Scientific discussion

1. Introduction:

Glivec is currently authorised for Ph+ CML and GIST in the European Union. This is an extension of the currently approved Glivec indications to include the following new orphan indication: "Treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy and of adult patients with relapsed or refractory Ph+ ALL as monotherapy".
The proposed dose of Glivec for patient with Ph+ ALL is 600 mg/day.

Acute lymphoblastic leukaemia is a heterogeneous disease with distinct biologic and prognostic groups, consisting of a wide variety of genetic lesions, including translocations, hyperdiploidy and even normal appearing genotypes. ALL represents 20% of adult acute leukaemias. About 10,000 patients with Acute Lymphoblastic Leukaemia (ALL) are diagnosed annually in adults in Europe, where the annual incidence rates were 1.3 per 100, 000 in men and 0.9 in women. ALL has a bimodal distribution. The incidence is 4-5 per 100,000 population between the age of 2-4, which decreases during later childhood, adolescence, and young adulthood before a second, smaller peak occurs in patients older than 50 years (incidence 1 per 100,000 population). Philadelphia chromosome-positive ALL occurs in 5% to 10% of paediatric cases and in approximately 25% of adult cases. It is the most common genetic abnormality and represents an independent adverse risk factor.

Ph^+ ALL results from a reciprocal translocation between chromosomes 9 and 22, t(9;22) (q34;q11), which results in the p210 BCR/ABL fusion protein when it involves the major breakpoint cluster region or the p190 fusion protein when it involves the minor breakpoint cluster region. Among patients with Ph+ALL, approximately 70% of adults and more than 90% of children have the p190 protein. The BCR-ABL fusion protein is a constitutive active protein kinase that alters signaling pathways that control the proliferation, survival, and self-renewal of hematopoietic stem cells. Because the kinase activity of BCR/ABL is causally involved in the leukaemic transformation in Ph^+ ALL, targeted suppression of its activity by imatinib was considered as a potential therapy against the pathophysiologic basis of this disease.

The only potentially curative approach to Ph+ALL is allogeneic stem cell transplantation, especially when compared with chemotherapy plus autologous stem cell transplantation, but it is not a viable option for many patients due to the lack of a suitable donor, to the toxicity related to transplant and to co-morbidities, related or not to age. Overall 3-year survival rate can reach 40% in selected patients.

Conventional cytotoxic chemotherapy, although able to induce a high CR rate, does not eradicate the disease and results in an overall median survival of approximately one year. Chemotherapy for ALL is also associated with a significant mortality, especially in elderly patients. Furthermore, many of these older patients cannot receive the standard ALL chemotherapy because of co-existing morbidity or adverse events that impede chemotherapy completion. Induction death rate can range from 8 to 50%, when the CR rate ranges from 31 to 85% and the median overall survival from 1 to 14 months. Therefore, there is a critical need for an effective therapy with lower toxicity with the potential of inducing and maintaining a minimal residual disease status (complete molecular response) over the long term.

2.Clinical aspects:

Imatinib is a protein-tyrosine kinase inhibitor, which inhibits the Bcr-Abl tyrosine kinase at the in vitro, cellular and in vivo levels. The compound selectively inhibited Bcr-Abl phosphorylation and proliferation of Ph+ ALL cell lines as well as primary leukaemic cells obtained from Ph+ ALL patients. Because the kinase activity of Bcr-Abl is causally involved in leukaemic transformation in Ph+ leukaemias such as Ph+ ALL and Ph+ CML, targeted suppression of its activity by imatinib is considered a useful therapy directed against the pathophysiologic basis of these leukaemias.

Clinical efficacy

The submitted dossier includes clinical efficacy trials performed in two populations of patients, corresponding to the subgroups included in the claimed ALL indication:

- Newly diagnosed Ph+ ALL patients (Previously untreated patients received imatinib in combination with induction and/or consolidation chemotherapy).
- Relapsed and/or refractory Ph+ ALL patients (Patients in first or subsequent relapse after either standard chemotherapy, autologous or allogeneic bone marrow transplantation, or high dose treatment with peripheral blood stem cell support, or patients refractory to standard chemotherapy (no complete remission achieved after two conventional induction chemotherapy cycles). These patients were treated with imatinib as monotherapy or in combination with induction chemotherapy.

No pharmacokinetics studies have been submitted in this variation dossier, but this is considered acceptable by the assessors, as there is not any rationale to suspect a different pharmacokinetic profile in this patient subpopulation.

No dose finding studies have been performed. The currently accepted doses of 400 mg or 600 mg per day have been studied for efficacy in all phase of treatment. The majority of data have been generated at a dose of 600 mg, which is the recommended dose for this indication. In addition, imatinib doses of 800 mg per day have been used in combination with steroids in a small number of patients.

Efficacy and safety data are available for a total of 758 patients. These patients were included in 1 controlled and 9 uncontrolled open-label clinical trials, enrolling a total of 443 patients with relapsed/refractory Ph+ ALL and 315 newly diagnosed patients. A separate age subpopulation analysis was performed in a total of 250 patients ≥55 years old, 146 with relapsed/refractory Ph+ ALL and 104 with newly diagnosed disease.
A summary of the main efficacy studies in Ph+ ALL can be found in the following table:

Study/ Author	Treatment	Purpose	All - N	Elderly -N	Daily dose of imatinib
Studies in newly diagnosed Ph+ ALL/CML-LBC					
ADE10 Ottmann 2005	Imatinib mono-therapy induction plus consolidation including imatinib	Efficacy, Safety	28	28	600 mg
	Chemotherapy induction plus consolidation including imatinib		27	27	600 mg
AFR09 Delannoy 2005	Imatinib post induction therapy combined with steroids	Efficacy, Safety	30	30	600 mg
AIT04 Vignetti 2005	Imatinib induction therapy in combination with steroids	Efficacy, Safety	19	19	800 mg
AAU02 Lickliter 2005	Imatinib combined with chemotherapy	Safety, efficacy	12		600 mg
ADE04 Wassmann 2005	Imatinib combined with chemotherapy	Efficacy, safety	92		400 mg, 600 mg 600 mg (n=12 in cohort 1 and n=45 in cohort 2)
AJP01 Towatari 2004, Yanada 2005	Imatinib combined with chemotherapy	Efficacy, Safety	80		600 mg
AUS01 Thomas 2004a	Imatinib combined with chemotherapy	Efficacy, safety	27		400 mg

Total number of patients			**315**	**104**	
Studies in relapsed/refractory Ph+ ALL/CML-LBC					
03001 Druker 2001	Imatinib mono-therapy induction	Safety, efficacy	20		300 mg to 1000 mg 600 mg (n=2)
0109 Ottmann 2002, Ph+ ALL CSR0109	Imatinib mono-therapy induction	Efficacy, safety,	56	18	400 mg to 600 mg 600 mg (n= 46)
0114 Wassmann 2004 Ph+ ALL CSR0114	Imatinib mono-therapy induction	Safety, efficacy data limited to TTP & overall survival	353	128	600 mg
AAU02 Lickliter 2005	Imatinib combined with chemotherapy	Safety, efficacy	9		600 mg
AUS01 Thomas 2004a	Imatinib combined with chemotherapy	Efficacy, Safety	5		400 mg
Total number of patients			**443**	**146**	
Overall population			**758**	**250**	

Study endpoints include haematological response (complete haematological remission [CHR], no evidence of leukaemia [NEL], return of chronic phase [RTC], haematopoiesis/partial response [PR], marrow response and morphologic response), cytogenetic response, complete molecular remission, duration of complete remission, overall survival, and time to progression, relapse, resistant disease and induction death.

The definitions of criteria used for response were similar among studies and were defined as follows:

- Haematological response (to be confirmed after ≥4 weeks) included any of the following:
  1) Complete haematological remission which required that all of the following were present: bone marrow cellularity and blast count < 5%, no circulating peripheral blood blasts, ANC ≥ 1.5 x 10^9/L, Platelet count ≥ 100 x 10^9/L, and no evidence of extra-medullary involvement
  2) No evidence of leukaemia in peripheral blood and bone marrow, without full peripheral blood recovery required that all of the following were present: blast count < 5%, no circulating peripheral blood blasts, ANC ≥ 1.0 x 10^9/L, platelet count ≥ 20 x 10^9/L (platelet transfusion independent and no evidence of bleeding), and no evidence of extramedullary involvement
  3) Return of chronic phase haematopoiesis/partial response (PR). For a PR, only the first criterion below were to be fulfilled. For a return to chronic phase haematopoiesis, all of the following criteria were to be fulfilled: percentage of peripheral blasts in blood or bone marrow < 15%, percentage of blasts plus promyelocytes in the peripheral blood or bone marrow < 30%, and peripheral basophils < 20%.
  4) Marrow response (marrow-CR) was defined as a decrease in marrow blasts to either no more than 5% or between 5 to 15%, regardless of the peripheral-blood cell counts
  5) Morphologic response was defined as follows: (1) M1, 0% to 5% bone marrow blast cells; (2) M2, more than 5% to 25% bone marrow blast cells; or (3) M3, more than 25% bone marrow blast cells.
- Cytogenetic response was defined by the percentage of Ph chromosome positive metaphases in bone marrow and was defined as follows: complete (0% Ph-positive cells); major (1-35%); minor (36-65%); minimal (66-95%); none (96-100%).
- Complete molecular remission was defined by reverse transcriptase polymerase chain reaction (RT-PCR) negativity in addition to haematological criteria for complete haematological remission.

2.1. NEWLY DIAGNOSED PH+ ALL

The design of most of the studies conducted in this population of patients was open and uncontrolled, only one study being open and controlled [Study ADE10] that was performed in elderly population.

Controlled trials – imatinib monotherapy induction in newly diagnosed elderly Ph+ ALL patients

Study Author	Study objective, population	Study design	Efficacy endpoint
ADE10 Wassmann 2003, Ottmann 2004, Ottmann 2005	efficacy/safety of imatinib induction compared to standard induction chemotherapy in elderly Ph+ ALL patients (>55 years)	Open label, randomized, multi-centre, phase II	Haematological remission rate, remission duration, minimal residual disease, relapse rate, DFS, OS

Patients (>55 years) with Ph+ LL were randomized to receive either 28 days of single-agent **imatinib** induction at a daily dose of 600 mg (group I) or induction chemotherapy according to the GMALL elderly protocol 07/02 (group II). Intrathecal CNS-directed prophylactic therapy was allowed during induction but limited to four applications. To determine the anti-leukaemic efficacy, minimal residual disease analysis was performed by quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) assessment of BCR-ABL transcript level in serial peripheral blood and bone marrow samples.

Results

A total of 55 elderly patients (>55 years) with newly diagnosed Ph+ ALL or lymphoid blast crisis from 32 referring centres were enrolled in this study conducted by the German Multi-centre Study for Adult ALL group (GMALL). The median age was 68 years. Twenty-eight patients were enrolled in the imatinib induction arm and twenty-seven in the chemotherapy induction arm. All patients alive after induction received imatinib as part of the chemotherapy consolidation.

Patients were well matched for age, gender, disease type, bcr-abl breakpoint, and WBC and platelet count at diagnosis. However, a complex karyotype was more frequent in the imatinib induction group (42% versus 25%).

Response to induction was significantly superior in the front-line imatinib arm, as compared with chemotherapy induction (p=0.003).

- Twenty-six of the 27 evaluable patients achieved a CR (96.3%) and one patient a PR (3.7%). One patient was not evaluated at this time point but, like the PR patient, achieved a CR after consolidation cycle C1.
- Thirteen (50%) of the 26 evaluable patients enrolled in the induction chemotherapy group achieved CR, two patients achieved a PR (7.7%). Nine patients (34.6%) were refractory and 2 patients died during chemotherapy induction; no patient failed imatinib induction.

Significantly fewer patients in the IND^{chemo} arm (n=6; 23.1%) had recovered their ANC and platelet counts at the end of induction (p=0.008). Seven patients (26.9%) achieved a CRi after IND^{chemo}, a PR was recorded in 2 patients (7.7%). Severe adverse events were significantly more frequent during induction chemotherapy (90% vs. 39%; p=0.005).

Of the 9 patients (34.6%) refractory to chemotherapy, 5 were crossed over to imatinib induction after 2 weeks, while 4 patients received imatinib after completing IND^{chemo}. Nine of the 11 poor responders (9 refractory and 2 PR patients) achieved a CR in response to imatinib, two crossover patients were refractory. Taken together, 100% of patients randomized to IND^{IM} and 85.2% (23/27) of patients randomized to the IND^{chemo} arm achieved a CR, the latter group due to the efficacy of post-induction imatinib as "salvage" therapy in chemotherapy failures.

Molecular response

Prestudy Bcr-abl transcript levels in bone marrow were comparable in the imatinib induction arm (median 1.1 x 10^{-2}) and in the chemotherapy induction arm (median 1.0 x 10^{-2}). During induction

imatinib, bcr-abl transcript levels were significantly lower than during induction chemotherapy after 2 weeks ($2.6x10^{-4}$ versus $2.2x10^{-3}$; p=0.02) and after 4 weeks ($5.6x10^{-5}$ versus $3.2x10^{-3}$; p=0.02).

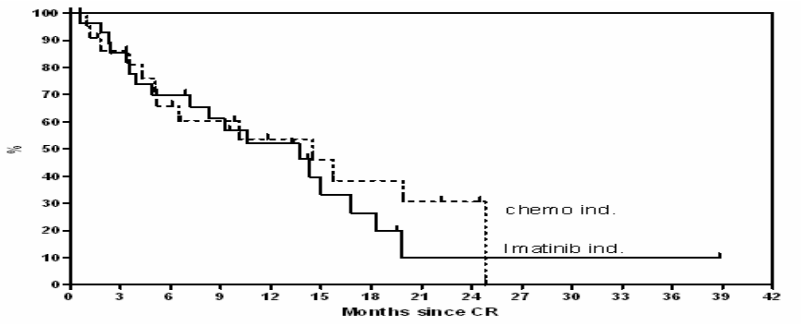
After consolidation, the complete molecular response rates were evenly distributed between patients randomized to the imatinib induction (9 of 26 evaluable, 34.6%) and to chemotherapy induction (8 of 22 evaluable, 36.4%) and appeared to occur earlier in the imatinib induction arm (96 days, range 30-205 days) than in the chemotherapy induction arm (162 days, range 22-248 days) (p=0.187).

Disease- free survival and overall survival

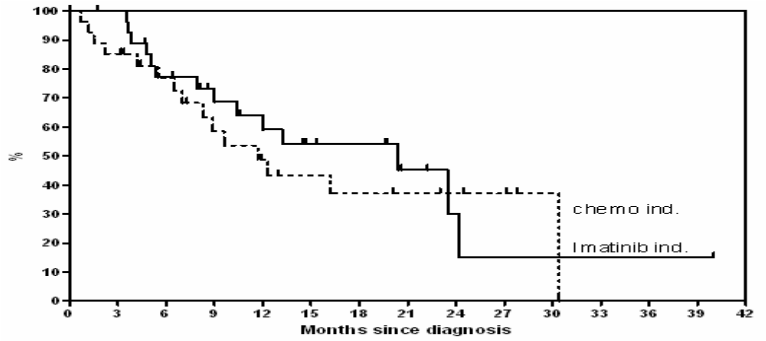
Estimated median remission duration of the whole cohort is 15.7 months, 15 months in the imatinib induction group and the 19.9 months in the INDchemo group (p=0.54). At 12 months, the estimated probabilities of being relapse-free in the two induction groups were 67.5±11% and 70.8±11%, respectively.

At 12, 18 and 24 months, the estimated rates of DFS in the whole cohort were 53.7%, 28.8% and 20.6%, respectively. Corresponding values for OS were 53.8%, 45.3% and 29.4%. The estimated rates of DFS and OS by induction treatment did not differ significantly between the two treatment groups.

Disease free survival by induction type (study ADE10)



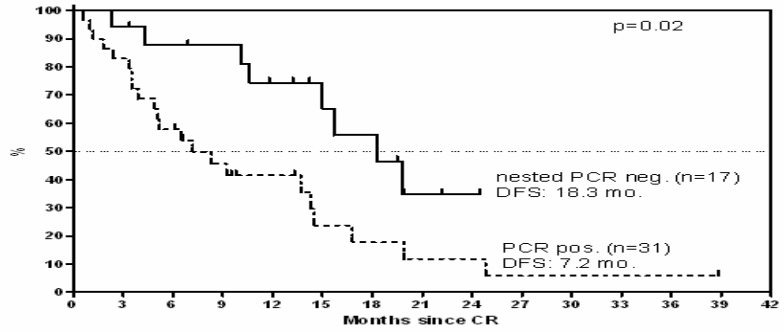
Overall survival by induction type (study ADE10)



A complete molecular response was predictive of a more favourable outcome in terms of remission duration and DFS. Disease-free survival was 18.7 months in patients achieving PCR negativity, as compared to 7.2 months in patients who remained MRD positive (p=0.02). Using the Kaplan-Meier method, the probabilities of DFS in the good and poor molecular responders were 74.3±11.1% and 41.5±9.6% after 12 months and 34.8±14.8% and 11.9±7.6% after 24 months.

Relapse was associated with BCR-ABL mutations in 81% of patients. Molecular analysis at relapse was performed in 16 out of 21 relapsed patients. Of these, 13 patients had at least one bcr-abl mutation and 3 did not. All patients with at least one bcr-abl mutation and one patient without were on treatment with imatinib at the time of relapse.

Disease free survival by MRD response (study ADE10)



Uncontrolled Studies

A total of 211 patients with newly diagnosed Ph+ ALL or CML-LBC were treated with imatinib in combination with induction and/or consolidation chemotherapy in four open label, multi-centre, uncontrolled non-randomized, phase II studies:

- [Study ADE04] Part A, an open label, multi-centre, non-randomized, phase II study to determine the safety and efficacy of imatinib and minimal residual disease after induction therapy
- [Study AAU02], an open label, non-randomized, phase II pilot study of imatinib in combination with induction chemotherapy
- [Study AJP01], an open label, non-randomized, phase II study to evaluate imatinib combined with dose-intensive chemotherapy

- [Study AUS01].a phase II study to assess the efficacy of imatinib combined with intensive hyper-CVAD chemotherapy

Results

The comparison of inclusion and exclusion criteria does not indicate major differences in the population treated. Patients received imatinib in combination with induction and/or consolidation chemotherapy at doses of 400 mg/day (62 patients – 29%) or 600 mg/day (149 patients – 71%). Out of the 211 patients, 207 (98%) were patients with Ph+ ALL.

– Complete haematological response (CHR) rates ranged between 58% and 95%. The lowest response rate was observed in study AAU02. In this study, patients received only 7 days of imatinib as pre-induction treatment. Also, in study ADE04, no difference in response rate was observed between cohort 1 and cohort 2 after induction phase II (94% vs. 95%, respectively), despite earlier administration of imatinib treatment in cohort 2. This could be explained by the different response rates after chemotherapy induction phase I (78% of the patients responded in cohort 1 and only 56% in cohort 2).

– Of note, earlier administration of imatinib resulted in a higher molecular response rate.

[Study AAU02] The authors hypothesized that pre-treatment with imatinib would overcome inherent drug resistance to induction chemotherapy mediated by Bcr-Abl.

Study	Study objective, population	Patients	Dose regimen	Efficacy endpoint
AAU02/ CMLALL1 Lickliter 2005	Efficacy / safety; CML-BC or Ph+ ALL	24 Pre-phase	**imatinib**: 600 mg daily for 7 days Induction therapy: arm 1, arm 2, arm 3 (see below)	haematological + cytogenetic response
Arm 1		CML-MBC: 3	idarubicin 12 mg/m^2 iv days 1-3 + cytarabine 200 mg/m^2 iv days 1-7 + **imatinib** 600 mg days 1-7	
Arm 2		CML-LBC: 2 relapsed Ph+ ALL: 7	as arm 1 + vincristine 2 mg iv days 1, 8, 15, 22 + prednisone 40 mg/m^2 po days 1-28 + **imatinib** 600 mg days 1-7	
Arm 3		de-novo Ph+ ALL: 12	Protocol LALA 94*	

Among 22 evaluable patients, combined imatinib and chemotherapy induction resulted in 14 (64%) complete haematological responses and all but 1 patient achieved a major cytogenetic response. There were 7 (88%) complete haematological responses (CHR) among 9 evaluable patients with CML-LBC and relapsed Ph+ALL and 7 (58%) CHR among 12 de-novo Ph+ ALL.

Major cytogenetic responses were seen in all newly diagnosed Ph+ ALL patients enrolled in the study. No molecular response was assessed in this study.

The in-vivo inhibition of Bcr-Abl by imatinib was monitored in leukaemic cells during the imatinib-only prephase using Western blot analysis of CrkL phosphorylation status. Marked dephosphorylation of CrkL was observed in peripheral blood and/or marrow in all but 1 of 8 evaluable cases. Imatinib potently inhibited Bcr-Abl activity in vivo in Ph+ acute leukaemic blasts and its combination with induction chemotherapy was tolerable.

Neutrophils recovered to $\geq 1.0 \times 10^9$/L at a median of day 24 of induction chemotherapy, with only 1 patient showing delayed recovery (> day 42). There was 1 induction death on day 18 from overwhelming sepsis and multi-organ failure. No unexpected non-haematological toxicities were observed.

The one-year overall survival rate was 61.1 ± 13.5 %.

[Study AUS01] was designed to determine the clinical efficacy (overall response rate, event-free survival, and survival) and safety of the intensive hyper-CVAD regimen given in combination with imatinib. The molecular response rate and duration were also evaluated.

Therapy was given with 8 induction-consolidation courses alternating hyper-CVAD with high dose MTX and ara-C, concurrently with 400 mg **imatinib** mesylate daily on days 1 to 14. Higher doses of imatinib were given during the consolidation phase owing to the known dose-response phenomenon observed in the studies of imatinib in CML and the absence of concurrent myelosuppressive therapy.

Study	Study objective, population	Patients	Dose regimen	Efficacy endpoint
AUS01 Thomas 2004a, Thomas 2004b	imatinib + intensive hyper-CVAD chemo-therapy Ph+ ALL	32	hyper-CVAD regimen cyclophosphamide 300mg/m^2 on days 1-3; vincristine 2mg day 4 and 11; doxorubicine 50 mg/m^2 day 4 and dexamethasone 40 mg daily on days 1-4 and 11-14 **imatinib** 400 mg daily days 1 to 14	Response rate, event free survival, survival

From April 2001 to February 2004, 32 patients with Ph+ ALL have been treated (Thomas 2004b). Twenty-six patients had active disease, either untreated (n=21) or refractory (n=5) to one induction course without imatinib. Six patients were in CR at study entry after one induction course without imatinib mesylate. Median age was 48 years (range, 17–75); 59% were male. Five had CNS disease (16%).

Twenty-five of 26 patients (96%) with active disease at study entry achieved CR (1 failed to meet platelet criteria for CR). Median days to response were 21 days. Two of 26 patients (8%) required 2 courses to achieve CR. Unexpected toxicities related to the addition of imatinib mesylate were not observed.

Complete molecular remission (confirmed by nested PCR) was achieved in 3 (27%) of the 11 newly diagnosed Ph+ ALL patients after hyper-CVAD and imatinib alone and in 12 (60%) of 20 patients overall. In the preliminary data reported by Thomas et al on the first 20 patients enrolled. Bone marrow cytogenetics performed at CR (approximately day 21 of the induction course) showed normalization to diploid karyotype in 10 (91%) of the 11 patients. Levels of marrow quantitative RT-PCR positivity (ratio of bcr-abl/abl x 100) less than 0.05 occurred in 8 of the 15 patients with the hyper-CVAD and imatinib regimen alone.

Allogeneic stem cell transplant (SCT) was performed in 13 patients in CR within a median of 3 months from start of therapy (range, 1–12). For patients unwilling or unable to undergo allogeneic SCT, serial assessments of quantitative RT-PCR demonstrated stable to decreasing levels of Bcr-Abl transcripts over time, particularly with initiation of higher dose imatinib during maintenance therapy. Molecular response rate (negative bone marrow RT-PCR for bcr-abl confirmed by nested PCR) was approximately 50% in 19 pts who did not undergo allogeneic SCT. Disease free survival of the study group with current follow-up was not different whether patients were censored or uncensored at the time of allogeneic SCT (data not presented).

There were 2 patients who discontinued protocol therapy for persistence or recurrence of Ph+ disease by routine karyotyping without evidence of overt ALL.

Outcome appears better with the hyper-CVAD and imatinib regimen with 2-year DFS rates of 87% (all pts) compared with 28% for hyper-CVAD alone or 12% for VAD ($p<.001$). After a median follow-up of 2 years (range, 4–36 months), 1 primary refractory patient relapsed at 12 months (bcr-abl/abl RT-PCR ratio <.05 at 9 months), 1 patient relapsed day 149 after matched related SCT despite negative nested PCR for bcr-abl, and 2 patients changed therapy after 5 months for persistent marrow Ph+ metaphases without overt leukaemia relapse.

All but 5 of the 20 patients remained alive in CR with hyper-CVAD and imatinib-based therapy (9/10 after hyper-CVAD and imatinib alone). Five patients died in CR, 3 older patients related to co-morbid conditions (2 were negative for bcr-abl by nested PCR) and 2 related to complications of allogeneic SCT. Of the deaths with hyper-CVAD and imatinib with or without SCT, two were related to ALL

relapse. The overall survival of patients treated with hyper-CVAD and imatinib mesylate was compared with those treated with non–imatinib mesylate–containing hyper-CVAD and VAD regimens. Differences remain significant with exclusion of the 5 patients in CR at start of hyper-CVAD and imatinib mesylate (not shown). Note: a long-term survivor at 15 years in the VAD group is not shown.

A comparison with historical controls was performed as part of [Study AUS01]. A significantly better outcome of patients treated with hyper-CVAD combined with imatinib is reported than with either VAD (31 patients) or hyper-CVAD alone (50 patients) on CR rates (P <0.01), DFS (p <0.001), and overall survival (p <0.001), [Study AUS01]. Of note, there was no significant difference in survival or DFS with censoring at the time of allogeneic stem cell transplantation (SCT), although 2 out of 10 patients that did not undergo a SCT were in cytogenetic response on imatinib monotherapy maintenance for 2 years, but the historical rate of allogeneic SCT in first CR for Ph+ ALL was 20%, compared to 50% with imatinib.

[Study ADE04] In this open-label, multicentre, uncontrolled, non-randomised phase II study, the GMALL group investigated the safety and efficacy of imatinib in Ph+ALL or CML-LBC patients and the minimal residual disease after induction therapy or SCT. This study was divided into two parts. Overall 80 to 100 patients were planned (approximately equal distributions between the post-induction group (study A) and the post transplant group (study B)). Patients with *de novo* Ph+ALL or CML-LBC were eligible for part A of the study if they had completed phase I of induction chemotherapy based on the GMALL protocols 06/99 or 07/01 irrespective of complete haematological remission and of haematological recovery.

Study	Study objective, population	Study design	Patients	Dose regimen	Efficacy endpoint
ADE04 (Study A) Wassmann 2005	Safety, efficacy; CML-LBC or Ph+ALL	Open label, multi-centre, uncontrollednon-randomized, phase II	Total: 47 Ph+ALL: 43; CML-LBC: 4 (cohort 1) Ph+ALL: 45 (cohort 2)	**imatinib** 400-600 mg daily either intercurrently (cohort 1) or concomitant (cohort 2) to induction chemotherapy (cyclophosphamide 1000 mg/m^2 iv on d24, d44; Ara-C 75mg/m^2 iv d26-d29, d33-d36, d40-d43; 6-mercaptopurine 60 mg/m^2 p.o d24-d44, methotrexate 15 mg i.th. d26, d33, d40) **imatinib** 600 mg: (n=12 in cohort 1, n=46 in cohort 2)	conversion rate to MRD negativity, time to MRD negativity, remission induction rate, DFS, OS,

Only results obtained in the Part A of this study will be discussed because few data evaluating the use of imatinib in the post-SCT setting are available. A total of 92 patients were enrolled in Study A.

- Cohort 1 encompasses 47 pts (median age 46 years (range 21-65), patients received imatinib at a daily oral dose of 400 mg (n=36) or 600 mg (n=12). Imatinib was initiated 18 days (5-52d) after completion of induction and given for a median of 28 days (13-176). 26 patients received a second imatinib cycle after the first consolidation cycle.
- Cohort 2 encompasses 45 patients (median age 41 years (range 19-63).

Co-administration of imatinib with induction phase II resulted in a complete remission in 43 (95%) out of 45 patients and was superior to the alternating administration of chemotherapy and imatinib in terms of inducing PCR negativity for bcr-abl transcripts (52% versus 19%, p=0.01).

BCR-ABL transcripts levels after induction phase I did not differ significantly in the two study cohorts (alternating or parallel schedule). The median BCR-ABL/GAPDH ratio was 4.5 x 10^{-4} versus 4.9 x 10^{-4}. At this time point, the percentage of patients with PCR negativity was 7% for the alternating schedule cohort and 5% for parallel schedule cohort. During induction phase II, minimal residual disease (MRD) levels decreased by a median of 0.9 log with the alternating schedule i.e. with chemotherapy alone (p=0.009) and by 1.6 log (from 4.9 x 10^{-4} to 9.8 x 10^{-6}) with simultaneous imatinib and chemotherapy (p<0.0001).

BCR-ABL/GAPDH ratios at the end of induction were 1.1 log lower in patients who had received induction phase II concurrently with imatinib, although this difference was not statistically significant (p=0.3). Similarly, the proportion of patients who were PCR negative at the end of induction phase II

therapy did not differ significantly between alternating and parallel treatments cohorts, reaching 26% and 27%, respectively. With both schedules, the 4-week post-induction imatinib cycle was associated with an additional, approximately 1 log decrease of BCR-ABL transcript levels assessed prior to consolidation (p=0.3). Notably, the proportion of patients in whom BCR-ABL transcripts became undetectable prior to consolidation increased to 52% in the parallel treatment cohort. This effect was not observed in the alternating treatment cohort. The difference in PCR negativity in the two treatment groups was statistically significant (p=0.01).

The authors also examined whether the haematological response after induction phase I could influence the molecular response to concurrent imatinib and chemotherapy induction phase II. pre-study BCR-ABL transcript levels were higher in patients with a poor response after induction phase I than in patients who had achieved a complete remission (median 7.6 x 10^{-3} versus 5 x 10^{-5} , p=0.0001). Following co-administration of imatinib and induction phase II, MRD levels decreased by a median of 1.1 log in the prior good responders and by 2.2 log in the poor responders. When patients with a poor response and a good response to induction phase I were compared regarding their molecular response after induction phase II with or without imatinib, neither median MRD levels (median 5.3 x 10^{-5} versus 3.8 x 10^{-6} , p=0.16) nor the proportion of patients who were PCR negative differed significantly (27% vs 26%; p=n.s). These data indicate that in newly diagnosed Ph+ALL, a poor haematological response to the initial phase of remission induction chemotherapy can be compensated by the subsequent administration of imatinib in combination with chemotherapy.

No patient enrolled in the alternating schedule cohort relapsed during the post induction imatinib cycle. Overall 40 (85%) of the 47 patients from this cohort underwent allogeneic (n=36) or autologous (n=4) stem cell transplantation. The median time from diagnosis to transplant was 165 days (range, 103 to 287 days). Three patients relapsed while receiving imatinib after consolidation therapy, with a median remission duration of 4.9 to 6.2 months. Two patients who were not eligible for transplantation relapsed 7.6 and 12 months after imatinib was discontinued, the remission duration was 8.6 and 14.4 months. One patient withdraw consent after consolidation and relapsed 6.4 months after imatinib was discontinued. None of the 40 patients enrolled in the parallel administration schedule cohort who remained on study relapsed or died prior to consolidation therapy or stem cell transplantation.

The probability of subsequent relapse was not significantly different in the two groups of patients (33% versus 19%; p-value: not significant).

[Study AJP01] The JALSG has started this open-label, non-randomized, multi-centre, phase II study of imatinib administered concurrently to dose-intensive chemotherapy in newly diagnosed Ph+ ALL. This study was conducted with patients aged between 15 and 64 years with newly diagnosed BCR-ABL-positive ALL. Eligibility criteria included adequate functioning of the liver (serum bilirubin level < 34.2 μM [2.0 mg/dL]), kidneys (serum creatinine level <152.50 M [2.0 mg/dL]), and heart (no severe abnormalities detected on electrocardiograms and echocardiographs), and an Eastern Cooperative Oncology Group performance status between 0 and 3. Written informed consent was obtained from all patients prior to registration. The primary endpoint of this study is the complete remission rate. The secondary endpoints are the remission duration, DFS, OS, and the conversion rate and time to minimal residual disease negativity. Minimal residual disease is assessed by RT-PCR.

Study	Study objective, population	Patients	Dose regimen	Efficacy endpoint
AJP01 Towatari 2004, Yanada 2005	Efficacy, safety in combination with intensive chemothera-py; de-novo Ph+ ALL	newly diagnosed Ph+ ALL: 80		complete remission rate, DFS, OS, remission duration, conversion rate and time to minimal residual disease negativity
Induction therapy			**imatinib** 600 mg/d d8-d63 combined with dose-intensive chemotherapy cyclophosphamide 1200 mg/m^2 i.v. d1; daunorubicin 60 mg/m^2 i.v. d1-d3; vincristine 1.3 mg/m^2 d1, d8, d15, d22; predniso-lone 60 mg/m^2 p.o. /day	
Consolidation therapy			alternating chemotherapy course (high dose chemotherapy with methotrexate 1 g/m^2 i.v. d1 and Ara-C 2 g/m^2/12h d2-d3) + **imatinib** 600 mg/d for 4 weeks (total of 8 courses)	

A total of 80 patients were planned to be enrolled in this study. Interim results for the first 24 patients enrolled were presented at the American Society of Clinical Oncology meeting in June 2004. Final results on the eighty patients entered into the trial between September 2002 and January 2005 were reported by Yanada et al. 2005 . Median age was 48 years (range, 15 to 63 years).

Induction therapy resulted in complete remission (CR) in 77 (96.2%) patients, resistant disease in one, and early death in two, as well as polymerase chain reaction negativity of bone marrow in 71.3%.

The profile and incidence of severe toxicity were not different from those associated with our historical chemotherapy alone regimen.

Relapse occurred in 20 patients (26%) after median CR duration of 5.2 months.

Allogeneic haematopoietic stem cell transplantation (HSCT) was performed for 41 patients, 39 of whom underwent transplantation during their first CR.

The 1-year event-free and overall survival rates were estimated to be 60.6%, and 76.1%, respectively, both of which were significantly better than those for the historical controls treated with chemotherapy alone ($p<0.0001$ for both).

Among the current trial patients, the probability for OS at 1 year was 73.3% for those who underwent allogeneic HSCT and 84.8% for those who did not. When only patients who underwent allogeneic transplantation during first remission were analyzed, compared with historical controls treated with chemotherapy alone (ALL93, n=10), cases treated with imatinib-combined regimen (ALL202, n=39) showed better outcomes for event-free survival, but not for overall survival. When only patients who did not undergo allogeneic transplantation were analyzed, compared with historical controls treated with chemotherapy alone (ALL93, n=22), cases treated with imatinib-combined regimen (ALL202, n=31) showed better outcomes for both event-free survival and overall survival.

PCR negativity was confirmed for 18 (26.4%) of 68 samples on day 28, and for 33 (50.0%) of 66 samples on day 63, with a total of 51 cases (63.8%) demonstrating PCR negativity without HSCT during the follow-up period.

The results of [Study AJP01], were compared with the results of study JALSG ALL93 conducted previously by the same collaborative group. This historical comparison indicated that the imatinib-containing regimen induced a superior CR rate (96% versus 51% - $p<0.0001$), event-free survival and overall survival ($p<0.0001$). In concordance with study AUS01, the probability of survival was similar for transplanted patients irrespectively of the pre-transplant regimen, but was significantly better for the patients who did not undergo allogenic transplantation ($p<0.0006$).

Imatinib as induction/consolidation therapy in combination with steroids

A total of 49 elderly Ph+ ALL patients (≥55 years) were treated with **imatinib** as induction/consolidation therapy in combination with steroids. These patients were enrolled in two uncontrolled clinical trials:

- [Study AFR09] open-label, non-randomized, multi-centre, phase II study post-induction therapy (alternating imatinib plus steroids and chemotherapy) and
- [Study AIT04] open-label, non-randomized, multi-centre, phase II study in combination with steroids.

The comparison of inclusion and exclusion criteria for these two studies with study ADE10 does not indicate major differences in the population treated.

Out of the 49 patients, a total of 30 (61%) received imatinib at a dose of 600 mg daily. All patients were Ph+ ALL patients.

The complete haematological response rate in the overall population was 89%, with a molecular response rate of 20% (26% in the evaluable population).

[Study AFR09] In this open label, non randomized, multicentre, phase II study, the Group for Research on Adult Acute Lymphocytic Leukaemia (GRAALL) investigated the effects of imatinib post-induction therapy in elderly patients (>55 years) with Ph+ ALL. Patients were treated with steroids during one week and then offered a specific therapy including treatment with steroids, cyclophosphamide, daunorubicin, and vincristine followed, irrespective of response to induction therapy, by imatinib, 600 mg daily, combined with intermittent steroids during 2 months.

From January 2003 to November 2004, 30 patients aged 58 to 78 years (median: 65.8 years) were included in the study. The median follow-up of surviving patients was 15 months.

Twenty-one (72%, CI: 52-87%) of the twenty-nine assessable patients were in complete response after induction chemotherapy vs 6/21 (28.5%, CI: 11-52%) in the historical controls (21 Ph+ALL patients treated by the same collaborative group in a previous protocol given similar induction chemotherapy but with no steroids before chemotherapy (p=0.003)). Two patients died during chemotherapy induction treatment vs. none in the control group.

Out of 6 patients alive with disease at completion of induction, after salvage with imatinib, five additional patients were in complete remission. One patient, that had no bone marrow assessment performed after induction and could therefore not be assessed for response, was in complete remission after consolidation therapy.

In the control group, out of 12 patients offered salvage therapy after failing induction, four obtained a complete remission, while one died during salvage therapy. In the control group, six (28.5%, CI: 11-52) of the twenty-one patients were in complete remission (p=0.003), and 15 were alive with leukaemia. Overall, 27 (90%, CI: 73-98) of the 30 patients enrolled in the AFR09 study achieved a complete remission versus 10 (47.6%, CI: 25.5-70) of the 21 patients in the control group (p=0.001).

Molecular response was assessed in 15 out of 21 patients in haematological CR after induction therapy. Four patients were good molecular responders. After consolidation therapy, 13 (62%) of the 21 CR patients were good molecular responders, 7 (33%) of them had BCR-ABL transcripts below the detection level.

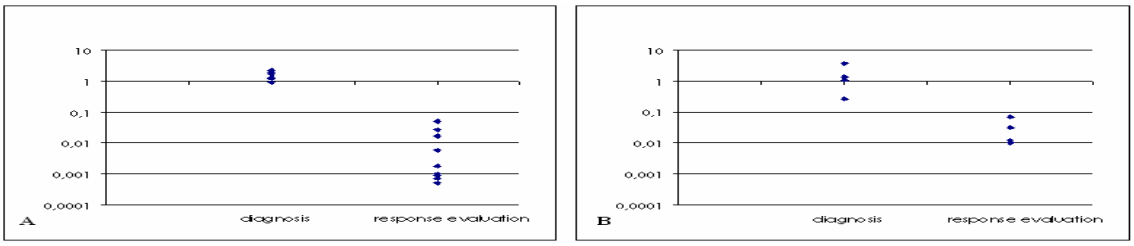
The projected overall survival is 68% at 1 year vs. 43% in the control group (p=0.001, log-rank test). The 1 year projected relapse-free survival is 59% vs 11% (p=0.001). Out of the 8 non responders, one patient died from infection and one from sudden death and 6 were alive with leukaemia.

[Study AIT04] In 2001, the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) started a phase II pilot study. The purpose was to verify the activity and safety of **imatinib** combined with prednisone during the induction phase in elderly (>60 years) Ph+ ALL patients.

As of May 2005, out of the 19 patients enrolled (median age: 69 years), 18 were evaluable for response and only 4 (21%) had a dose reduction of more than 50%. All 18 evaluable patients achieved haematological CR and 3/18 (17%) had a complete molecular response but with detectable though small numbers of p190 BCR/ABL copies by quantitative RT-PCR.

The BCR-ABL fusion transcript at diagnosis was measured by quantitative RT-PCR in 15 cases (11 expressing the minor p190 transcript, 9 the major p210 transcript, and one both). The median BCR-ABL/ABL ratios were 1.7281 (range 0.9263-1.5617) in the p190 positive patients and 1.2094 (range 0.2621-3.6730) in the three p210 and the single p210+s90 cases. In these 15 cases, the BCR-ABL levels were also evaluated at the time of evaluation of response (after 45 days of treatment). At this time point, the median BCR-ABL/ABL ratios were 0.0018 (range 0.0005-0.0520) in the p190 group and 0.0210 (range 0.0099-0.0673) in the p210 or p210+190 positive group. By comparing the number of copies at diagnosis and after induction treatment, a median reduction of BCR-ABL/ABL ratios of 2.8 logs (range 1.2-4.3) in the p190 group and 1.8 logs (range 0.5-2.5) in p210 or p210+190 positive group (Vignetti et al 2005).

BCR-ABL/ABL ratios at diagnosis and after 45 days of treatment in p210 (A) or p210+190 (B) positive groups (study AIT04)



Six patients relapsed after a median time of 6 months (range 3 – 14.7), and 10 patients (56%) were alive in continuous remission after a median duration of 14 months (range 2 - 26) from response. The projected overall survival at 1 year was close to 80%, with a probability at 2 years close to 50%. Moreover, imatinib given together with steroids was able to induce a marked reduction of the level of BCR/ABL copies which was highly predictive of the outcome, with a significantly lower probability of relapse for the p190 positive cases (n=11) in whom there was a ≥ 2.8 log reduction.

Imatinib in Newly diagnosed elderly patients

A total of 104 elderly patients with de-novo Ph+ ALL or CML-LBC were treated in combination with chemotherapy and or steroids within one controlled study (Study ADE10) and two uncontrolled studies (Study AFR09, Study AIT04). (table..)

Patients received imatinib either: as monotherapy (28 patients, Study ADE10), as combined consolidation therapy post chemotherapy induction (27 patients, Study ADE10), as post-induction therapy combined with steroids (30 patients, Study AFR09) or as induction therapy combined with steroids (19 patients, Study AIT04). A total of 85 (82%) of these patients received imatinib at a posology of 600 mg daily.

Outcome with imatinib in newly diagnosed elderly patients

Study	n	Dose regimen	CHR (%)	MCyR (%)	CMR (%)	DFS	OS
Controlled study							
ADE10	Ph+ALL:55						
	imatinib monotherapy induction plus consolidation including imatinib, n=28	600 mg/d	26/27 (96.3)	NA	9/26* (34.6)	53.7%** estimated at 12 months	53.8%** estimated at 12 months
	chemotherapy induction plus consolidation including imatinib, n=27		16/26 (50)	NA	8/22* (36.4)		
Sub-total	55						
Uncontrolled studies							
AFR09	Ph+ALL: 30 Imatinib post induction therapy	600 mg daily	21/29* (72)	NA	7/21 (33)	60% at 1 year	68% at 1 year
AIT04	Ph+ALL: 19 Imatinib induction in combination with steroids	800 mg daily	18/18 (100)	NA	3/18 (17)	Median DFS: 15 months	Median OS: 20 months
Sub-total	49						
Total no. of patients	104						
Total no. of patients (%) 600 mg/d		85/104 (81)					

CHR: Complete haematological response, MCyR: Major Cytogenetic Response, CMR: Complete Molecular response, DFS: Disease-free survival, TTP: Time to progression, OS: Overall survival, NA: Not available
* After consolidation with chemotherapy plus imatinib 600 mg daily
** For the whole population

Efficacy conclusions on newly diagnosed Ph+ ALL

In a controlled study of imatinib versus chemotherapy in 55 newly diagnosed elderly patients, imatinib used as single agent induced a significantly higher rate of complete haematological response than chemotherapy (96.3% vs. 50%; p=0.0001). When salvage therapy with imatinib was administered in patients who did not respond or who responded poorly to chemotherapy, it resulted in 9 (81.8%) patients out of 11 achieving a complete haematological response. This clinical effect was associated with a higher reduction in bcr-abl transcripts in the imatinib treated patients than in the chemotherapy arm after 2 weeks of therapy (p=0.02). All patients received imatinib and consolidation chemotherapy after induction and the levels of bcr-abl transcripts were identical in the two arms at 8 weeks. As expected on the basis of study design, no difference was observed in remission duration, disease-free survival or overall survival, although patients with complete molecular response and remaining in minimal residual disease had a better outcome in terms of both remission duration (p=0.01) and disease-free survival (p=0.02). The role of resistance to imatinib in relapse is unclear. Thirteen out of 16 evaluable patients relapsed in [Study ADE10] had a bcr-abl mutation at relapse, but it is not known if these mutations pre-dated imatinib treatment (Hofmann et al. 2003).

The results observed in a population of 211 newly diagnosed adult Ph+ ALL patients treated with imatinib in combination with chemotherapy are consistent with the results from [Study ADE10]. Imatinib in combination with chemotherapy induction resulted in a complete haematological response rate of 93% (147 out of 158 evaluable patients) and in a major cytogenetic response rate of 90% (19 out of 21 evaluable patients). The complete molecular response rate was 48% (49 out of 102 evaluable patients).

Similarly, in two clinical trials in which 49 newly diagnosed Ph+ ALL patients aged 55 years and over were given imatinib combined with steroids with or without chemotherapy, there was a complete haematological response rate of 89% in the overall population and a complete molecular response rate of 26% in 39 evaluable patients. Median disease-free survival and median overall survival were longer than 1 year in both studies.

Only two studies had a CR rate lower than 90%: [Study AAU02] where imatinib was given for only 7 days as pre-induction treatment and [Study AFR09] where imatinib was not given during induction, but only during consolidation. Of note, in this latter study the CR rate was superior to historical controls.

Comparison with historical controls treated at the same institution or by the same collaborative group on CR rates and time to events indicates an advantage of adding imatinib.

Overall, imatinib demonstrated activity in the populations treated, with a consistent high level of response and a time to event effect that is equal or better than historical controls. The lack of differences in the time to event results in the only randomized study can be explained by the design of the study that compared imatinib and chemotherapy only in the induction phase. This precludes conclusions on the long term effect of either approaches, although the better molecular response on imatinib might translate in a better long term outcome.

2.2. RELAPSED AND/OR REFRACTORY PH+ ALL PATIENTS

The design of all studies performed in this population of patients was open and uncontrolled. The studies included the following populations:

- Patients in first or subsequent relapse after either standard chemotherapy, autologous or allogeneic bone marrow transplantation, or high dose treatment with peripheral blood stem cell support, or
- Patients refractory to standard chemotherapy (no complete remission achieved after two conventional induction chemotherapy).

These patients were treated with imatinib as monotherapy or in combination with induction chemotherapy.

Imatinib monotherapy

Three Novartis-sponsored studies assessed the efficacy of imatinib as monotherapy in 429 relapsed or refractory Ph+ ALL patients:

– [03001], phase I, dose escalating pilot study

– (0109 CSR Ph+ ALL], open label, non-randomized, multi-centre, phase II study

– [0114 CSR Ph+ ALL]. phase II, multi-centre, expanded access study

The inclusion and exclusion criteria for these studies were consistent according to the subpopulation targeted.

Uncontrolled trials –imatinib monotherapy in relapsed/refractory Ph+ ALL or CML-LBC patients

Study	Study objective; population	Study design	Patients	Dose regimen	Efficacy endpoint
03001 Druker 2001	efficacy/safety; Ph+ ALL or CML-LBC	Phase I, dose escalating pilot study	Total: 20 Ph+ALL n=10; CML-LBC: n=10	imatinib: 300-1000 mg 600 mg (n=2)	Anti-leukaemic activity by decrease in peri-pheral WBC counts and percent Ph+ cells in bone marrow
0109 Ph+ ALL Ottmann 2002	efficacy/safety; Ph+ ALL or CML-LBC	Open label, non randomized, multi-centre, Phase II study	Ph+ALL: n=48; CML-LBC: n=8	imatinib: 400-600 mg daily 600 mg (n=46)	Confirmed hemato-logical response, duration of hemato-logical response, cytogenetic response
0114 Ph+ ALL Wassmann 2004	Safety, expanded access program in Ph+ALL	Phase II, multi-centre,	353	600 mg daily	Time to progression

A total of 429 relapsed/refractory patients with Ph+ ALL or CML-LBC were enrolled in these studies assessing the efficacy of imatinib as monotherapy. Out of these, 401 (93%) patients received imatinib at a dose of 600 mg daily. A total of 411 (98%) of the patient population were diagnosed as Ph+ ALL.

Study 03001 In this phase I Novartis sponsored dose escalating pilot study, 58 patients were enrolled, out of these, 20 patients were CML in lymphoid blast crisis (CML-LBC 10 patients) or Ph+ ALL (10 patients). Of the 20 patients with lymphoid blast crisis or Ph+ ALL:

4 (20%) had a complete haematological response (CHR) and 10 (50%) had a marrow response. In patients who showed a response to the drug, the reduction in peripheral blasts typically occurred within one week after initiation of the therapy. The median duration of therapy was 74 days (range 1–349). Major cytogenetic responses were observed in patients with CML-LBC: complete response in 2 patients, and partial response (defined as less than 35% Ph+ cells) in one patient. Of the 14 patients with lymphoid blast crisis or Ph+ ALL who showed a response to imatinib, 12 relapsed within a median of 58 days after the initiation of treatment (range 42-123), one underwent allogeneic stem cell transplantation, one was still in remission after 243 days of imatinib. There was no obvious difference in response rates or the durability of responses between patients with lymphoid blast crisis and those with Ph+ ALL.

Study 0109 Ph+ ALL: This subsequent phase II study was initiated to evaluate the clinical efficacy and safety of imatinib in the treatment of patients with CML in accelerated phase and relapsed or refractory Ph+ ALL. In this open label, non-randomized, multi-centre, multinational Novartis-sponsored trial, 56 patients (48 patients with Ph+ ALL and 8 patients in lymphoid blast crisis) were enrolled. For the purpose of this application, a sub-analysis was performed on these 56 patients and the results were split by age (< 55 years old, n= 38 and ≥ 55 years old, n=18).

Patients were subdivided according to their initial dose of **imatinib**, 400 mg (10 patients) or 600 mg daily, the majority (46 patients) being in the latter initial dose group. Patients were scheduled to receive treatment for 24 weeks and then were continued indefinitely in cases where the investigator judged that further treatment was of clinical benefit. Simultaneous treatment with cytotoxic agents or steroids was not permitted. The primary efficacy endpoint of this study was sustained haematological response (lasting at least 4 weeks), defined as complete haematological response. Secondary endpoints were the induction of cytogenetic response, time to progression, and overall survival.

Of the 48 patients with Ph+ ALL, 65% had experienced one or more relapses after prior chemotherapy and 35% were primarily refractory to chemotherapy. In 21% of the patients relapse occurred after autologous or allogeneic stem cell transplantation. Thus, the patients selected for this study had particularly poor prognostic features. The median age was 50.5 years (range, 22-78 years).

Efficacy. An initial dose of 400 mg was found not effective because no haematological responses were observed in patients treated at this dose level.

Treatment with an initial dose of 600 mg daily produced sustained haematological responses in 12 (26%) patients. Four (33%) of them achieved sustained CHR. In addition, unconfirmed haematological responses were seen in 27 (59%) patients treated with an initial dose of 600 mg. The median time to haematological response was 1 month in the whole patient population. However, as a single agent the median duration of haematological response was short at 3.4 months in the whole population.

Confirmed major cytogenetic responses were seen in 12 (26%) out of 46 patients treated with 600 mg. Seven (58%) of them achieved a complete cytogenetic response (CCyR). Despite the fact that the study protocol permitted dose increases up to a total of 800 mg daily in all patients who failed to show an adequate therapeutic response, the rates of CCyR appeared to be dose-dependent with consistently higher rates of MCyR and CCyR in patients treated with an initial dose of 600 mg daily than in those receiving 400 mg daily.

The median time to progression (TTP) and median survival in patients started with 600 mg was 2.6 months (95% CI: 1.9-3.0 months) and 5 months (95% CI: 4.2 -7.2 months), respectively. Parts of the results of this study have been published earlier (Ottmann et al 2002).

Study 0114 Ph+ ALL: The objective of this open-label, non-randomized, multi-centre trial was to provide patients with Ph+ CML in accelerated phase (AP) or relapsed/refractory Ph+ ALL with expanded access to **imatinib** until the product was commercially available. The dosage was 600 mg daily with a permitted dose escalation of up to a maximum of 800 mg imatinib per day. Eligible

patients (males/females, ≥18 years of age with Ph+ CML, in the accelerated phase of the disease, or relapsed/refractory Ph+ ALL) were treated in this protocol between 15-May-2000 and 03-Jun-2003.

A total of 353 patients with relapsed/refractory Ph+ ALL were treated in this study. For the purpose of this application, a sub-analysis was performed on these and the results were split by age (<55 years, n=225 and ≥ 55 years, n=128).

Overall, 211 of the 353 patients progressed (discontinued due to progression or death). Time to progression (TTP) was censored for the remaining 142 patients: 12 patients discontinued due to adverse events, 2 had abnormal lab values, 62 discontinued to undergo BMT, 8 for reasons other than safety or efficacy and 58 patients were still on treatment when transferred to national health care system or patient assistance programs. The estimated proportions [95% CI] of patients without progression was 12.4% [6 - 19] at 12 months. The median time to progression was 3.2 months with 95% CI = [3 - 4].

At time of analysis, of the 353 patients, 61 (17.3%) patients had died while on study treatment, 17 (4.8%) patients within 28 days after the last study drug administration and 13 (3.7%) patients later than 28 days following discontinuation of study drug (mostly due to progression of disease).

The estimated probabilities [95% CI] of being alive with Ph+ ALL was 40.8% [28 - 54] at 12 months. The median survival was 8.9 months with 95% CI =[7 - NA] in patients ≥55 years old and 11.4 months with 95% CI =[6 - NA] in patients < 55 years old.

Wassmann et al reported the results of an analysis performed in 68 patients with relapsed or refractory Ph+ ALL (n= 66) or minimal residual disease (n= 2) who were enrolled in **study 0109** (n= 14) and **study 0114** (n= 54). **Imatinib** doses were 600 mg (n=63), 400 mg (n=4), or 300 mg (n=1). The overall haematological response rate in these 68 patients was close to 70%, with 30% showing complete haematological response, 29% showing complete marrow response, and 11% in partial marrow response. A complete cytogenetic response was induced in 89% of patients in CHR and 77% of patients in complete marrow response with sufficient cytogenetic and/or FISH data.

However, molecular and cytogenetic remissions were rarely sustained, and relapse occurred after a median of 4 months (range, 0.5-5.0 months). Median TTP in patients with CHR was 5.4 months, compared to 1.7 months in patients with a partial response ($p < 0.0001$). Overall survival of all patients was 22.6% ± 5.4% at 18 months.

Imatinib in combination with chemotherapy

Two uncontrolled phase II studies provided efficacy data of imatinib used in combination with chemotherapy in a total of 14 relapsed/refractory Ph+ ALL or CML-LBC patients:

- [Study AAU02] open label, non-randomized pilot study that enrolled 7 relapsed/refractory patients with Ph+ ALL and 2 patients with CML-LBC to receive imatinib 600 mg/day in combination with induction chemotherapy
- [Study AUS01] study including 5 refractory Ph+ ALL patients treated with imatinib 400 mg/day in combination with induction chemotherapy (intensive hyper-CVAD).

The two studies were comparable in terms of inclusion/exclusion criteria.

A total of 9 (64%) out of the 14 patients received imatinib at a dose of 600 mg daily. A total of 14 (86%) of the patient population was Ph+ ALL.

These studies are described in more detail as follows:

[Study AAU02] The authors (Lickliter et al 2004 ,Lickliter 2005) hypothesized that pretreatment with imatinib would overcome inherent drug resistance to induction chemotherapy mediated by Bcr-Abl. The combination was evaluated in 24 patients with Ph+ acute leukaemias (3 CML in myeloid blast crisis, 2 CML in lymphoid blast crisis, 7 relapsed Ph+ ALL and 12 de-novo Ph+ ALL).

All patients received a 1-week pre-phase of **imatinib** alone at 600 mg daily.

- In blast-phase CML and relapsed Ph+ ALL, **imatinib** was continued concomitantly with induction chemotherapy (standard-dose idarubicin/ara-C with vincristine/prednisone added for lymphoid

leukaemias) for an additional week. Imatinib was then ceased, but recommenced as a single agent after blood-count recovery.

- Patients with de-novo Ph+ ALL received the imatinib pre-phase and then commenced the French cooperative group LALA-94 protocol without concomitant imatinib.

Neutrophils recovered to $\geq 1.0 \times 10^9$/L at a median of day 24 of induction chemotherapy, with only 1 patient showing delayed recovery (> day 42). There was 1 induction death on day 18 from overwhelming sepsis and multi-organ failure. No unexpected non-hematological toxicities were observed.

There were 7 (88%) complete hematological responses (CHR) among 9 evaluable patients with CML-LBC and relapsed Ph+ALL and 7 (58%) CHR among 12 de-novo Ph+ ALL.

Major cytogenetic responses were seen in all the evaluable patients (8/8, 100%). Complete cytogenetic responses were seen in 5 (63%) of patients (Lickliter et al 2005). The in-vivo inhibition of Bcr-Abl by imatinib was monitored in leukaemic cells during the imatinib-only prephase using Western blot analysis of CrkL phosphorylation status. Marked dephosphorylation of CrkL was observed in peripheral blood and/or marrow in all but 1 of 8 evaluable cases. Imatinib potently inhibited Bcr-Abl activity in vivo in Ph+ acute leukaemic blasts and its combination with induction chemotherapy was tolerable. PCR negativity was confirmed for 18 (26.4%) of 68 samples on day 28, and for 33 (50.0%) of 66 samples on day 63, with a total of 51 cases (63.8%) demonstrating PCR negativity without HSCT during the follow-up period (Yanada et al 2005).

Among all patients, the estimate one-year survival rate was 61.1 ± 13.5%.

Study AUS01 was designed to determine the clinical efficacy (overall response rate, event-free survival, and survival) and safety of the intensive hyper-CVAD regimen given in combination with imatinib. The molecular response rate and duration were also evaluated. Adults (≥ 15 years) with Ph+ ALL, newly diagnosed or minimally treated (<2 courses of hyper-CVAD or conventional chemotherapy without imatinib) were eligible to enter this phase II trial of imatinib and hyper-CVAD conducted by the M.D. Anderson Cancer Center. Entry criteria included ECOG performance status 0 to 2. Patients with uncontrolled serious infections or active secondary malignancy were not eligible. No investigational anti-leukaemic therapy could have been administered within the 7 prior days. Therapy was given with 8 induction-consolidation courses alternating hyper-CVAD with high dose MTX and ara-C, concurrently with 400 mg imatinib mesylate daily on days 1 to 14. Higher doses of imatinib were given during the consolidation phase owing to the known dose-response phenomenon observed in the studies of imatinib in CML and the absence of concurrent myelosuppressive therapy.

From April 2001 to February 2004, 32 patients with Ph+ ALL have been treated (Thomas 2004b). Twenty-six patients had active disease, either untreated (n=21) or refractory (n=5) to one induction course without imatinib. Six patients were in CR at study entry after one induction course without imatinib mesylate. Median age was 48 years (range, 17–75); 59% were male. Five had CNS disease (16%).

Complete molecular remission (confirmed by nested PCR) was achieved in 2 (50%) of the 4 refractory Ph+ ALL patients after hyper-CVAD and imatinib alone.

Imatinib in elderly relapsed/refractory Ph+ ALL patients

A total of 146 elderly Ph+ ALL or CML-LBC patients were treated with imatinib as monotherapy. These patients were enrolled in 2 uncontrolled Phase II studies:

[0109 CSR Ph+ ALL], open label, non-randomized, multi-centre study 109

[0114 CSR Ph+ ALL]. Multi-centre, expanded access study 0114

142 (97%) out of the 146 patients received imatinib at a dose of 600 mg daily in studies 0109 and 014, which are described previously in this report. The results obtained in the elderly population are shown in the table below:

Outcome with imatinib monotherapy in elderly relapsed/refractory Ph+ ALL or CML-LBC patients

Study	n	Imatinib Dose (mg/day)	CHR (%)	MCyR (%)	CMR (%)	Median TTP months (95%C.I.)	Median OS months (95%C.I.)
0109	18	400-600 600 (n=14)	5/14* (35)	7/14 (50)	NA	2.8 (1.4-5.6)	7.4 (3.0-10.1)
0114	128	600	NA	NA	NA	3.1 (3.0-4.0)	8.9 (7.0-NA)
Total no. of patients	146						

CHR: Complete hematological response, MCyR: Major Cytogenetic Response, CMR: Complete Molecular response, DFS: Disease-free survival, TTP: Time to progression, OS: Overall survival, NA: Not available, NI: No information
Total no. of patients (%) receiving 600 mg/d: 142/146 (97)
* No responses were seen in the 4 patients treated with imatinib at 400 mg daily.

Efficacy conclusions on relapsed/refractory Ph+ ALL

When imatinib was used as single agent in patients with relapsed/refractory Ph+ ALL, in the 66 patients evaluable for efficacy, it resulted in a hematological response rate of 33% (12% complete) and a major cytogenetic rate of 23%. The median time to progression in the overall population of 429 patients ranged from 1.9 to 3.1 months, and the median overall survival in the 409 patients evaluated from 5 to 9 months.

In 14 patients, imatinib in combination with induction chemotherapy resulted in a complete hematological response rate of 92% in 12 evaluable patients and in a major cytogenetic response rate of 100% in 8 evaluable patients. Molecular response was assessed in four patients, and two responded completely.

Treatment of Ph+ ALL patients aged 55 years and over was analyzed separately because of the lack of curative treatment for this population. A population of 146 refractory or relapsed patients aged 55 years and over received imatinib as monotherapy. Out of 14 evaluable patients treated with imatinib 600 mg daily, complete hematological response was observed in 5 patients (35%) and major cytogenetic response in 7 patients (50%). Of note, four patients who were treated with a lower dose of imatinib (400 mg daily) did not respond, suggesting that this dose is insufficient. In the overall population of 146 patients, median disease-free survival ranged from 2.8 to 3.1 months and median overall survival from 7.4 to 8.9 months. These results are comparable or better than observed with chemotherapy in a population of elderly newly diagnosed ALL patients.

2.3. Pediatric patients with Ph+ ALL

These results are included in this submission upon request of the EMEA following CHMP Scientific Advice of 17 February 2005. Data is presented from 5 pediatric patients with Ph+ ALL treated with imatinib in the phase I dose escalating pilot study (study 03001).

In **Study 03 001**, included in previous submission dossiers, a total of eight pediatric patients were treated with **imatinib** at doses of 125 to 425 mg/day. The indication and main criteria for inclusion were: patients <18 years old with either Ph+ CML in the chronic phase, resistant to or intolerant of IFN, or Ph+ acute leukaemia (myeloid or lymphoid blast crisis, or Ph+ ALL or AML). Out of these 8 children, five are presented here to be included in this application: 4 with Ph+ ALL and 1 with LBC. Data reported by Champagne et al in 10 paediatric patients treated in a phase I study conducted by the Children Oncology Group are also included.

The overall hematological response in these two studies was 73% (11 responders out of 15 patients treated), with a CHR rate of 13%. In the small number of paediatric patients with Ph+ leukaemia included in study 03 001, the efficacy of imatinib was broadly similar to that observed in adult patients with similar disease types. Three out of the five treated paediatric patients (60%) achieved either a partial or a complete response. Out of the five-paediatric patients treated in Study 03001, two achieved a complete cytogenetic response and one a minimal cytogenetic response. In the phase I study conducted by the Children Oncology Group (COG), among these 10 patients with lymphoid phenotype 7 (70%) achieved M1 marrow responses and 1 (10%) achieved M2 response. The median survival for patients with advanced lymphoid leukaemia was 15 months.

2.4. Other sources of data

Additional supportive data were provided by four publications that were not included in the overview of the data because audits were not performed. These publications are consistent with the previously assessed studies using imatinib in Ph+ ALL: the two first publications obtained a high efficacy in combination with chemotherapy in newly diagnosed patients, which made possible to undergo a transplant with a positive outcome. The other two publications describe studies with a shorter number of patients where it is more difficult to reach valid conclusions

3. Safety Aspects

The safety of imatinib in this indication was evaluated on the basis of the results from clinical trials performed in two populations of patients: newly diagnosed Ph+ ALL patients (previously untreated patients who received imatinib in combination with induction and/or consolidation chemotherapy) and relapsed/ refractory Ph+ ALL patients (where imatinib was used as a single agent).
Additionally, the safety of imatinib was analysed as a separate entity in patients ≥55 years old with Ph+ ALL (usually not considered suitable for intensive therapy including allogeneic or autologous bone marrow transplantation), which formed part of the main population of the study.
The information submitted includes a total of 758 patients. However, the data from investigator-initiated studies was extracted from manuscripts, and, therefore, much information is missing. Data from serious adverse events reports submitted to the applicant are also presented (cut-off date: 31-Jul-2005).
When available, frequency, type and severity of the adverse events (AE) and serious adverse events (SAE), rate of deaths, laboratory results were considered. All patients who received at least one dose of imatinib were considered in the safety evaluation.

The company states that blinding was not feasible due to the complexity of the chemotherapy regimen used to treat Ph+ ALL patients, and that large randomized studies were not feasible, either due to a combination of the rarity of the disease and the variety of chemotherapy used.

No pooling of data or combined safety analysis was performed, since the company considered that the clinical trials presented in this application were conducted in patients at different stages of the disease, as well as in patients treated with imatinib and different chemotherapy regimens. Duration of treatment, dose intensity, and dose exposure in the different populations are very heterogeneous.

3.1. Adverse events

Relapsed/refractory Ph+ ALL

Description of AE by system organ class (SOC) is available only for studies 0109 and 0114, therefore only existing for imatinib monotherapy in relapsed/refractory Ph+ ALL. Study 0109 was a phase II study and study 0114 was part of an expanded access program. As stated by the applicant, safety information for study 0114 was not consistently collected and AE rates are therefore much lower.

The overall frequency of patients experiencing adverse events was remarkably higher in study 0109 (100%) versus study 0114 (37.7%). The most frequently affected SOC were gastrointestinal (94.6% and 21.2% of patients, for studies 0109 and 0114 respectively), and general disorders (with 82.1% and 19% of patients, respectively). Other frequently affected SOC for study 0109 were: infections (60.7%), skin disorders (58.9), musculoskeletal (55.4%) and respiratory, thoracic and mediastinal disorders (55.4 %). Blood and lymphatic system disorders were reported in 53.6 % of patients.

The most common grade 3 or 4 AE by SOC in study 0109 and study 0114 were related to blood and lymphatic system (42.9% and 15%, respectively), infection (21.4% and 4.5%, respectively) and general disorders (17.9% and 7.9%, respectively).

The frequency of AE by SOC was similar in patients aged under and ≥ 55 years, except for a slight increase in study 0109 for general and administration site conditions (76.3% versus 94.4%), eye (21.1% versus 33.3%) and psychiatric disorders (18.4% versus 38.9%).

Most frequent treatment related AE in study 0109 (mostly grades 1 and 2) were nausea (76.8%), vomiting (62.5%) and peripheral oedema (33.9%). Drug related AE for study 0114 were not collected and are not submitted. In study 03001, most frequent treatment related AE (imatinib monotherapy) were nausea (55%), vomiting (41%) and oedema (41%). No information of overall AE or AE split by age is available for this study.

The rates of most frequent AE and most frequent treatment related AE (nausea and vomiting) were also similar for the population ≥ 55 years, followed by peripheral oedema (50 %) in study 0109.

Newly diagnosed patients

No information is available on the distribution of adverse events by SOC from the published studies. The most frequent adverse events reported were infections of different types, reported in 23 out of 91 post-induction courses (25%) followed by fatigue and peripheral neuropathy (reported in 8 and in 7 of the post-induction courses, respectively). Fluid retention was reported in 6 patients (grade 1-2 in five of them) and increase in hepatic enzymes and creatinine in 5 patients (grade 1-2 in all of them). No induction mortality was observed.

In the rest of the publications, only grade 3 or 4 events were reported and these events were mostly summarized for the entire treatment period.

3.2. Serious adverse events and deaths

Refractory/relapsed patients

In the overall population of 423 refractory/relapsing patients included in studies 0109 and 0114, there were only 6 deaths considered due to adverse events (4/56 in study 0109 and 2/353 in study 0114); none was considered drug-related. An underreporting of deaths is unlikely in study 0114, but is not discarded by the applicant either. Out of the 14 patients in studies AAU02 and AUS01, 3 died on study. One of these patients died from hemoptysis due to a fungal pneumonia, another from Aspergillus pneumonia and the third of them from osteomyelitis from vertebroplasty for traumam-related vertebral fracture.

Discontinuation due to adverse events was 20 % in study 0109, the main reason being general disorders. Discontinuation occurred in 5% of patients in study 0114, mainly due to progressive disease.

Serious adverse events were common, with 99 patients treated with imatinib monotherapy experiencing a SAE (24%). As expected, the frequency of SAE is again much lower in study 0114 (17%) than in study 109 (68%). The most frequently SOC affected by SAEs in study 0109 was progressive disease (36% SOC neoplasm), followed by infections (27%) and general disorders and administration site conditions (21.4%), while in study 0114 it was general disorders (6%), followed by blood & lymphatic systems disorders (4.5%) and infections (4%). Causality is not provided.

SAEs in AAU02 and AUS01 were not reported by disease group.

The rate of patients who presented SAE was slightly higher for patients ≥ 55 years in study 0109, compared to patients under 55 years (77.8% versus 63.1%), including grades 3 or 4 (66.7% versus 55.3%), while it was similar in study 0114. The rate of patients ≥ 55 who discontinued treatment due to AE was higher (27.8 %) when compared to the population under 55 (15.8%) in study 0109. Neoplasms (i.e. disease progression) were the most common reason for premature discontinuation of therapy. No such difference was detected in study 0114.

Newly diagnosed Ph+ ALL

In the overall population of 315 newly diagnosed Ph+ ALL patients, a total of 26 patients (8.2%) died, 13 of them (4.1%) of adverse events. No death was attributed to study drugs, although the different follow ups are provided in each study. A total of 70 patients (22.2%) discontinued treatment because of adverse events. SAE were reported with variable frequency, depending on the regimen combined with imatinib. The lowest frequency (4%) was reported in study AJP01, and the highest (81%) in study AUS01 that used a high-dose chemotherapy regimen in combination with imatinib. The most frequent SAEs were related to the SOC infection and infestation in studies AUS01 (56%), AAU02 (50%), AFR09 (10%) and APJ01 (1%), and to the nervous system in study AIT04 (11%).

For the ≥ 55 year population, the incidence of SAE in study ADE10 was lower in the chemotherapy induction arm than in the imatinib induction arm (100 % versus 39.2%). SAEs during imatinib monotherapy were not considered drug related, the most frequent being neutropenic fever in two patients and nausea and vomiting in two patients. The rate of reported SAES were similar in study AFR09 (30 %) and in study AIT04 (26.3%), although most frequent SAES in study AFR09 were infections (10%) versus peripheral neuropathy (10.5%) in study AIT04.

3.3 Laboratory findings

Relapsed/Refractory Ph+ ALL patients

In relapsed/refractory patients most frequent adverse events as regards laboratory findings with imatinib monotherapy were anaemia (43% and 8% in study 0109 and 0114 respectively), thrombocytopenia (30% and 7%) and neutropenia (18% and 10%). Duration of grade 3 or 4 haematological abnormalities ranges usually between 1-4 weeks. The haematological adverse events from studies AAU02 and AUS01 are not split by stage of disease, and therefore are discussed in the newly diagnosed Ph+ ALL patients section.

Haematological profile was similar in patients under 55 years and in patients ≥ 55. Only thrombocytopenia was more frequent in the group of patients under 55 years (28.9% versus 16.7 % respectively). The median time to first CTC grade 3 or 4 neutropenia in patients treated with imatinib 600 mg was about 35 days in patients under 55 years old and 8 days in older patients. Thrombocytopenia was seen for the first time at a median of about 15 days in < 55 years old and 4 days in older patients. The hematological profile in patients under and ≥ 55 years is comparable.

Regarding biochemistry findings, a total of 6 patients (11%) experienced liver toxicity. Of these, 3 patients (5%) from study 0109 experienced a grade 3 elevated SGPT. Two patients experienced Grade 3 elevated alkaline phosphatase and 1 patient had Grade 3 elevated bilirubin. No Grade 3/4 liver toxicity is reported in study AAU02 and study AUS01, although an increase of transaminases to Grade 1/2 and of bilirubin to Grade 1/2 was reported in 5 cycles of therapy. No worsening increase in transaminases or bilirubin CTC grade 3 or 4 was seen in patients ≥ 55.

An increase in creatinine to Grade 1/2 in 5 cycles and an instance of hyponatremia Grade 3/4 were also reported as adverse events in study AUS01.

Newly diagnosed Ph+ ALL patients

Regarding haematology, the only data that was consistently reported is time to recovery. No delayed hematological recovery is reported in studies AFR09 and AIT04, and persistent neutropenia was reported in two patients in study AJP01. In study ADE04, cohort 2, the duration of grade 3 or 4 thrombocytopenia and neutropenia was 12 days (range 3-57) and 16 days (range 3-47 days), respectively. In study AJP01, the median time to white blood cells recovery was 19 days and the median time to platelet recovery was 22 days. The median time to haematological recovery after each cycle of chemotherapy with the hyperCVAD and imatinib regimen was not different from the prior regimens.

There is in general little information about laboratory findings within the published studies as they are mainly focused on liver toxicity, although in some studies the effect on the related target organ is presented as an AE. No Grade 3 or 4 liver toxicities were reported in any study with the exception of AJP01, where one patient experienced a Grade 3/4 liver toxicity and in study ADE04, where transient Grade 3/4 non-hematological toxicity was observed.

3.4. Other evidence

Since 2001 the post marketing experience has been reviewed on an ongoing basis in the Periodic Safety Update Reports (PSUR). Based upon cumulative reviews in the most recent PSUR version 6 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.

Review of published literature

No safety data are provided by (Lee S et al 2005). Lee KH et al (2005) reported that all patients had grade 4 neutropenia with febrile neutropenia in 10 patients, requiring antibiotics treatment. One patient died of septic shock on day 14 of treatment. Bone marrow recovery was anyhow not delayed. Four patients experienced a Grade 3 or higher hyperbilirubinemia that resolved after the interruption of both L-asparaginase and imatinib. Other Grade 3 or 4 toxicities (nausea, epigastric pain, myalgia, liver enzyme abnormalities and weight gain) were reported in a few patients. Shimoni et al 2003 reported a total of 8 patients with Ph+ ALL or lymphoid blast crisis out of 15 patients treated with imatinib 600 or 400mg as single agent either as treatment of refractory disease or maintenance while a transplant donor was found. Imatinib was generally well tolerated, with a few patients developing bone pain, muscle cramp and fluid retention. A high incidence of severe liver toxicity was observed after the transplant procedure. The contribution of imatinib, continued until a few days before this high dose chemotherapy to this toxicity, is unclear.

3.5. Safety in special populations

Elderly patients

No subgroup analysis in elderly population, considered as ≥ 65 years, is submitted.

The safety information regarding patients ≥ 55 years has already been commented. No major differences were detected in the analysis by subgroup when compared to the population under 55. Out of 250 patients belonging to this age category 70 (28%) died; 31 (21%) out of 146 with relapsed/refractory disease and 14 (13.5%) out of 104 with newly diagnosed disease. None of the deaths reported in relapsed/refractory patients was attributed to adverse event, while a total of 4 patients (3.8%) with newly diagnosed diseased and treated with a combination of imatinib and chemotherapy died of adverse event.

Serious adverse events were reported in 34 patients (23%) out of 146 treated with imatinib monotherapy and in 52 patients (50%) out of 104 treated in combination with cytotoxic chemotherapy and/or steroids. Half of these SAE was reported in the parallel schedule cohort from study ADE04. The most frequently affected SOC by SAE were general disorders, blood and lymphatic disorders and infections with imatinib monotherapy and infection and infestation, hepatobiliary disorders and the nervous system with the combinations.

A total of 24 patients discontinued due to adverse events (9.6%), 12 patients treated with imatinib monotherapy (8.2%) and 12 treated in combination with chemotherapy or steroids (11.5%).

Paediatric patients

Five patients under 18 received imatinib in study 03001.

Nausea and vomiting were observed in all patients and were the most frequently reported AE with a suspected relationship to the study drug. No patients experienced grade 3 or 4 AE or SAE with a suspected relationship to study drug. One patient developed grade 4 neutropenia and thrombocytopenia and one patient developed grade 3 cytopenia.

As part of a study in all Ph+ leukemias, imatinib was administered to children under the age of 18 with Ph+ relapsed or refractory Ph+ ALL or Ph+ CML in lymphoid blast crisis (Champagne 2004). The starting dose was 260 mg/m^2. The imatinib dosage in subsequent cohorts was escalated in approximate 30 % increments from 260 to 340, 440 and 570 mg/m^2. Sixteen patients received imatinib for at least 6 months and 8 for at least 12 months. Premature discontinuation occurred in 13 of 17 with advanced myeloid or lymphoid leukaemia. Eleven of them died with evidence of refractory or recurrent disease, two additional patients died of disease recurrence following stem cell transplantation. The results of this paediatric study were described in the ISS of Glivec® for treatment of children with Ph+ CML.

The safety profile in this paediatric population was comparable to that in adults with the notable exceptions of a much lower incidence of musculoskeletal complaints and of superficial edema. There were no new safety findings. Nausea and vomiting were the most frequent AE, although they were less

frequent than in adults (nausea 4%, vomiting 3.5 %, fatigue 3.5 %, increased in hepatic enzymes 3%). Data on laboratory values are not available.

Due to the potential risks to the human fetus, women of childbearing potential were advised to avoid becoming pregnant and to use effective contraception during treatment. No cases of pregnancies were reported.

Discussion on Safety

Even though no major deviations were expected, the only Novartis sponsored study where information was consistently collected was study 0109. Relevant data can also be obtained from study 0114 and non-Novartis studies, although limitations intrinsic to this kind of evidence, such as underreporting of AE, are present.

Nevertheless, the safety profile of imatinib is consistent with that expected in ALL population (refractory and relapsing patients or newly diagnosed in combination with chemotherapy) and seems not different either from that seen previously with imatinib treatment in other disease populations. Apparently, when administered in combination with chemotherapy, no synergic effect regarding AE seems to have been evidenced with the only possible exception of hepatotoxicity. A precaution on the concomitant use of other hepatotoxic drugs, as suggested by the applicant, needs to be added on the SPC. However, the limited amount of information makes a further discussion of drug interactions necessary.

Even though the safety and efficacy analysis in the population ≥ 55 years, who usually cannot benefit from a bone marrow transplant, is essential in order to properly perform an adequate benefit-risk ratio in this population with unquestionably specific needs, a subanalysis of data of patients over 65 years might have been informative and is expected. Otherwise, a downward bias regarding safety in traditionally considered elderly population cannot be discarded.

Overall Discussion and Benefit-Risk Assessment

The prognosis of adult patients with newly diagnosed Ph+ ALL treated with chemotherapy is poor, with a less than 10% probability of long-term survival. Complete Remission rates with standard chemotherapy in younger patients range from 60-90% with a median CR duration of about 12 months.

The present application is intended to seek approval for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy, and relapsed or refractory Ph+ ALL as monotherapy. A total of 758 Ph+ ALL patients with either newly diagnosed or relapsed/refractory were enrolled in ten clinical studies, nine of which were open-label, non-randomized, phase II studies and only one was randomized.
Glivec at the proposed regimen demonstrated adequate efficacy and safety. The value of imatinib seems clear regarding the positive effect mainly on cytogenetic and molecular responses, and there is a well-characterized biological basis to support its use in this disease. The use of imatinib in combination with chemotherapy allows a higher percentage of patients to get a bone marrow transplant that might be a curable therapy for this disease. However, the majority of the presented studies have important flaws that preclude meaningful conclusions regarding the value of imatinib in the long-term time-to-event variables, such as disease-free survival or overall survival for Ph+ ALL patients. The groups in the different studies are in general scarce and very heterogeneous concerning not only the disease status but also in the schedule the imatinib is used with chemotherapy, either prior, concomitant or post-chemotherapy. Therefore, it is not currently known the optimal schedule of imatinib in combination with chemotherapy in the different phases of ALL treatment, i.e. induction, consolidation and maintenance, and whether imatinib treatment should be prolonged after the classical 2-year maintenance therapy. The high remission rate obtained with imatinib treatment leads to a higher proportion of candidates to receive a transplant, which is an adequate surrogate for clinical benefit. In the transplant setting there is also positive preliminary data with imatinib, but questions such as the potential use of imatinib in the conditioning regimen or the post-transplant optimum schedule remain to be answered.

Relapsed/ refractory Ph+ ALL is also a disease situation in which there are no effective treatments available; therefore, new effective drugs are needed. In this population of relapsed or refractory patients, imatinib in monotherapy produced a response rate that can be considered relevant: approximately 60% of patients achieved a remission or clearance of blasts with about 20% complete haematological remissions and 25% of major cytogenetic responses. Disappointingly, these responses have a very short duration and overall survival was only a few months; the clinical benefit of these results are not clear, due in part to the absence of an appropriate comparator. The elderly patients' results are positive and consistent with that of the whole studies population, which is interesting for a drug with a good tolerability. As the studies submitted used imatinib 600 mg in combination with different chemotherapy schedules obtaining positive results and there is no standard therapy, the proposal to use imatinib concomitantly with Ph+ ALL chemotherapy is acceptable.

As the experience with imatinib is limited, further investigations of the use of imatinib in combination with chemotherapy are recommended to improve current outcomes.

The company does not propose to conduct more studies in this indication. Other studies with imatinib in Ph+ ALL patients must also be presented.

The paediatric data submitted in this application are clearly insufficient. Taking into account the interest of having adequate treatments in this age group and also the currently authorised indication of CML blast crisis in children, there is a solid rationale to support the interest of this use of imatinib. The MAH is required to provide more data in Ph+ ALL in children.
Clinical safety concerns were also resolved satisfactorily. Until more information is available, a warning about the use of imatinib in combination is included in the SPC.

In conclusion, the positive efficacy and safety clinical results obtained with imatinib were apparently more consistent in the newly diagnosed Ph+ ALL population than in the relapsed/refractory group. The results were superior to those obtained with chemotherapy in the historical controls without added toxicity and allowed more patients to get a bone marrow transplant. The evidence presented can be considered sufficient to grant the proposed new labelling.

The changes proposed for the SPC are in accordance with the updated studies results and reflect adequately the comments made by the CHMP.
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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 paediatric data submitted in this application are clearly insufficient. Taking into account the interest of having adequate treatments in this age group and also the currently authorised indication of CML blast crisis in children, there is a solid rationale to support the interest of this use of imatinib. The MAH is required to provide adequate data in Ph+ ALL in children or, in its absence, an investigation plan of imatinib in Ph+ ALL should be provided to the CHMP. - *Novartis will follow-up on any investigator-initiated trials in pediatric Ph+ ALL patients and will keep the EMEA informed about any additional data in this patient population as part of the annual re-assessment.* - *With reference to the new EU guidance on paediatrics, as soon as the Paediatric committee will be in place, Novartis will approach the committee with a proposal within the*	31/07/2006

	Paediatric Investigational Plan (PIP) for Glivec.	
Clinical	In relapsed/refractory Ph+ ALL patients, the use of imatinib in monotherapy, although promising, is not completely satisfactory; therefore, combination with chemotherapy should be further investigated in order to optimise the results in this patient population. *Preliminary data is known utilizing imatinib in combination with chemotherapy in this population. However, the use of imatinib in combination with chemotherapy in newly diagnosed patients with Ph+ALL is increasing and these patients will likely be refractory to imatinib therapy if they suffer a relapse. Additionally, new second generation Bcr-Abl inhibitors have demonstrated activity in this imatinib refractory setting. For this reason Novartis does not feel that launching further investigations to optimize the results in this refractory patient population would be either fruitful or accomplishable. The MAH will report and discuss any data emerging from independent trials in the annual re-assessment report for Glivec.*	31/07/2006

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.