resection of primary gastrointestinal stromal tumor (GIST)" conducted in the US. This trial was stopped early, and unblinded. Results were presented in 2007 in the American Society of Clinical Oncology Annual Meeting (De Matteo R, Abstract 10079A).

Following resection of primary GIST, patients were randomized to one of the two arms: imatinib at 400 mg/day or matching placebo for one year. This randomization was stratified according to tumor size (≥ 3 and < 6 cm, ≥ 6 and < 10 cm, ≥ 10 cm).

Upon recurrence, patients were to be unblinded: (i) In the imatinib arm, if the disease recurred during the year of initial treatment, the imatinib dose was to be increased to 800 mg/day. If the disease recurred after the year of initial treatment, the drug was to be restarted at 400 mg/day and could be increased to 800 mg/day, and (ii) in the placebo arm, if the disease recurred at any time, imatinib was started at 400 mg/day and could be increased to 800 mg/day.

Due to the third efficacy interim analysis (IA) results, the data monitoring committee recommended discontinuation of placebo-controlled randomization in April 2007. All patients registered between 12/04/2007 and 18/042007 received imatinib. Accrual was discontinued permanently on 18/04/2007. Patients receiving placebo as of 01/04/2006 and those randomized to placebo between that date and 12/04/2007 were eligible to crossover to one year of imatinib upon unblinding of the study.

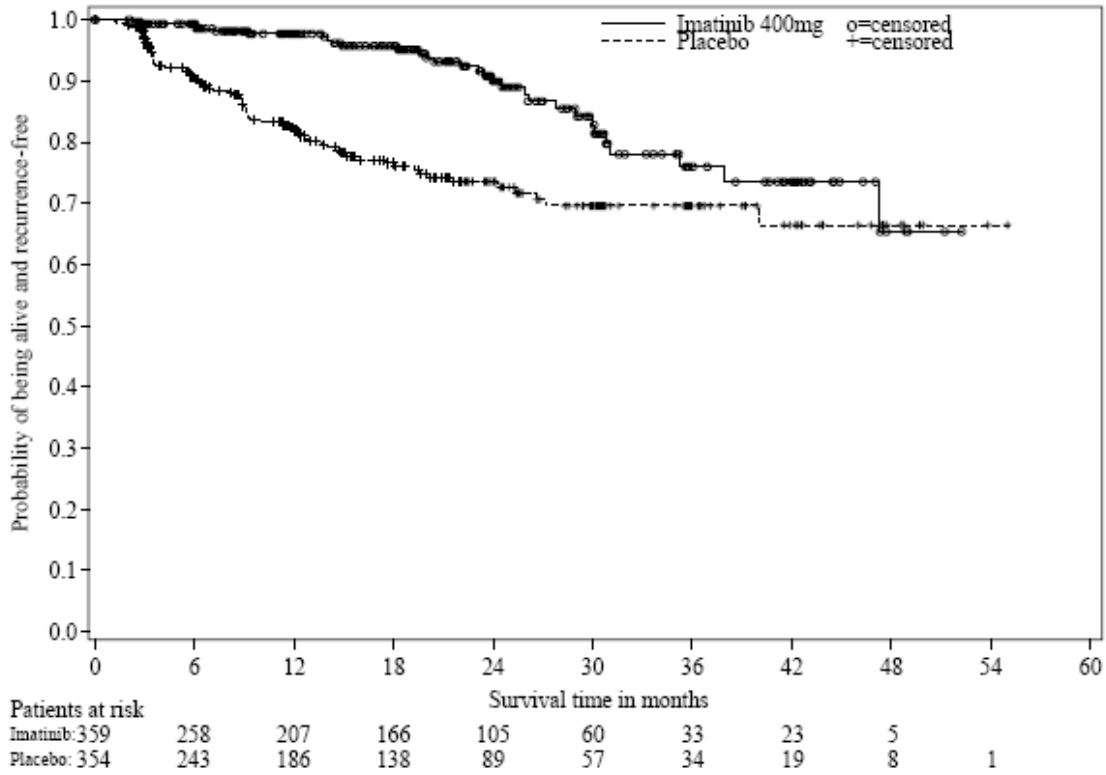
The original primary endpoint was overall survival. The original Protocol envisaged 380 eligible patients being recruited providing 90% power to detect a 35% lower hazard rate of OS at approximately 6.8 years after the start of the study, based on an overall one sided α level of 0.05.

Following a protocol amendment in July 2005 (Protocol version A4), the primary endpoint was changed from OS to RFS and the sample size section changed accordingly. Under the new design, 732 eligible patients (803 patients in total including 60 patients with forced randomization to placebo and 11 patients allocated to treatment using an unbalanced randomization scheme) were to be recruited to provide 90% power to detect a HR of 0.714 at 7.36 years (or 387 events), based on a one-sided α level of 0.025. Accrual of patients into the study continued until 18-Apr-2007; however, after unblinding on 12-Apr-2007 patients were only assigned to the imatinib arm.
In total, 773 patients were registered. Sixty patients were wrongly assigned, and 713 patients were randomised to study treatment (ITT population). 367 (51.4%) completed the study protocol, while 315 (44.2%) did not.

2. 2. Clinical Efficacy

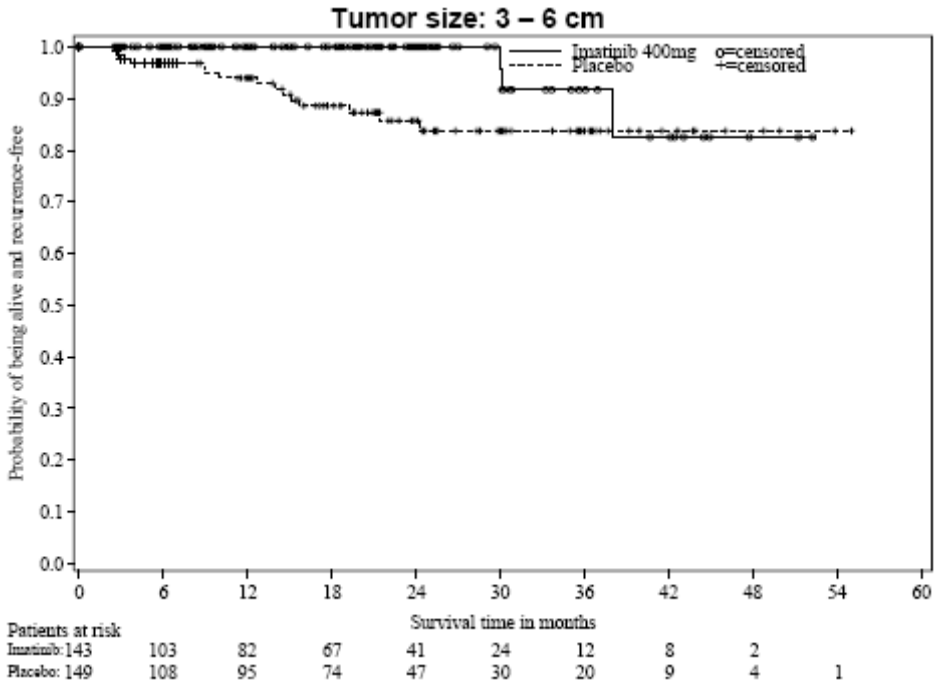
Median RFS follow-up time for the ITT population was 14.0 months. There is a significant overall difference in RFS probability estimate by first documented recurrence in favour of the imatinib group (two-sided p-value < 0.0001 compared with a two sided p-value significance boundary of 0.002). The difference is observed as early as 6 months (99.3% vs. 90.7%), continues through to the end of the treatment period at 12 months (97.7% vs. 82.3%) and remains large up to 30 months (84.2% vs. 69.6%) before decreasing progressively.

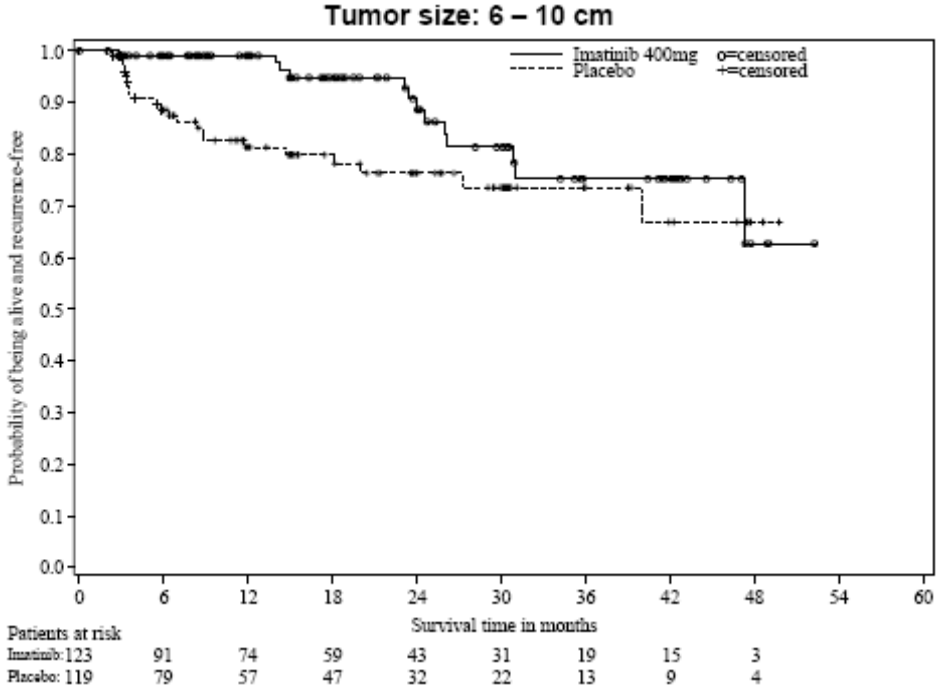
Figure 11-2 Kaplan-Meier estimate of Recurrence-Free Survival (ITT population)

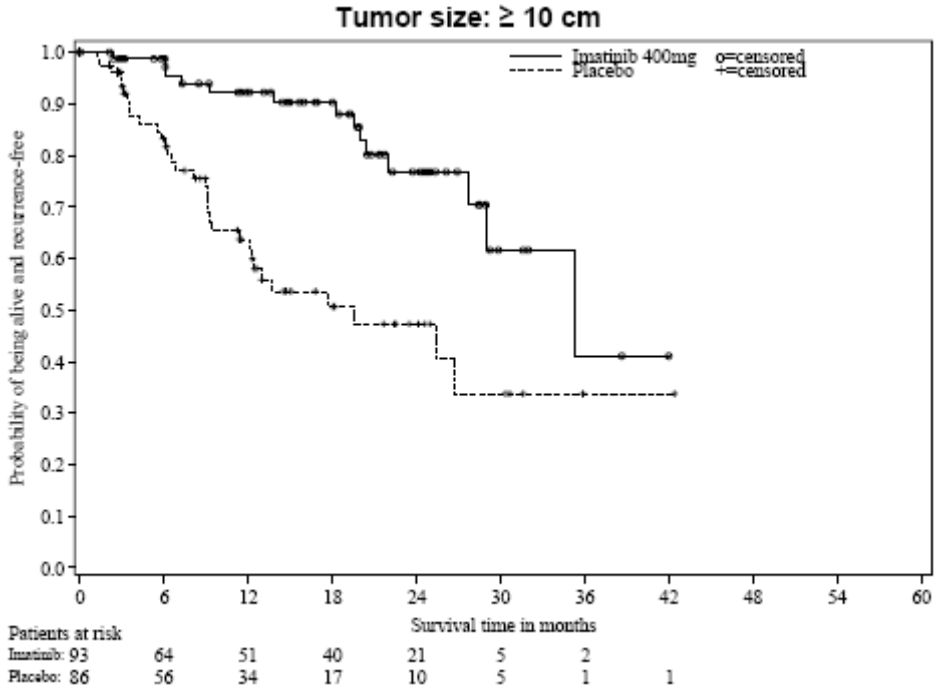


There were 30 patients with events in the imatinib group (8.4%) compared to 70 patients with events in the placebo group (19.8%). Of the 30 patients with events in the imatinib group, 25 patients recurred and 5 died of causes other than GIST without prior recurrence. Of the 25 patients who recurred in the imatinib group according to medical review only 2 recurred while on treatment or within 30 days following last dose; all others recurred more than 30 days following withdrawal from treatment. In contrast, of the 70 patients with events in the placebo group, 62 patients recurred and remained alive at cut-off, 7 patients recurred and subsequently died, and one died without prior recurrence. Of the 69 patients who recurred according to medical review, 50 recurred while on treatment.

The study was stratified by tumor size. There is consistent treatment effect in favour of imatinib for all tumor size categories. The treatment effect estimates were significant for the smallest tumour size (HR=0.228, 95% CI: 0.066, 0.787, p= 0.0105), the medium tumor size (HR=0.496, 95% CI: 0.250, 0.987; p=0.0415) and the highest tumour size (HR= 0.296, 95% CI: 0.157, 0.556; p <.0001).


Tumor size: 3 – 6 cm
Imatinib 400mg o=censored
Placebo +=censored
Probability of being alive and recurrence-free
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 6 12 18 24 30 36 42 48 54 60
Survival time in months
Patients at risk
Imatinib: 143 103 82 67 41 24 12 8 2
Placebo: 149 108 95 74 47 30 20 9 4 1

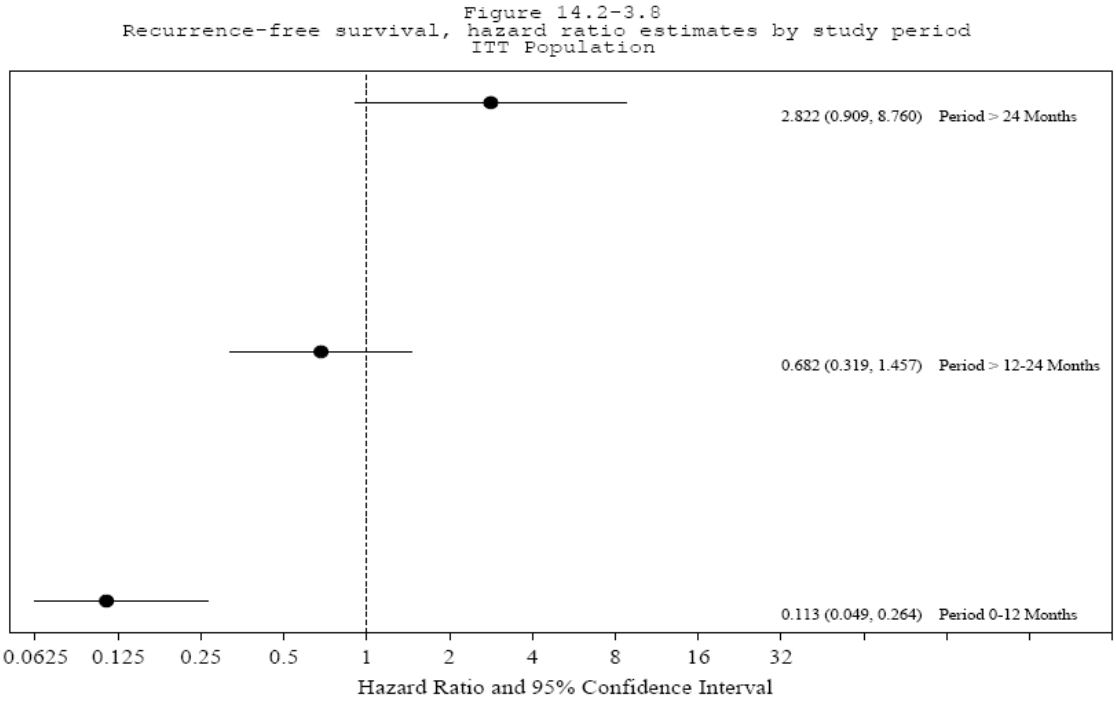

Tumor size: 6 – 10 cm
Imatinib 400mg o=censored
Placebo +=censored
Probability of being alive and recurrence-free
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 6 12 18 24 30 36 42 48 54 60
Survival time in months
Patients at risk
Imatinib: 123 91 74 59 43 31 19 15 3
Placebo: 119 79 57 47 32 22 13 9 4



Other treatment analyses have been also performed**.** The study was not powered to detect a difference in individual subgroups and no adjustments for multiplicity were implemented. Treatment effect is consistent across the different subgroups. In the reported analysis there are some subgroups for which the HR 95% CI does include 1. These subgroups are: location other than stomach, age group > 70, and race other than white. In all of these groups there is a HR tendency in favour of imatinib.

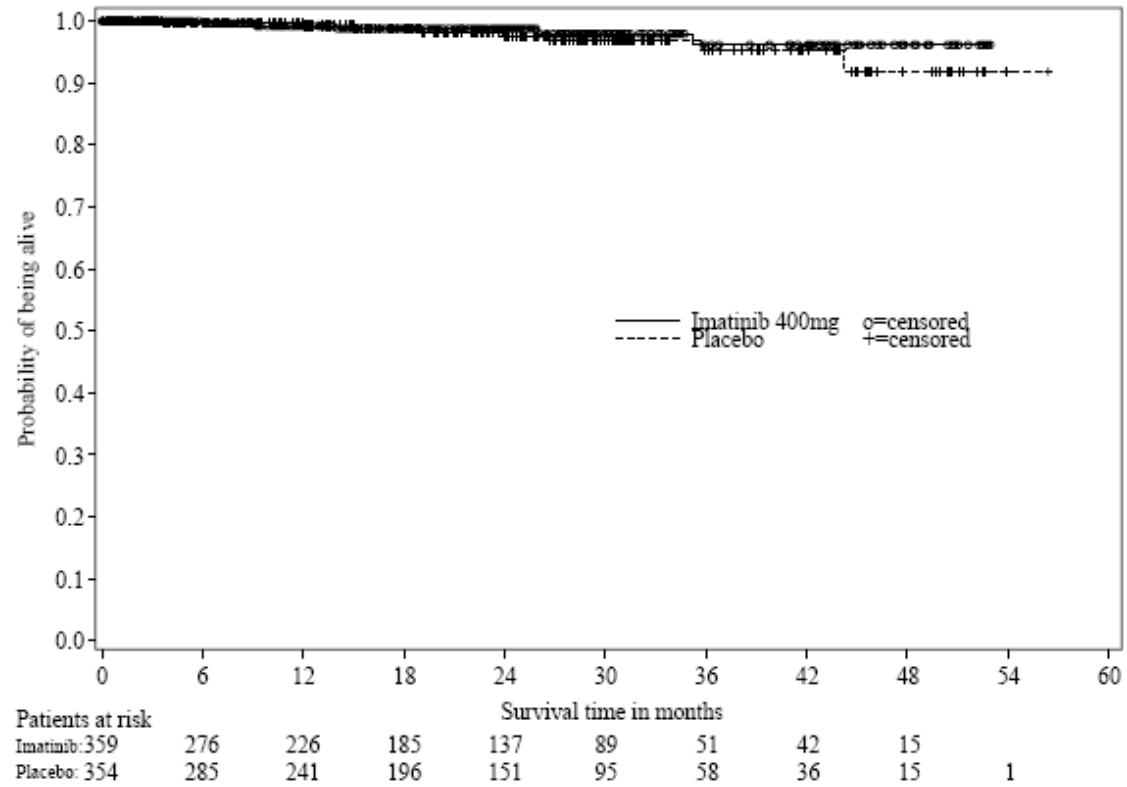
The treatment for patients with stomach tumours are highly in favour of imatinib (HR=0.285, 95% CI: 0.154, 0.527) while the treatment group difference for patients with other sites of tumor is not statistically significant, whilst shows a favorable tendency in favour of imatinib (HR=0.579, 95% CI: 0.309, 1.086; p=0.0845).

The overall HR for the full study period is large and statistically significant. However there is a high variation on recurrence rate along time between both arms. During the first 12 months there were only 6 events out of 359 patients (1.67%) on imatinib compared with 51 events out of 354 patients (14.41%) observed on placebo (HR= 0.113, 95% CI 0.049, 0.264; p<0.0001). Whilst there is a clear benefit regarding RFS in favour of imatinib during the first 12 months, this benefit decreases over time. During the second year (12-24 months) there is no clear benefit, with an equivalent rate of events, with 12 events out of 198 patients (6.06 %) on imatinib and 15 events out of 173 patients (8.67 %) on placebo (HR=0.682, 95% CI: 0.319, 1.457; p= 0.3235). After the second year (>24 months) there is a strong statistical tendency favouring placebo, accounting 12 events out of 93 (12.90 %) on imatinib and 4 events out of 82 (4.88 %) on placebo (HR= 2.822, 95% CI: 0.909, 8.760; p-= 0.0726). This finding suggests that the greatest effect of imatinib is seen while on treatment up to one year following randomisation. The difference between the groups then decreases over time, even an inverse benefit is observed. This data should be taken with caution, since only 175 patients, 93 on imatinib and 82 on placebo, have a follow up longer than 24 months, and after this period the benefit observed for imatinib during the first year appears to be inverted. A further number of patients with longer follow up could probably reduce the magnitude of the observed benefit.



There was no difference on overall survival (OS) (HR=0.663, 95% CI 0.217, 2.028; p= 0.468). The survival data is immature and, due to the unblinding of the study and the cross over possibility, it is improbable that any benefit could be shown, even if it would be present. Eight deaths were recorded on the placebo group, 5 due to GIST, and 5 deaths were recorded on Imatinib, none recorded as being due to GIST. These results can not lead us to drive any definitive conclusion, since there are very few events and median follow up is no longer enough.

Figure 11-6 Kaplan-Meier estimates of Overall Survival (ITT population)



Tumor tissue, blood specimens and serum specimens were collected. Correlative science analyses have not been reported at this moment.

2. 3. Clinical Safety

Overall safety of Glivec in resected GIST is similar to the reported in advanced GIST, with no unexpected AE.

Despite AE were common in both arms, severe adverse events were observed in 30.9% of patients on Imatinib, and in 18% on placebo. Most severe AE (grades 3 or higher) were neutrophils count decrease or gastrointestinal, and were manageable with conservative treatment. Most toxicities appears during the first 3 months, and treatment during 1 year appears acceptable.

No GIST related deaths were reported in the imatinib group. However, two patients died of other cancers during the follow-up period (lung cancer and rectal cancer). The cancer More patients discontinued treatment on Imatinib (17%) than on placebo (3%) as it was expected. Deaths were similar in both arms. Additional information concerning the two patients who died of other cancers during the follow-up period, and more details on the 20 cases of neoplasms, were provided.

2. 4. Supplementary Information provided at the request of the CHMP

As part of the responses to the CHMP request for supplementary information the MAH provided:

- Data on the efficacy of Glivec at relapse from 23 out of 25 patients relapsed in the Glivec arm in Z9001 study and from 21 selected patients reported by European investigators. In both groups median PFS was longer than 18 months. These data suggest that Glivec continues to be a good option at relapse, with prolonged disease control in most patients. However the available data is currently scarce, the quality of responses is not available and definitive conclusions cannot be drawn. Lower efficacy of Glivec at relapse cannot be excluded and this issue should be further studied.
- A committment to provide during 2009 additional data related to prognostic factors other than size: mitotic index, location and mutational status. These data was considered important to stratify according to currently accepted risk subgroups.
- the limited experience available on dose escalation to Glivec 800. Only three patients from the ACOSOG trial and 1 patient from the European Investigators report had been treated with Glivec 800 mg.

As the CHMP was concerned that the approval of Glivec in this indication could compromise ongoing research, the MAH contacted the responsible of the two other ongoing adjuvant trials in kit-positive resected GIST. Both trials, the EORTC and the SSGXVIII/AIO, had closed accrual in October 2008, and responsible from both trials found highly unlikely that the availability of Glivec in the adjuvant setting would compromise the trials development.

In December 2008 the CHMP considered Glivec not approvable for the whole population in the indication claimed by the Applicant, but the acceptability of an indication restricted to high risk resected GIST could be considered. With this aim, the MAH was asked to provide more information and prior to the final CHMP discussion, consultation with the SAG was proposed.

Therefore the MAH revised the claimed indication to: *Glivec is indicated for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. The risk of relapse should be assessed by the treating physician based on tumors size, mitotic index , location of the primary tumor and other prognostic factors. Currently there is insufficient data to support the use of Glivec in the adjuvant setting of GIST in patients who have a low risk of recurrence after surgery*

2. 5. Overall Discussion

The discussion focused on the extent that the data from the pivotal study could allow a straightforward identification of patients at high risk of relapse that might benefit from Glivec adjuvant therapy and the possibility to extrapolate this patient population to the currently used criteria for risk categorization in clinical practise.

The MAH has provided additional information on mitotic index (MI) from banked tissue samples in the Z9001 trial. MI from 556 out of 713 (78%) ITT patients are available. The MI population includes 72% of the events. As reported by the MAH, the MI were performed by pathologist blinded to the clinical information and no selection bias is apparent when compared by tumor size, location, treatment exposure duration or events distribution. Re-analysis according to the NIH and the AFIP criteria based on the population with available MI is provided. The tumor size is not available in the data set and a modification of the NIH and AFIP criteria, including the size stratification designed in the trial, was applied.

According to the NIH modified criteria, the RFS improvement is limited to the high risk group (HR 0.29; 95% CI 0.18-0.49). This benefit is not confirmed in the intermediate (HR 0.59; 95% CI: 0.17-2.10) or low risk population (NE). Applying the modified AFIP criteria, which also includes tumor site, there is a statistically significant RFS improvement in both high (HR: 0.27; 95%CI 0.15-0.48) and moderate (HR:0.16; 95% CI: 0.03-0.70) risk groups. This benefit is not observed in the low (NE) and the very low (NE) risk groups. These results reflect a different distribution of events. As it was expected, most of the events are included in the high and intermediate risks groups.

These re-analyses point out that the benefit is mainly limited to the high risk groups. The equal distribution in HR improvement across all studied size groups observed in the original analysis, is not confirmed in the re-analysis according to NIH and AFIP criteria. This could be explained by a redistribution of many small tumors, with high MI and locations at high risk of recurrence, to moderate or high risk groups, and conversely a "downgrading" of many tumors with low MI and in locations at low risk of recurrence, to the AFIP low risk groups (i.e. gastric tumors > 6 cm and low MI).

The NNT in the AFIP criteria high risk group is 3.4 (2.3 at 12 months and 2.6 at 24 months) and in the moderate risk group is 7.4 (14.1 at 12 months, and 4.1 at 24 months). The estimated NNH, defined harm as discontinuations due to AE in the trial, was 7.3.

Despite these re-analyses could be subject to many methodological criticisms, the information provided could be more easily exported to the current population, and fits better with the risk of recurrence of each group.

The knowledge related to risk stratification is continuously evolving, and new stratification criteria including mutational status are expected in the forthcoming years. Mutational analyses has not been provided at this moment, but the company should commit to provide these results when available.

In conclusion, with the provided information, this analyses observe an improvement in the RFS in the high and moderate risk groups in the AFIP classification. However due to the brief available follow-up, many issues remain to be solved: Does this benefit in RFS translates into an improvement in OS?, does Glivec retain the same activity at relapse?, how long should treatment be taken 1, 2 or 3 years..?.

For these reasons, patients at high risk of relapse might benefit from this treatment. However further follow-up and OS data should be carefully assessed. The proposed indication is directed to high risk Kit-positive resected GIST. More data are needed in moderate risk tumors, and no benefit is apparent in the low risk group.

A detailed plan for the provision of additional data (and nature of the expected analysis) allowing a further characterization of patients at high risk of relapse according to currently used criteria and how the relationship of this risk categorization with patient outcome will be assessed.

The MAH commits to provide follow-up information from the Z9001 trial at scheduled time points in November 2010 and November 2011. This last report will have a median follow up of 5 years, which will bring more information related to quality of the RFS improvement and overall survival.

Additionally, reports from the SSG XVIII/AIO, comparing 1 versus 3 years of treatment in high risk tumors, will be also provided by November 2011. Results from the EORTC study 62024, with OS as the primary endpoint in moderate and high risk groups, will also be provided when available (event pending).

The company also commits to provide information on the mutational status of the enrolled patients and future risk classifications.

A revised Risk Minimization Plan for Glivec is to be submitted post-approval with the objective of the RMP is to ensure that the use of Glivec will be effectively restricted to patients who have a high risk of relapse of their GIST after surgery. Evaluation of the effectiveness of this RM plan is planned.

2.6. Discussion at the SAG- Oncology meeting of 6 March 2009

As a general comment, the SAG noted that a major shortcoming of the clinical data presented was that no mutational data from the study was presented so that important prognostic factor for response and survival could not be taken into account. Absence of such information is difficult to justify since mutational status can be established from paraffin material (although sometimes complicated).

Question 1: Does the SAG believe that the submitted data are mature enough to allow a reliable assessment on the effect of Glivec on RFS?

In the pivotal clinical study Z9001, Glivec was administered for one year. The SAG agreed that this should be reflected in the prescribing information and that the optimal treatment duration with Glivec is not known. Clinical trials are ongoing to address this important issue.

The SAG unanimously agreed that the follow-up was very short and that more mature data would have been preferable for a reliable assessment of efficacy and in particular any impact of treatment on overall survival. An updated analysis of efficacy with additional follow-up since the last updated should be presented.

The SAG agreed that the data submitted establish that imatinib has a clear effect on delaying recurrence. However, no effect on the proportion of patients that eventually recur within 4-5 years was observed. Furthermore, no effect on overall survival was observed based on the available data.

The SAG debated whether a delay of recurrence, in the absence of an effect on proportion of patients that eventually recur or overall survival, constitutes a clinical benefit.

- The majority of the SAG agreed that delaying recurrence by some years in the proportion of patients expected to recur represents a significant clinical benefit. According to this view, it is reasonable to assume that use of imatinib to delay recurrence should not adversely affect the outcome of further therapies in patients who eventually recur and who will require additional treatments.
- According to a minority view, it is important to consider that the majority of patients are cured by surgery alone and would be treated unnecessarily with imatinib. Besides the burden to patients of unnecessary treatment, an additional concern is the possibility that adjuvant use of imatinib may induce resistance to further treatments and further limit the available treatment options after recurrence. According to this view, benefits or at least a lack of a detrimental effect in terms of overall survival would have to be established in order to address these concerns. At the end of the observation period there was no clear difference in RFS, and in the absence of a clear effect on recurrence prevention (as opposed to just delaying recurrence), no effect on overall survival is expected.

Question 2: Does the SAG consider RFS in this clinical context equally relevant for all risk groups (i.e. high, intermediate and low risk groups)?

The risk of death in low-risk patients is close to that of the normal population. Given the unknown impact on the overall outcome of adjuvant treatment with imatinib, the SAG agreed that adjuvant treatment with imatinib should not be indicated for low-risk patients. The NIH classification can be considered an acceptable classification system to identify low-risk patients, until more reliable systems based on molecular markers have become established.

Question 3: Does the SAG consider that from study Z9001a subgroup of patients at high risk of relapse could get particular benefit of adjuvant therapy with Glivec? Is this subgroup easily extrapolable to current practice, where additional risk characterization criteria other than tumor size are used?

The SAG unanimously agreed that adjuvant treatment with imatinib is not indicated in low-risk patients. Concerning the higher risk groups, the SAG agreed that high risk patients were no more or less likely to benefit as intermediate risk patients.

The NIH classification can be considered an acceptable classification in clinical practice to stratify patients into risk groups, until more reliable systems based on molecular markers have become established.

3. Overall Conclusion and Benefit –Risk Assessment

In conclusion, The Z90001 trial is the first study in adjuvant kit-positive resected GIST, and is the only phase 3 trial that include all tumours higher than 3 cms. This study shows an improvement in RFS (HR= 0.3989, 95%CI 0.259-0.610; $p<0.0001$) with Glivec 400 mg for 1 year in >3 cms resected KIT-positive GIST. The trial is stratified according to the size and the relative benefit is observed in all size groups. However, this result comes from an early stopped study, with brief median follow up (14 months) that has yield immature data and has raised important questions.

The data are immature to study overall survival, and more mature results from this and others trials will take several years to become available. Additionally, the surrogate value of RFS for OS in GIST has not been studied to date, and no definitive conclusions can be drawn at this moment.

The results are time dependent. Despite the results are highly statistically significant at 12 months, after stopping Glivec this effect is diluted, and there is an increase in the relapse rate at 24 months, suggesting a delay, rather than an avoidance, of several recurrences. Whether this delay will finally translate into a benefit in overall survival is still a matter of debate, and cannot be assumed from the data provided.

The available data on the efficacy of Glivec at relapse after adjuvant treatment are very limited. The applicant was asked to provide the available efficacy results of Glivec at relapse in patients previously treated with the adjuvant treatment. The MAH has provided data on the efficacy of Glivec at relapse from 23 out of 25 patients relapsed in the Glivec arm in Z9001 study and from 21 selected patients reported by European investigators. In both groups median PFS is longer than 18 months. This data suggest that Glivec continues to be active at relapse, with prolonged disease control in most patients. However the data are currently scarce, the quality of responses is not available and definitive conclusions cannot be drawn. Lower efficacy of Glivec at relapse cannot be excluded and this issue should be further studied.

The original data provided from the Z9001 trial may be difficult to extrapolate to the current treatment of GIST, since it has been stratified according to size, and current classifications and the two ongoing phase 3 trials in resected GISTs incorporate other factors: mitotic count, location and recently mutational status. The MAH has provide the mitotic index in 78% of patients and 72% of the events, and the data has been re-analyzed according to the NIH and the AFIP criteria. In these re-analyzes the RFS improvement is limited to the high risk group in the NIH criteria and to the moderate and high risk group in the AFIP criteria analysis. New risk criteria including mutational status are warranted, and the company has committed to provide mutational results when available. The currently available data make recommendations more easily exportable. No benefit has been demonstrated in the low risk

group, and no other ongoing trials include this group. The NNT in the AFIP criteria high risk group is 3.4 (2.3 at 12 months and 2.6 at 24 months) and in the moderate risk group is 7.4 (14.1 at 12 months, and 4.1 at 24 months), conversely the estimated NNH, defined harm as discontinuations due to AE in the trial, was 7.3 for the treated population. Further data is needed in the moderate risk group to accept a benefit.

The two other adjuvant trials in resected GIST, the EORTC and SSGXVIII/AIO trials, are currently ongoing, and have recently closed accrual. The MAH has contacted with the responsible of the ongoing trials, and they find highly unlikely that the availability of Glivec in the adjuvant setting would compromise the trials development. These trials could potentially bring important answers, like overall survival results, and the optimal duration of Glivec.

The surrogate value of RFS in this disease and with this treatment cannot be directly accepted and OS data should be revised when available. However, an improvement in RFS of such magnitude in a group at intermediate or high risk of relapse, could be of benefit for some patients even if this does not translate into a survival increase.

Taking into account that Glivec appears to retain activity at relapse in most patients with conventional doses (400 mg), the acceptable safety profile of the treatment and that survival data will take several years to become available, it appears reasonable to consider whether, in high risk treatment with Glivec as adjuvant therapy could be approvable. The overall benefit/risk conclusion for the new claimed indication for: "the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST" is positive.
Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.

This evaluation will definitively require further follow up at scheduled time points and the inclusion of accepted prognostic factors like mutational status when available. The RMP should be further revised in order to make sure that the target population is appropriately treated.

Risk Management Plan

A summary of the important identified risks and proposed Pharmacovigilance actions and risk minimization activities is presented in table 5.

Safety concern	**Proposed Pharmacovigilance activities (Routine and additional)**	**Proposed Risk minimization activities (Risk and additional)**
Myelosuppression	Monitoring of laboratory data for ongoing clinical trials All other routine PhV activities	Labelled in SPC section 4.2 Posology and Method of Administration 4.4. Special Warnings and precautions for use 5.3 Preclinical data 4.8 Undesirable Effects
Oedema and fluid retention	routine PhV activities	Labelled in SPC section 4.4. Special Warnings and precautions for use 4.8 Undesirable Effects
GI and CNS haemorrhage	Monitoring of laboratory data for ongoing clinical trials All other routine PhV activities	Labelled in SPC section 4.4. Special Warnings and precautions for use 4.8 Undesirable Effects
GI ulceration, perforation and obstruction	Routine PhV activities	Labelled in SPC section 4.4. Special Warnings and precautions for use 4.8 Undesirable Effects
Hepatotoxicity	Monitoring of laboratory data for ongoing clinical trials All other routine PhV activities	Labelled in SPC section 4.2 Posology and Method of Administration

		4.4. Special Warnings and precautions for use 5.1 Pharmacodynamic properties 5.2 Pharmacokinetic Properties 4.8 Undesirable Effects
Skin Rashes and severe cutaneous reactions	routine PhV activities	Relevant preferred terms are labelled in SPC section 4.8 Undesirable Effects
Hypothyroidism	Thyroid hormone level measurements in patients without a thyroid history are included in ongoing and planned mechanistic studies All other routine PhV activities	Labelled in SPC section 4.4. Special Warnings and precautions for use 4.8 Undesirable Effects
Hypophosphataemia	Ongoing and planned mechanistic studies All other routine pharmacovigilance activities	Relevant preferred terms are labelled in SPC section 4.8 Undesirable Effects
Cardiac Failure	Subclinical LVD monitored by 2D echocardiography in the nilotinib studies with imatinib as active comparator All other routine pharmacovigilance activities	Labelled in SPC section 4.4. Special Warnings and precautions for use 4.8 Undesirable Effects
Renal Failure	Routine pharmacovigilance activities	Labelled in SPC section 4.2 Posology and Method of Administration 4.4. Special Warnings and precautions for use 5.2 Pharmacokinetic Properties 4.8 Undesirable Effects
Acute Respiratory Failure, Pulmonary Hypertension and Pulmonary Fibrosis	Routine pharmacovigilance activities	Relevant preferred terms are labelled in SPC section 4.8 Undesirable Effects
Second Malignancies in Survivors	Extnded data collection up to 8 years in designated registration study Regular Annual Review of age-adjusted standardised incidence ratios from registration studies All other routine pharmacovigilance activities	Labelled in SPC section 5.3 Preclinical safety data
Disseminated intravascular coagulation	Routine pharmacovigilance activities	No risk minimization activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should the PhV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimization activities may be proposed if necessary.
Hypoglycaemia	Monitoring of laboratory data for ongoing clinical trials All other routine PhV activities	Relevant preferred terms are labelled in SPC section 4.8 Undesirable Effects

Suicidality	Routine PhV activities	No risk minimization activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should the PhV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimization activities may be proposed if necessary.
Tolerability during Pregnancy and Pregnancy outcomes	Pregnancy Registry for imatinib and nilotinib All other routine pharmacovigilance activities	Labelled in SPC section 4.6 Pregnancy and Lactation and 5.3 Preclinical safety
Rhabdomyolysis and myopathy	Routine PhV activities	No risk minimization activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should the PhV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimization activities may be proposed if necessary.
Ovarian haemorrhage and haemorrhagic ovarian cyst	Routine pharmacovigilance activities	Relevant preferred terms are labelled in SPC section 4.8 Undesirable Effects

The MAH commits to provide to submit a revised Risk Minimization Plan for Glivec. The objective is to ensure that the use of Glivec will be effectively restricted to patients who have a high risk of relapse of their GIST after surgery. Evaluation of the effectiveness of this plan is planned.

4. CONCLUSION

On 19 March 2009 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 Annex II.

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]
Non-clinical	The MAH should present the study OECD 219 sediment-dwelling organism, as requested	April 2009
Clinical	The MAH commits to submit the mutational data from ACOSOG-Z9001 study	June 2010
Clinical	Novartis commits to submit a study report on follow-up of the ASCOSOG-Z9001 study based on data cut-off date of March 15, 2010.	November 2010
Clinical	Novartis commits to submit a study report on follow-up of the ASCOSOG-Z9001 study based on data cut-off date of March 15,	November 2011

	2011.	
Clinical	Novartis commits to submit a study report of the European study, SSG XVIII/AIO. This study is a randomized Phase III trial that examines one year versus three years of imatinib therapy 400 mg/day in adjuvant GIST patients with a high risk of recurrence.	November 2011
Clinical	Novartis commits to submit manuscripts of the European study, EORTC Study 62024. This study is an open-label, multicenter, phase III trial comparing adjuvant therapy with imatinib 400 mg/day for 2 years vs. no treatment in patients with KIT(CD117)+ intermediate or high risk GIST following complete resection.	Reporting is expected 2015 at the earliest.
PhV	The MAH commits to submit a revised RMP	April 2009

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.