Sponsor

Novartis

Generic Drug Name

Nilotinib

Therapeutic Area of Trial

Philadelphia chromosome-positive (Ph+) leukemias including chronic myelogenous/myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL)

Approved Indication

Tasigna (nilotinib) is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Tasigna is indicated for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant or intolerant to prior therapy that included imatinib.

Protocol Number

CAMN107A2101

Title

A phase IA/II multicenter, dose-escalation study of oral AMN107 on a continuous daily dosing schedule in adult patients with Gleevec® (imatinib)-resistant/intolerant CML in chronic or accelerated phase or blast crisis, relapsed/refractory Ph+ ALL, and other hematologic malignancies

Study Phases

Phase IA/II

Study Start/End Dates

25-May-2004 to 20-Sep-2012

Study Design/Methodology

This was a Phase IA/II open-label, multicenter study to evaluate the safety, tolerability, biologic activity, and pharmacokinetic (PK) profile of nilotinib administered on a twice daily (bid) oral dosing schedule in adult patients. Phase I of the study was designed to identify the maximum tolerated dose (MTD) of nilotinib in patients with Philadelphia chromosome positive (Ph+) leukemia. The Phase II consisted of six arms (3 arms had 2 strata): imatinib-resistant relapsed/refractory Ph+ ALL (acute lymphoblastic leukemia) (ALL) (E4), chronic myeloid/myelogenous leukemia (CML)-BC (blast crisis) (E3, E9), CML-AP (accelerated

phase) (E1, E7), or CML-CP (chronic phase) (E2, E8), hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL) (E5) and systemic mastocytosis (SM) (E6).

The extension protocol allowed Phase I and Phase II patients to continue to receive nilotinib until the End-of-Study evaluation visit which was planned to occur 30-Nov-2011 defined as the Last Patient Last Visit and last dose of study drug in the extension phase, or until death, the development of intolerable toxicity, or the Investigator determined that it was no longer in the patient's best interest to continue therapy, whichever came first. Patients who discontinued study drug for reasons other than death were followed for survival every 3 months until planned end of study date of 30-Nov-2011. However, actual end of study date is 20-Sep-2012.

The extension phase was designed to enable patients to have additional access to drug and collect long term efficacy data. All serious adverse events and AEs leading to dose adjustments or study discontinued continued to be collected. Of the 939 patients receiving treatment in the core study, 189 patients continued to receive treatment in the extension phase. Only three (3) out of the ten (10) trial arms had more than 10 patients where comprehensive safety and efficacy analyses were done. Seven (7) arms did not have the pre-determined number of patients continuing into the extension to support a final comprehensive analyses. Data listings from those arms were reviewed by the clinical team for any significant safety concerns and none were found.

Centers

100 centers in 22 participating countries (Australia, 3; Austria, 1; Belgium, 4; Canada, 4; Denmark, 1; Finland, 1; France, 10; Germany, 8; Hong Kong, 1; Italy, 14; Korea, 5; Norway, 1; Netherlands, 2; New Zealand, 1; Poland, 5; Singapore, 1; Spain, 2; Sweden, 1; Switzerland, 2; Taiwan, 1; United Kingdom, 8; USA, 24).

Test Product, Doses, and Mode of Administration

Nilotinib hard gelatin capsules (50 mg and 200 mg) at starting doses of:

- 50 mg QD for schedule 1 oral dosing of Phase IA component
- 400 mg BID for both schedule 2 oral dosing of Phase IA and Phase II components of the study.

Statistical Methods

Phase I

Phase I of the study was designed to identify the maximum tolerated dose (MTD) of nilotinib in patients with Philadelphia chromosome positive (Ph+) leukemia. A two-sample (QD and BID doses) MCRM was used for dose-level selection and MTD determination. All data were summarized by the initial dose cohorts: 50mg QD, 100mg QD, 200mg QD, 400mg QD, 600mg QD, 800mg QD, 1200mg QD, 400mg BID, and 600mg BID.

Phase II

Arms 1, 5, and 6 used a Simon 2-stage minimax design to assess efficacy. Arms 2, 3 and 4 used a Fleming single-stage design to assess efficacy. The number, percentage and associated 95% confidence interval (CI) of responders are presented. The analysis of the primary efficacy variables was performed on the Conventional ITT or full analysis set (FAS) populations. The null hypothesis H0: $p \leq 0.10$ was tested against the alternative hypothesis H1: $p \geq 0.10$. Patients who discontinued before responding were considered to be non-responders.

In Ph+ ALL (E4), there were two subsets within the FAS (minimal residual disease (MRD) and non-MRD patients). Efficacy analyses are presented on the non-MRD subset of the FAS.

The incidence of treatment-emergent adverse events (new or worsening from baseline) was summarized by system organ class, severity (based on CTCAE grades -- version 3), type of adverse event, and relation to the study drug by dose cohort.

Extension Phase

Phase I cumulative analysis of 8 patients enrolled in the extension phase was combined across the participating centers. Phase II cumulative analysis was performed by disease indication combined across the participating centers.

Pharmacokinetic Analysis

The PK parameters of AMN107 were computed by compartment model independent methods. Descriptive statistics of PK parameters include mean, SD, and CV, min and max.

Study Population: Key Inclusion/Exclusion criteria

Ages Eligible for Study: 18 Years and older

Genders Eligible for Study: Both

Accepts Healthy Volunteers: No

Key inclusion Criteria:

- Patients with CML in blast crisis, CML in accelerated phase defined as never in blast crisis phase, or CML in chronic phase defined as never been in blast crisis phase or accelerated phase who have:
  - developed progressive disease during therapy with at least 600 mg of imatinib per day, -OR-
  - patients with CML on imatinib therapy, at any dose, developing progressive disease and the presence of a genetic mutation likely to result in imatinib resistance -OR-
  - have developed an intolerance to imatinib.
- Relapsed or refractory Ph+ ALL
- Hypereosinophilic syndrome/chronic eosinophilic leukemia.
- Systemic mastocytosis who have a clinical indication for treatment.
- Prior imatinib therapy for patients with Ph+ ALL, HES/CEL and SM is permitted but is not required
- CML patients who have been treated with an investigational tyrosine kinase inhibitor who otherwise meet the definition of imatinib-resistance or intolerance are eligible
- Written informed consent prior to any study procedures being performed

Key Exclusion Criteria:

- Impaired cardiac function
- Patients with severe/chronic or uncontrolled medical conditions (including but not limited to diabetes, infections, GI impairment, CNS infiltration, liver and kidney disease).
- Prior and concomitant use of certain medications (including but not limited to warfarin, chemotherapy, hematopoietic colony-stimulating growth factors, medications that can affect electrocardiogram test results, other investigational drugs).
- Women who are pregnant or breastfeeding.
- Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention.
- Patients unwilling to comply with the protocol.
- Known diagnosis of human immunodeficiency virus (HIV) infection.

Other protocol-defined inclusion/exclusion criteria may apply

Extension Phase Inclusion criteria

All the ongoing patients from Phase IA and II, who completed the final visit of the core phase and would continue to benefit from treatment, were entered into the extension phase:

- all ongoing Ph+ ALL, CML -BC, -AP, -CP Group B, HES/CEL, and SM patients from Phase II and all ongoing Phase I patients.
- CML -BC, -AP, -CP Group A patients from Phase II with at least 24 months of study drug treatment.

Participant Flow

Patient disposition all phases and arms

Disposition reason n (%)	Phase I Ongoing N = 119	CML-CP with prior imatinib only (Group A E2) N = 321	CML-CP with prior imatinib & other TKI (Group B E8) N = 49	CML-AP with prior imatinib only (Group A E1) N = 137	CML-AP with prior imatinib & other TKI (Group B E7) N = 25	CML-BC with prior imatinib only (Group A E3) N = 136	CML-BC with prior imatinib & other TKI (Group B E9) N = 34	Ph+ ALL E4 N = 41	HES/CEL E5 N = 16	SM E6 N = 61
Discontinued in core study without entering extension study	**111 (93.3)**	**215 (67.0)**	**34 (69.4)**	**122 (89.1)**	**24 (96)**	**129 (94.9)**	**33 (97.1)**	**39 (95.1)**	**13 (18.8)**	**53 (86.9)**
Abnormal laboratory values	0	3 (0.9)	0	7 (5.1)	0	2 (1.5)	0	2 (4.9)	0	0
Abnormal test procedure results	1 (0.8)	4 (1.2)	1 (2.0)	0	0	0	0	1 (2.4)	0	1 (1.6)
Administrative problems	4 (3.4)	14 (4.4)	3 (6.1)	5 (3.6)	2 (8.0)	9 (6.6)	1 (2.9)	0	2 (12.5)	5 (8.2)
Adverse events	15 (12.6)	64 (19.9)	6 (12.2)	24 (17.5)	7 (28.0)	21 (15.4)	3 (8.8)	7 (17.1)	5 (31.3)	18 (29.5)
Death[1]	8 (6.7)	3 (0.9)	0	3 (2.2)	2 (8.0)	5 (3.7)	0	2 (4.9)	0	1 (1.6)
Disease progression	70 (58.8)	92 (28.7)	19 (38.8)	64 (46.7)	10 (40.0)	75 (55.1)	24 (70.6)	26 (63.4)	5 (31.3)	11 (18.0)
Lost to follow-up	1 (0.8	2 (0.6)	0	1 (0.7)	0	0	1 (2.9)	0	0	1 (1.6)
Not stated	0	0	0	1 (0.7)	0	0	0	0	0	0
Protocol violation	1 (0.8)	7 (2.2)	1 (2.0)	2 (1.5)	1 (4.0)	2 (1.5)	0	0	0	1 (1.6)
Patient withdrew consent	11 (9.2)	26 (8.1)	4 (8.2)	15 (10.9)	2 (8.0)	15 (11.0)	4 (11.8)	1 (2.4)	1 (6.3)	15 (24.6)
Entered extension study	**8 (6.7)**	**106 (33.0)**	**15 (30.6)**	**15 (10.9)**	**1 (4.0)**	**7 (5.1)**	**1 (2.9)**	**2 (4.9)**	**3 (18.8)**	**8 (13.1)**
Completed	4 (3.4)	67 (20.9)	8 (16.3)	8 (5.8)	1 (4.0)	6	0	0	2 (12.5)	6 (9.8)
Discontinued in extension study	**4 (3.4)**	**39 (12.1)**	**7 (14.3)**	**7 (5.1)**	**0**	**1**	**1 (2.9)**	**2 (4.9)**	**1 (6.3)**	**2 (3.3)**
Abnormal laboratory values	0	1 (0.3)	0	0	0	0	0	0	0	0
Administrative problems	0	2 (0.6)	1 (2.0)	0	0	0	0	0	0	1 (1.6)
Adverse events	2 (2.5)	10 (3.1)	3 (6.1)	2 (1.5)	0	0	0	1 (2.4)	0	1 (1.6)

Disposition reason n (%)	Phase I Ongoing N = 119	CML-CP with prior imatinib only (Group A E2) N = 321	CML-CP with prior imatinib & other TKI (Group B E8) N = 49	CML-AP with prior imatinib only (Group A E1) N = 137	CML-AP with prior imatinib & other TKI (Group B E7) N = 25	CML-BC with prior imatinib only (Group A E3) N = 136	CML-BC with prior imatinib & other TKI (Group B E9) N = 34	Ph+ ALL E4 N = 41	HES/CEL E5 N = 16	SM E6 N = 61
Death[1]	0	4 (1.2)	0	0	0	1	0	0	0	0
Disease progression	1 (0.8)	12 (3.7)	3 (6.1)	4 (2.9)	0	0	1 (2.9)	1 (2.4)	0	0
Lost to follow-up	0	3 (0.9)	0	0	0	0	0	0	0	0
Protocol violation	0	1 (0.3)	0	0	0	0	0	0	0	0
Patient withdrew consent	1 (0.8)	6 (1.9)	0	1 (0.7)	0	0	0	0	1 (6.3)	0

[1] Includes only those patients for whom death was reported as the primary reason for discontinuation of therapy.

Baseline Characteristics

Demographic characteristics

Phase I

	All QD Doses* N = 69	400mg BID N = 32	600mg BID N = 18	All N = 119
Age (years)				
Mean	57.5	54.1	55.1	56.2
SD	14.82	16.82	14.54	15.29
Median	61.0	56.5	58.0	60.0
Min	15.0	21.0	18.0	15.0
Max	83.0	82.0	77.0	83.0
Age category				
< 35 years	6 (8.7)	4 (12.5)	1 (5.6)	11 (9.2)
>= 35 -< 55 years	17 (24.6)	11 (34.4)	7 (38.9)	35 (29.4)
>= 55 -< 65 years	21 (30.4)	4 (12.5)	4 (22.2)	29 (24.4)
>= 65 years	25 (36.2)	13 (40.6)	6 (33.3)	44 (37.0)
Sex				
Male	37 (53.6)	14 (43.8)	6 (33.3)	57 (47.9)
Female	32 (46.4)	18 (56.3)	12 (66.7)	62 (52.1)
Race				
Caucasian	60 (87.0)	27 (84.4)	13 (72.2)	100 (84.0)
Black	2 (2.9)	2 (6.3)	4 (22.2)	8 (6.7)
Oriental	1 (1.4)	1 (3.1)	0	2 (1.7)
Hispanic	5 (7.2)	2 (6.3)	1 (5.6)	8 (6.7)
Missing[1]	1 (1.4)	0	0	1 (0.8)
WHO performance status				
Grade 0	32 (46.4)	17 (53.1)	9 (50.0)	58 (48.7)
Grade 1	27 (39.1)	13 (40.6)	5 (27.8)	45 (37.8)
Grade 2	10 (14.5)	2 (6.3)	4 (22.2)	16 (13.4)

* This category includes all QD initial doses: 50mg, 100mg, 200mg, 400mg, 600mg, 800mg, and 1200mg (7, 7, 10, 10, 6, 19, and 10 patients, respectively, in QD initial dose cohorts).

[1]One patient listed as missing was of Saudi Arabian origin. The closest race description from the available choices was Oriental. Therefore, race was not entered for this patient, but the afore-mentioned explanation was provided as a comment.

Phase II

	CML-CP with prior imatinib only (Group A E2) N = 321	CML-CP with prior imatinib & other TKI (Group B E8) N = 49	CML-AP with prior imatinib only (Group A E1) N = 137	CML-AP with prior imatinib & other TKI (Group B E7) N = 25	CML-BC with prior imatinib only (Group A E3) N = 136	CML-BC with prior imatinib & other TKI (Group B E9) N = 34	PH+ ALL E4 N = 41	HES/CEL E5 N = 16	SM E6 N = 61
Age (years)									
Mean	56.6	56.8	56.4	55.8	52.9	46.6	47.8	58.2	51.9
SD	13.27	13.61	13.28	13.39	14.44	15.53	15.95	17.25	12.02
Median	58.0	58.0	57.0	59.0	54.0	48.5	46.0	62.0	52.0
Range	21-85	18-78	22-82	19.0-73.0	18-79	24.0-72.0	18.0- 75.0	25.0-84.0	29.0- 79.0
Age category – n (%)									
<35 years	22 (6.9)	3 (6.1)	8 (5.8)	2 (8.0)	16 (11.8)	10 (29.4)	12 (29.3)	2 (12.5)	4 (6.6)
≥35 to <55 years	104 (32.4)	16 (32.7)	49 (35.8)	7 (28.0)	53 (39.0)	11 (32.4)	15 (36.6)	4 (25.0)	29 (47.5)
≥55 to <65 years	97 (30.2)	12 (24.5)	39 (28.5)	11 (44.0)	32 (23.5)	8 (23.5)	5 (12.2)	3 (18.8)	21 (34.4)
≥65 years	98 (30.5)	18 (36.7)	41 (29.9)	5 (20.0)	35 (25.7)	5 (14.7)	9 (22.0)	7 (43.8)	7 (11.5)
Sex – n (%)									
Male	162 (50.5)	24 (49.0)	76 (55.5)	17 (68.0)	83 (61.0)	25 (73.5)	22 (53.7)	13 (81.3)	34 (55.7)
Female	159 (49.5)	25 (51.0)	61 (44.5)	8 (32.0)	53 (39.0)	9 (26.5)	19 (46.3)	3 (18.8)	27 (44.3)
Race – n (%)									
Caucasian	297 (92.5)	39 (79.6)	109 (79.6)	22 (88.0)	113 (83.1)	23 (67.6)	37(90.2)	15 (93.8)	58 (95.1)
Asian	5 (1.6)	7 (14.3)	15 (10.9)	2 (8.0)	9 (6.6)	7 (20.6)	2(4.9)	0	0
Black	15 (4.7)	2 (4.1	9 (6.6)	1 (4.0)	8 (5.9)	3 (8.8)	1(2.4)	0	0
Other	3 (0.9)	1 (2.0)	3 (2.2)	0	5 (3.7)	1 (2.9)	1(2.4)	1 (6.3)	3 (4.9)
Pacific islander	1 (0.3)	NA	1 (0.7)	NA	NA	NA	NA	NA	NA
Native American	NA	NA	NA	NA	1 (0.7)	NA	NA	NA	NA
WHO performance status – n (%)									
Grade 0	234 (72.9)	33 (67.3)	73 (53.3)	11 (44.0)	38 (27.9)	14 (41.2)	Not Available	9 (56.3)	26 (42.6)
Grade 1	80 (24.9)	13 (26.5)	56 (40.9)	12 (48.0)	64 (47.1)	10 (29.4)		6 (37.5)	25 (41.0)
Grade 2	6 (1.9)	2 (4.1)	7 (5.1)	2 (8.0)	30 (22.1)	10 (29.4)		1 (6.3)	8 (13.1)
Grade >2	0	0	1 (0.7)	0	2 (1.5)	0		0	1 (1.6)
Missing	1 (0.3)	1 (2.0)	0	0	2 (1.5)	0		0	1 (1.6)

Outcome measures

Primary Outcome Results

Phase 1

Summary of MTD population and dose-limiting toxicities (Safety)

Initial Dose Cohort	Total no. of patients	No. patients in MTD population	No. patients excluded MTD [2]	No. of patients with DLT	DLT (Cycle 1)	
					Event	No. of patients with that event [5]
50 mg q.d.	7	6	1	0	N/A	N/A
100 mg q.d.	7	7	0	0	N/A	N/A
200 mg q.d.	10	9	1	0	N/A	N/A
400 mg q.d.	10	10	0	0	N/A	N/A
600 mg q.d.	6	5	1	1	Hyperbilirubinemia [3]	1
800 mg q.d.	19	17	2	2	Subarachnoid hemorrhage	1
					Increased ALT	1
					Increased AST	1
					Hyperbilirubinemia [3]	1
1200 mg q.d.	10	9	1	3	Hyperbilirubinemia [3]	1
					Increased Lipase	1
					Increased ALT	1
400 mg b.i.d.[1] (last dose-escalation assessment)	12	11	1	3	Subdural hematoma	1
					Hyperbilirubinemia[3]	1
					Increased ALT	1
					Thrombocytopenia	1
400 mg b.i.d.[1] (Final assessment)	32	29	3	7	Subdural hematoma	1
					Hyperbilirubinemia [3]	4
					Increased ALT	1
					Thrombocytopenia	1
					Epigastric pain, elevated lipase and amylase levels	1
					Pancreatitis	1
600 mg b.i.d.[1] (last dose-escalation assessment)	10	10	0	3	Bone marrow aplasia	1
					neutropenia	1
					Hyperbilirubinemia[3,4]	2
600 mg b.i.d[1] (Final assessment)	18	18	0	5	Bone marrow aplasia	1
					Neutropenia	1
					Elevated lipase	1
					Musculoskeletal pain	1
					Abdominal pain	1
					Hyperbilirubinemia[3,4]	3

Initial Dose Cohort	Total no. of patients	No. patients in MTD population	No. patients excluded MTD [2]	No. of patients with DLT	DLT (Cycle 1)	
					Event	No. of patients with that event [5]

1 The initial sample size of the cohort included 12 patients in the 400 mg b.i.d. cohort and 10 patients in the 600 mg b.i.d. cohort at the time when MTD of 600 b.i.d. was initially determined as a result of the dose-escalation. The cohort was later expanded to further explore lower grade toxicity. The 32 patients in the final assessment for 400 mg b.i.d include the 12 patients in the last dose escalation assessment, and 20 additional patients. The 18 patients in the final assessment for 600 mg b.i.d. include the 10 patients in the last dose escalation assessment, and 8 additional patients. MCRM model confirmed the MTD, based on the final population.

2 9 patients were excluded from the MTD population, including 8 patients who did not have at least 21 of 28 days of nilotinib for the first 28 days, and 1 patient who did not have 3 unique samples collected in hematology and chemistry within 30 days post-baseline of treatment. Of these 9 patients, 8 discontinued due to disease progression [4 patients on days 6, 13, 20, and 22] and due to AEs [4 patients due to cardiac ischemia day 1, pneumonia day 10, lung edema day 13, and back pain possibly causing interruption of study drug for 13 days during cycle 1 [patient discontinued after 76 days]), and 1 patient died [day 28].

3 Hyperbilirubinemia = Total or Direct or Indirect

4 One patient had 2 DLT events of Hyperbilirubinemia (Total and Direct) and is counted only once in this DLT category

5 Patients with several DLT events are counted in each event categories for that dose cohort.

CML-CP: Rate of major cytogenetic response (MCyR)

CML-CP with prior imatinib only (Group A E2) rate of cytogenetic response (Conventional ITT)

	N (%)
Rate of MCyR	191 (59.5)

CML-CP=chronic myeloid leukemia in chronic phase; ITT=intent to treat; MCyR=major cytogenetic response

CML-CP with prior imatinib and other TKI (Group B E8) rate of cytogenetic response (FAS)

	N (%)
Rate of MCyR	22 (44.9)

CML-CP=chronic myeloid leukemia in chronic phase; ITT=intent to treat; MCyR=major cytogenetic response; TKI=tyrosine kinase inhibitor

CML-AP: Rate of confirmed overall hematologic response (HR)

CML-AP with prior imatinib only (Group A E1) rate of confirmed overall hematologic response (Conventional ITT)

	N (%)
Rate of confirmed overall HR	76 (55.5)

CML-AP=chronic myeloid leukemia in accelerated phase; HR=hematologic response; ITT=intent to treat

CML-AP with prior imatinib and other TKI (Group B E7) rate of confirmed overall hematologic response (FAS)

Best response	Confirmed N = 25 n (%)
Overall Hematologic response	10 (40.0)

; CML-AP=chronic myeloid leukemia in accelerated phase; FAS=full analysis set; TKI=tyrosine kinase inhibitor

CML-BC: Rate of confirmed overall HR

CML-BC with prior imatinib only (Group A E3) confirmed overall hematologic response rates (Conventional ITT)

	LBC N = 31 n (%)	MBC N = 105 n (%)	Total N = 136 n (%)
Hematological response			
Overall hematologic response	6 (19.4)	25 (23.8)	31 (22.8)

CML-BC=chronic myeloid leukemia in blast crisis; ITT=intent to treat; LBC=lymphoid blast crisis; MBC=myeloid blast crisis

CML-BC with prior imatinib and other TKI (Group B E9) rate of confirmed overall hematologic response (FAS)

Best response	Confirmed N = 34 n (%)
Overall Hematologic response	2 (5.9)

CI=confidence interval; CML-BC=chronic myeloid leukemia in blast crisis; ITT=intent to treat; TKI=tyrosine kinase inhibitor

Relapsed/refractory Ph+ ALL (E4) hematologic response rates (FAS:non-MRD patients)

Best hematologic response	N = 40 n (%)
Overall (Complete, CRp, or Partial)	8 (20.0)

CRp=complete response with incomplete platelet recovery; MRD=minimal residual disease; PH+ ALL= Philadelphia chromosome positive acute lymphoblastic leukemia

HES/CEL (E5) overall hematologic response (complete or partial) based on Investigator assessment (FAS)

Best hematologic response	HES N = 13 n (%)	95% CI	CEL N = 3 n (%)	95% CI	Total N = 16 n (%)	95% CI
Overall (complete or partial)	2 (15.4)	1.9 - 45.4	1 (33.3)	0.8 - 90.6	3 (18.8)	4.0 - 45.6
Complete response	2 (15.4)	1.9 - 45.4	1 (33.3)	0.8 - 90.6	3 (18.8)	4.0 - 45.6
Absence of response	11 (84.6)		2 (66.7)		13 (81.3)	
Stable disease	4 (30.8)		0		4 (25.0)	
Progression	3 (23.1)		0		3 (18.8)	
Death	0		0		0	
Not assessable	4 (30.8)		2 (66.7)		6 (37.5)	

Best hematologic response	HES N = 13 n (%)	95% CI	CEL N = 3 n (%)	95% CI	Total N = 16 n (%)	95% CI

CEL=chronic eosinophilic leukemia; CI=confidence interval; FAS=full analysis set; HES=hypereosinophilic syndrome

SM (E6) rate of overall response as assessed by the Investigator (FAS)

Best response	Total N = 61 n (%)
Overall response (95% CI)	14 (23.0) (13.2 - 35.5)
Complete remission	1 (1.6)
Incomplete remission	5 (8.2)
Pure clinical response	1 (1.6)
Good partial response	4 (6.6)
Minor response	3 (4.9)
Absence of response	47 (77.0)
Stable disease	23 (37.7)
Progression	7 (11.5)
Not assessable	17 (27.9)

CI=confidence interval; FAS=full analysis set; SM= systemic mastocytosis

Secondary Outcome Results

Phase II

Cumulative result summaries are provided below. For arms with <10 patients enrolled into the extension phase only core phase result summaries are reported.

CML-CP with prior imatinib only (Group A E2) overall duration of cytogenetic response and KM-estimated rate of duration (Conventional ITT)

	Rate (%)	N	Number Censored	Median (months)	95% CI	Range
Overall duration of MCyR		**191**	**135**	**Not reached**	**-**	**0.03-76.68**
Rate of continuing MCyR						
12 month	88.16				83.40-92.92	
24 month	77.63				71.32-83.93	
36 month	71.24				64.21-78.27	
48 month	70.47				63.36-77.59	
60 month	68.77				61.45-76.10	
Overall duration of CCyR		**147**	**114**	**Not reached**	**-**	**0.95-75.07**

	Rate (%)	N	Number Censored	Median (months)	95% CI	Range
Rate of continuing CCyR						
12 month	92.78				88.46-97.09	
24 month	82.68				76.22-89.14	
36 month	80.08				73.19-86.97	
48 month	79.18				72.15-86.22	
60 month	77.11				69.70-84.53	

CCyR=complete cytogenetic response; CI=confidence interval; CML-CP=chronic myeloid leukemia in chronic phase; ITT=intent to treat; KM=Kaplan-Meier; MCyR=major cytogenetic response

CML-CP with prior imatinib only (Group A E2) overall duration of complete hematologic response (CHR) in patients without CHR at Baseline and KM-estimated rate of duration (Conventional ITT)

	Rate (%)	N	Number censored	Median (months)	95% CI	Range
Overall duration of CHR		**158**	**98**	**66.56**	**37.75-**	**0.03-76.91**
Rate of continuing CHR						
6 month	96.48				93.45-99.51	
12 month	85.04				78.97-91.10	
18 month	72.99				65.31-80.68	
24 month	63.60				55.13-72.07	
36 month	58.87				50.07-67.67	
48 month	55.61				46.56-64.67	
60 month	54.48				45.34-63.62	

CHR=complete hematologic response; CI=confidence interval; CML-CP=chronic myeloid leukemia in chronic phase; ITT=intent to treat; KM=Kaplan-Meier

CML-CP with prior imatinib only (Group A E2) major molecular response (MMR) in patients with post-baseline PCR data (Conventional ITT)

	Total N n (%)
Patients with post-baseline PCR data	299 106 (35.5)

- MMR is defined as a reduction in Bcr-Abl/control gene % transcripts to <= 0.10% based on international scale. The control gene used may be either Abl or Bcr.

N = Number of patients in the respective category

n = Number of patients with MMR

ITT=intent to treat; MMR=major molecular response; PCR=polymerase chain reaction

CML-CP with prior imatinib only (Group A E2) time to progression to accelerated phase (AP) or blast crisis (BC) (Conventional ITT)

	Rate (%)	N	Censored	Median (months)	95% CI	Range
Time to progression to AP/BC		**321**	**208**	**69.3**	**48.3-**	**0.1-77.8**
Rate of no progression to AP/BC						
12 month	83.31				78.83-87.79	
24 month	64.18				58.08-70.28	
36 month	60.53				54.20-66.86	
48 month	57.10				50.56-63.64	
60 month	54.75				48.08-61.41	

AP=accelerated phase; BC=blast crisis; CI=confidence interval; CML-CP=chronic myeloid leukemia in chronic phase; ITT=intent to treat

CML-CP with prior imatinib only (Group A E2) time to progression (TTP) (Conventional ITT)

	Rate (%)	N	Censored	Median (months)	95% CI	Range
Time to progression		**321**	**191**	**55.6**	**30.5 -**	**0.1-77.8**
Rate of no progression						
12 month	77.46				72.48-82.43	
24 month	59.90				53.80-66.01	
36 month	54.62				48.31-60.94	
48 month	51.91				45.48-58.34	
60 month	49.09				42.55-55.63	

CI=confidence interval; CML-CP=chronic myeloid leukemia in chronic phase; ITT=intent to treat; TTP=time to progression

CML-CP with prior imatinib only (Group A E2) overall survival (ITT)

	Rate (%)	N	Censored	Median (months)	95% CI	Range
Overall survival		**321**	**227**	**Not reached**	**77.93-**	**0.66-79.67**
Survival rate						
12 month	95.27				92.94-97.61	
24 month	87.13				83.40-90.86	
36 month	83.39				79.22-87.56	
48 month	78.77				74.13-83.40	
60 month	72.47				67.33-77.61	

CI=confidence interval; CML-CP=chronic myeloid leukemia in chronic phase; ITT=intent to treat

CML-CP with prior imatinib and other TKI (Group B E8) overall duration of major cytogenetic response and KM-estimated rate of duration (FAS)

	Rate (%)	N	Censored	Median (months)	95% CI	Range
Overall duration of MCyR		**22**	**17**	**Not reached**	**44.25 -**	**0.03 – 56.15**
Rate of continuing MCyR						
12 month	83.1				65.29-100.0	
24 month	75.5				54.02-96.98	
36 month	75.5				54.02- 96.98	
48 month	60.4				28.83-91.97	
60 month	NA				NA	

CI=confidence interval; CML-CP=chronic myeloid leukemia in chronic phase; FAS=full analysis set; KM=Kaplan-Meier; MCyR=major cytogenetic response; TKI=tyrosine kinase inhibitor

CML-CP with prior imatinib and other TKI (Group B E8) complete hematologic response rate for patients without CHR at baseline (FAS)

	CML-CP N = 35 n (%)
Complete hematologic response	27 (77.1)
95% CI	59.9 - 89.6

CHR=complete hematologic response; CI=confidence interval; CML-CP=chronic myeloid leukemia in chronic phase; FAS=full analysis set; TKI=tyrosine kinase inhibitor

CML-CP with prior imatinib and other TKI (Group B E8) overall survival (FAS)

	Rate (%)	N	Censored	Median (months)	95% CI	Range
Overall survival		**49**	**35**	**Not reached**	**-**	**3.45 – 76.65**
Survival rate						
6 month	100.0				100.0-100.0	
12 month	95.83				90.18-100.00	
18 month	91.57				83.67-99.48	
24 month	89.44				80.69-98.20	
36 month	82.94				72.17-93.72	
48 month	75.76				63.22-88.30	
60 month	65.54				50.13-80.96	

CI=confidence interval; CML-CP=chronic myeloid leukemia in chronic phase; FAS=full analysis set; TKI=tyrosine kinase inhibitor

CML-AP with prior imatinib only (Group A E1) duration of confirmed overall hematologic response (HR) and KM-estimated rate of duration (Conventional ITT)

	Rate (%)	N	Number censored	Median (months)	95% CI	Range
Overall duration of confirmed overall HR		**76**	**36**	**21.49**	**15.67-38.64**	**2.17-73.86**
Rate of continuing confirmed overall HR						
12 month	73.71				63.24-84.18	
24 month	48.61				35.39-61.83	
36 month	38.60				24.93-52.27	
48 month	29.69				15.95-43.43	
60 month	26.72				13.18-40.26	

CML-AP=chronic myeloid leukemia -- accelerated phase; CI=confidence interval; HR=hematologic response; ITT=intent to treat; KM=Kaplan-Meier

CML-AP with prior imatinib only (Group A E1) overall duration of MCyR and KM-estimated rate of duration (Conventional ITT)

	Rate (%)	N	Censored	Median (months)	95% CI	Range
Overall duration of MCyR		**44**	**25**	**33.97**	**19.61-**	**1.12-74.78**
Rate of continuing MCyR						
6 month	90.51				81.65-99.37	
12 month	77.23				64.08-90.39	

	Rate (%)	N	Censored	Median (months)	95% CI	Range
18 month	71.14				56.55-85.73	
24 month	64.36				48.42-80.31	
36 month	47.20				28.55-65.86	
48 month	42.48				23.54-61.43	
60 month	42.48				23.54-61.43	

CML-AP=chronic myeloid leukemia -- accelerated phase; CI=confidence interval; HR=hematologic response; ITT=intent to treat; KM=Kaplan-Meier; MCyR=major cytogenetic response

CML-AP with prior imatinib only (Group A E1) major molecular response (MMR) in patients with post-baseline PCR data (Conventional ITT)

	Total		
	N	n	(%)
Patients with post-baseline PCR data	122	18	(14.8)

- MMR is defined as a reduction in Bcr-Abl/control gene % transcripts to <= 0.10% based on international scale. The control gene used may be either Abl or Bcr.

N = Number of patients in the respective category

n = Number of patients with MMR

ITT=intent to treat; MMR=major molecular response; PCR=polymerase chain reaction

CML-AP with prior imatinib only (Group A E1) time to progression (Conventional ITT)

	Rate (%)	N	Censored	Median (months)	95% CI	Range
Time to progression		**137**	**56**	**15.9**	**10.1-20.1**	**0.1-75.7**
Rate of no progression						
12 month	54.59				45.38-63.81	
24 month	33.36				23.79-42.93	
36 month	28.87				19.33-38.41	
48 month	20.08				10.83-29.34	
60 month	16.43				7.58-25.28	

CML-AP=chronic myeloid leukemia -- accelerated phase; CI=confidence interval; ITT=intent to treat

CML-AP with prior imatinib only (Group A E1) overall survival (ITT)

	Rate (%)	N	Censored	Median (months)	95% CI	Range
Overall survival		**137**	**60**	**47.54**	**38.24-64.30**	**0.16-78.88**
Survival rate						
12 month	80.60				73.90-87.30	
24 month	68.83				60.88-76.77	
36 month	61.31				52.85-69.77	
48 month	49.32				40.48-58.16	
60 month	44.09				35.26-52.93	

CML-AP=chronic myeloid leukemia -- accelerated phase; CI=confidence interval; ITT=intent to treat

CML-AP with prior imatinib and other TKI (Group B E7) cytogenetic response rates (FAS)

Best response	CML-AP N=25 n (%)
Major (Complete plus Partial)	4 (16.0)
95% CI	4.5-36.1
Complete	2 (8.0)
Partial	2 (8.0)
Minor	4 (16.0)
Minimal	2 (8.0)
None	4 (16.0)

CI=confidence interval; CML-AP= chronic myeloid leukemia -- accelerated phase; FAS=full analysis set; TKI=tyrosine kinase inhibitor

CML-AP with prior imatinib and other TKI (Group B E7) overall survival (FAS)

Parameter	CML-AP N=25
Overall survival (months)	
Number censored	7
Median	13.90
95% CI	10.09-29.93
Continuing survival rate	
6 months	76.00
95% CI	59.26-92.74
12 months	63.53
95% CI	44.48-82.58
18 months	41.93
95%	22.01-61.85
24 months	37.27
95% CI	17.58-56.96

Kaplan-Meier estimated median survival and rates of survival are presented.

CI=confidence interval; CML-AP= chronic myeloid leukemia -- accelerated phase; FAS=full analysis set; TKI=tyrosine kinase inhibitor

CML-BC with prior imatinib only (Group A E3) time to and duration of hematologic response among responders (Conventional ITT)

	LBC N = 31 n (%)	MBC N = 105 n (%)	Total N = 136 n (%)
Number of responders	6	25	31
Time to response (months)			
Median	1.4	1.0	1.0
Minimum – maximum	1.0 - 6.0	0.9 -11.1	0.9 -11.1
Duration of response (months)			
Number censored	2	18	20
Median	3.6	26.3	26.3
Rate of continuing confirmed HR			
6 months (95%CI)	NA	77.28% (57.61-96.94)	64.68% (44.80-84.57)
12 months (95%CI)	NA	77.28% (57.61-96.94)	64.68% (44.80-84.57)
18 months (95%CI)	NA	70.25% (48.07-92.43)	58.80% (37.65-79.96)
24 months (95%CI)	NA	60.21% (33.89-86.54)	50.40% (26.72-74.09)

Duration and time to hematologic response are calculated only for patients with hematologic response.

CI=confidence interval: CML-BC= Chronic myeloid leukemia -- blast crisis; HR=hematologic response; ITT=intent to treat; LBC=lymphoid blast crisis; MBC=myeloid blast crisis

CML-BC with prior imatinib only (Group A E3) cytogenetic response rates (Conventional ITT)

	LBC N = 31 n (%)	MBC N = 105 n (%)	Total N = 136 n (%)
Major response	16 (51.6)	40 (38.1)	56 (41.2)
95% CI	33.1-69.8	28.8-48.1	32.8-49.9
Complete response	10 (32.3)	31 (29.5)	41 (30.1)
Partial response	6 (19.4)	9 (8.6)	15 (11.0)
Minor response	1 (3.2)	4 (3.8)	5 (3.7)
Minimal response	2 (6.5)	10 (9.5)	12 (8.8)
None	0	17 (16.2)	17 (12.5)

CI=confidence interval: CML-BC= Chronic myeloid leukemia -- blast crisis; ITT=intent to treat; LBC=lymphoid blast crisis; MBC=myeloid blast crisis

CML-BC with prior imatinib only (Group A E3) time to and duration of major cytogenetic response for responders (Conventional ITT)

	LBC N = 31 n (%)	MBC N = 105 n (%)	Total N = 136 n (%)
Number of responders	16	40	56
Time to response (months)			
Median	1.0	1.8	1.2
Minimum – maximum	1.0-1.3	1.0-2.7	1.0-1.9
Duration of response (months)			
Number censored	4	21	25
Median	3.2	10.8	5.8
Rates of continuing MCyR			
6 months (95%CI)	9.09% (0-25.84)	57.51% (40.16-74.86)	44.55% (29.79-59.31)
12 months (95%CI)	NA	48.66% (30.15-67.17)	38.19% (23.13-53.24)
18 months (95%CI)	NA	43.79% (24.83-62.75)	34.37% (19.07-49.67)
24 months (95%CI)	NA	43.79% (24.83-62.75)	34.37% (19.07-49.67)

Duration and time to hematologic response are calculated only for patients with hematologic response.
CI=confidence interval: CML-BC= Chronic myeloid leukemia -- blast crisis; ITT=intent to treat; LBC=lymphoid blast crisis; MBC=myeloid blast crisis; MCyR=major cytogenetic response

CML-BC with prior imatinib only (Group A E3) overall survival (ITT)

	LBC N = 31	MBC N = 105	Total N = 136
Overall survival (months)			
Number censored	2	34	36
Median	7.9	10.1	9.7
95% CI	5.36-13.14	7.98-12.65	7.52-12.48
Survival rate			
6 months (95% CI)	58.06% (40.69-75.44)	66.46% (57.40-75.52)	64.53% (56.47-72.60)
12 months (95% CI)	35.48% (18.64-52.33)	44.09% (34.52-53.67)	42.11% (33.76-50.47)
18 months (95% CI)	19.35% (5.45-33.26)	34.29% (25.12-43.47)	30.83% (23.01-38.66)
24 months (95% CI)	9.68% (0.00-20.08)	32.28% (23.23-41.33)	26.93% (19.39-34.48)

CI=confidence interval: CML-BC= chronic myeloid leukemia -- blast crisis; ITT=intent to treat; LBC=lymphoid blast crisis; MBC=myeloid blast crisis

CML-BC with prior imatinib and other TKI (Group B E9) best cytogenetic response (FAS)

	All patients N = 34	
Cytogenetic response	n (%)	95% CI
Major = complete + partial	8 (23.5)	10.7 - 41.2
Complete	1 (2.9)	0.1 - 15.3
Partial	7 (20.6)	8.7 - 37.9
Minor	2 (5.9)	
Minimal	2 (5.9)	
None	6 (17.6)	

- The calculation of confidence interval is based on the Pearson-Clopper formula.
- Response definition in terms of percentage of Ph+ metaphases:
0% = complete; >0% - <=35% = partial; >35% - <=65% = minor; >65% - <=95% = minimal; >95% = none.
- Any response category includes those patients evaluated as the corresponding category at any assessment and have no other superior assessment.
CI=confidence interval; CML-BC= chronic myeloid leukemia -- blast crisis; FAS=full analysis set; TKI=tyrosine kinase inhibitor

Overall survival (FAS)

Parameter	CML-BC N = 34
Overall survival (months)	
Number censored	3
Median	3.71
95% CI	2.86-6.97
Continuing survival rate	
6 months	36.83
95% CI	20.35-53.31
12 months	12.28
95% CI	1.02-23.53
18 months	9.21
95%	0.00-19.13
24 months	4.60
95% CI	0.00-12.68

CI=confidence interval: CML-BC= chronic myeloid leukemia -- blast crisis; FAS=full analysis set; MCyR=major cytogenetic response

Relapsed/refractory Ph+ ALL (E4) cytogenetic response rates (FAS:non-MRD)

Best cytogenetic response	**N = 40** **n (%)**
Major (Complete + Partial)	20 (50.0)
95% CI	33.8 - 66.2
Complete	13 (32.5)
Partial	7 (17.5)
Minor	3 (7.5)
Minimal	2 (5.0)
None	2 (5.0)

CI=confidence interval; FAS=full analysis set; MRD=minimal residual disease; PH+ ALL=Philadelphia chromosome positive acute lymphoblastic leukemia

Relapsed/refractory Ph+ ALL (E4) overall survival (FAS:non-MRD)

	N = 40
Overall survival (months)	**40**
Number censored	4
Median	5.16
95% CI	3.22 - 8.25
Rate of Survival	**% (95% CI)**
6 months	43.17 (27.45-58.89)
12 months	26.98 (12.79-41.17)
18 months	21.58 (8.41-34.76)
24 months	10.79 (0.83-20.76)

Kaplan-Meier estimated median survival and rates of survival are presented.

CI=confidence interval; FAS=full analysis set; MRD=minimal residual disease; PH+ ALL=Philadelphia chromosome positive acute lymphoblastic leukemia

HES/CEL (E5) overall survival (FAS)

	HES **N = 13**	**CEL** **N = 3**	**Total** **N = 16**
Overall survival (months)			
Number censored	11	2	13
Median	--	--	--
95% CI	--	0.49	--
Rate of survival (% [95% CI])			
6 months	92.3 (77.82-100.00)	66.7 (13.32-100.00)	87.5 (71.30-100.00)
12 months	84.6 (65.00-100.00)	66.7 (13.32-100.00)	81.3 (62.13-100.00)
18 months	84.6 (65.00-100.00)	66.7 (13.32-100.00)	81.3 (62.13-100.00)
24 months	84.6 (65.00-100.00)	--	81.3 (62.13-100.00)

CI=confidence interval; FAS=full analysis set; CEL=chronic eosinophilic leukemia; HES=hypereosinophilic syndrome

SM (E6) overall survival (FAS)

Overall survival (months)	Total N = 61
Number censored	51
Median	NA
Rate of survival - % (95% CI):	
6 months	91.3 (84.07-98.60)
12 months	91.3 (84.07-98.60)
18 months	85.3 (75.89-94.78)
24 months	81.2 (70.57-91.77)

CI=confidence interval; FAS=full analysis set; SM=systemic mastocytosis

One death was identified in the safety and epidemiology database which was not included in the clinical database at the time of database lock; the cause of death was reported as disease progression.

Safety Results

Cumulative result summaries are provided below. For arms with <10 patients enrolled into the extension phase, data listings were reviewed by the clinical team for any significant safety concerns. No significant concerns in serious adverse events and AEs leading to dose adjustments or study discontinuations were found.

Phase 1

AEs which are not SAEs and SAEs in at least 5% of patients regardless of study drug relationship by primary system organ class

Primary System Organ Class	Phase 1 AEs which are not SAEs N = 119 N(%)	Phase 1 SAEs N = 119 N(%)
Any primary system organ class	119 (100.0)	98 (82.4)
Blood and lymphatic system disorders	85 (71.4)	47 (39.5)
Cardiac disorders	36 (30.3)	17 (14.3)
Ear and labyrinth disorders	9 (7.6)	1 (0.8)
Gastrointestinal disorders	101 (84.9)	27 (22.7)
General disorders and administration site conditions	101 (84.9)	31 (26.1)
Hepatobiliary disorders	20 (16.8)	6 (5.0)
Infections and infestations	85 (71.4)	37 (31.1)
Injury, poisoning and procedural complications	37 (31.1)	5 (4.2)
Investigations	64 (53.8)	27 (22.7)
Metabolism and nutrition disorders	85 (71.4)	7 (5.9)
Musculoskeletal and connective tissue disorders	85 (71.4)	15 (12.6)

Primary System Organ Class	Phase 1 AEs which are not SAEs N = 119 N(%)	Phase 1 SAEs N = 119 N(%)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	3 (2.5)	4 (3.4)
Nervous system disorders	76 (63.9)	13 (10.9)
Psychiatric disorders	41 (34.5)	1 (0.8)
Renal and urinary disorders	28 (23.5)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	90 (75.6)	18(15.1)
Skin and subcutaneous tissue disorders	99 (83.2)	6 (5.0)
Vascular disorders	50 (42.0)	10 (8.4)

Most frequent adverse events which are not SAEs and SAEs (at least 10%) by preferred term

Preferred Term	Phase 1 AEs which are not SAEs N = 119 n (%)	Phase 1 SAEs N = 119 n (%)
-Any event	119 (100.0)	98 (82.4)
Anemia	61 (51.3)	2 (1.7)
Nausea	68 (57.1)	4 (3.4)
Thrombocytopenia	48 (40.3)	26 (21.8)
Febrile neutropenia	6 (5.0)	20 (16.8)
Pyrexia	56 (47.1)	22 (18.5)
Vomiting	55 (46.2)	4 (3.4)
Rash	51 (42.9)	3 (2.5)
Diarrhoea	48 (40.3)	7 (5.9)
Fatigue	46 (38.7)	1 (0.8)
Headache	44 (37.0)	2 (1.7)
Cough	45 (37.8)	1 (0.8)
Dyspnoea	36 (30.3)	6 (5.0)
Oropharyngeal pain	22 (18.5)	0 (0.0)
Constipation	36 (30.3)	0 (0.0)
Dehydration	14 (11.8)	3 (2.5)
Oedema peripheral	34 (28.6)	0 (0.0)
Weight decreased	15 (12.6)	0 (0.0)
Weight increased	13 (10.9)	0 (0.0)
Lipase increased	12 (10.1)	6 (5.0)
Blood bilirubin increased	14 (11.8)	3 (2.5)

Preferred Term	Phase 1 AEs which are not SAEs N = 119 n (%)	Phase 1 SAEs N = 119 n (%)
Myalgia	12 (10.1)	0 (0.0)
Anxiety	12 (10.1)	0 (0.0)
Decreased appetite	39 (32.8)	0 (0.0)
Pruritus	43 (36.1)	0 (0.0)
Hyperuricaemia	27 (22.7)	0 (0.0)
Hypokalaemia	23 (19.3)	1 (0.8)
Nasopharyngitis	25 (21.0)	0 (0.0)
Pain in extremity	28 (23.5)	1 (0.8)
Muscle spasms	24 (20.2)	1 (0.8)
Dizziness	27 (22.7)	0 (0.0)
Dry skin	26 (21.8)	0 (0.0)
Arthralgia	22 (18.5)	0 (0.0)
Bone pain	18 (15.1)	5 (4.2)
Back pain	19 (16.0)	3 (2.5)
General physical health deterioration	18 (15.1)	4 (3.4)
Asthenia	16 (13.4)	1 (0.8)
Chills	16 (13.4)	2 (1.7)
Hypocalcaemia	15 (12.6)	1 (0.8)
Neutropenia	18 (15.1)	14 (11.8)
Pneumonia	7 (5.9)	13 (10.9)
Dyspnoea exertional	15 (12.6)	1 (0.8)
Musculoskeletal pain	14 (11.8)	1 (0.8)
Rhinorrhoea	14 (11.8)	0 (0.0)
Epistaxis	12 (10.1)	0 (0.0)
Night sweats	17 (14.3)	0 (0.0)
Abdominal pain	28 (23.5)	8 (6.7)
Abdominal pain upper	22 (18.5)	4 (3.4)
Abdominal discomfort	13 (10.9)	1 (0.8)
Insomnia	15 (12.6)	0 (0.0)
Hypertension	18 (15.1)	1 (0.8)
Hypotension	14 (11.8)	1 (0.8)
Rash pruritic	14 (11.8)	0 (0.0)
Alopecia	12 (10.1)	0 (0.0)

Phase II & Extension

CML-CP with prior imatinib only (Group A E2)

Adverse events in at least 5% of patients regardless of study drug relationship by primary system organ class

	CML-CP with prior imatinib only (Group A E2) Total N = 321
-Any primary system organ class	**319 (99.4)**
Gastrointestinal disorders	246 (76.6)
Skin and subcutaneous tissue disorders	231 (72.0)
General disorders and administration site conditions	230 (71.7)
Musculoskeletal and connective tissue disorders	221 (68.8)
Infections and infestations	211 (65.7)
Nervous system disorders	190 (59.2)
Investigations	175 (54.5)
Blood and lymphatic system disorders	167 (52.0)
Respiratory, thoracic and mediastinal disorders	176 (54.8)
Metabolism and nutrition disorders	147 (45.8)
Eye disorders	103 (32.1)
Vascular disorders	97 (30.2)
Cardiac disorders	93 (29.0)
Psychiatric disorders	91 (28.3)
Injury, poisoning and procedural complications	69 (21.5)
Renal and urinary disorders	64 (19.9)
Hepatobiliary disorders	54 (16.8)
Reproductive system and breast disorders	50 (15.6)
Ear and labyrinth disorders	37 (11.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	25 (7.8)

CML-CP=chronic myeloid/myelogenous leukemia-chronic phase

Most frequent adverse events (at least 10%) by preferred term

Preferred Term	CML-CP with prior imatinib only (Group A E2) All grades N = 321 n (%)	CML-CP with prior imatinib only (Group A E2) Grade 3 or 4 N = 321 n (%)
-Any event	319 (99.4)	263 (81.9)
Nausea	122 (38.0)	4 (1.2)
Rash	118 (36.8)	6 (1.9)
Headache	115 (35.8)	9 (2.8)
Thrombocytopenia	107 (33.3)	77 (24.0)
Fatigue	105 (32.7)	12 (3.7)
Pruritus	104 (32.4)	3 (0.9)
Vomiting	94 (29.3)	3 (0.9)
Diarrhoea	93 (29.0)	10 (3.1)
Cough	91 (28.3)	3 (0.9)
Constipation	88 (27.4)	3 (0.9)
Arthralgia	86 (26.8)	8 (2.5)
Nasopharyngitis	80 (24.9)	2 (0.6)
Pyrexia	73 (22.7)	3 (0.9)
Anaemia	71 (22.1)	26 (8.1)
Pain in extremity	65 (20.2)	7 (2.2)
Myalgia	63 (19.6)	6 (1.9)
Back pain	63 (19.6)	7 (2.2)
Neutropenia	59 (18.4)	56 (17.4)
Lipase increased	55 (17.1)	32 (10.0)
Oedema peripheral	55 (17.1)	1 (0.3)
Dyspnoea	53 (16.5)	9 (2.8)
Asthenia	53 (16.5)	0
Decreased appetite	51 (15.9)	1 (0.3)
Abdominal pain	50 (15.6)	5 (1.6)
Abdominal pain upper	47 (14.6)	3 (0.9)
Bone pain	45 (14.0)	4 (1.2)
Muscle spasms	45 (14.0)	2 (0.6)
Upper respiratory tract infection	42 (13.1)	0
Alanine aminotransferase increased	40 (12.5)	10 (3.1)
Insomnia	40 (12.5)	4 (1.2)
Oropharyngeal pain	39 (12.1)	0
Dizziness	38 (11.8)	3 (0.9)
Hypertension	37 (11.5)	6 (1.9)

Preferred Term	CML-CP with prior imatinib only (Group A E2) All grades N = 321 n (%)	CML-CP with prior imatinib only (Group A E2) Grade 3 or 4 N = 321 n (%)
Night sweats	37 (11.5)	1 (0.3)
Dry skin	36 (11.2)	0
Alopecia	34 (10.6)	0
Dyspepsia	33 (10.3)	1 (0.3)
Hyperbilirubinaemia	33 (10.3)	11 (3.4)
Musculoskeletal pain	32 (10.0)	1 (0.3)

CML=chronic myeloid/myelogenous leukemia; CP=chronic phase

CML-CP with prior imatinib and other TKI (Group B E8)

Adverse events in at least 5% of patients regardless of study drug relationship by primary system organ class

	CML-CP with prior imatinib and other TKI (Group B E8) N = 49 n (%)
-Any primary system organ class	**48 (98.0)**
Skin and subcutaneous tissue disorders	35 (71.4)
Gastrointestinal disorders	32 (65.3)
Infections and infestations	31 (63.3)
Musculoskeletal and connective tissue disorders	29 (59.2)
General disorders and administration site conditions	28 (57.1)
Investigations	28 (57.1)
Blood and lymphatic system disorders	28 (57.1)
Nervous system disorders	21 (42.9)
Metabolism and nutrition disorders	21 (42.9)
Respiratory, thoracic and mediastinal disorders	16 (32.7)
Vascular disorders	13 (26.5)
Injury, poisoning and procedural complications	10 (20.4)
Hepatobiliary disorders	8 (16.3)
Cardiac disorders	7 (14.3)
Psychiatric disorders	7 (14.3)
Eye disorders	7 (14.3)
Renal and urinary disorders	6 (12.2)

	CML-CP with prior imatinib and other TKI (Group B E8) N = 49 n (%)
Reproductive system and breast disorders	4 (8.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (6.1)

CML-CP=chronic myeloid/myelogenous leukemia-chronic phase; TKI=tyrosine kinase inhibitor

Most frequent adverse events (at least 10% in any treatment group) by preferred term

Preferred Term	CML-CP with prior imatinib and other TKI (Group B E8) All grades N = 49 n (%)	CML-CP with prior imatinib and other TKI (Group B E8) Grade 3 or 4 N = 49 n (%)
-Any event	48 (98.0)	36 (73.5)
Rash	20 (40.8)	2 (4.1)
Thrombocytopenia	17 (34.7)	11 (22.4)
Neutropenia	15 (30.6)	15 (30.6)
Nausea	13 (26.5)	0
Fatigue	13 (26.5)	2 (4.1)
Asthenia	12 (24.5)	2 (4.1)
Headache	11 (22.4)	1 (2.0)
Anaemia	11 (22.4)	6 (12.2)
Constipation	10 (20.4)	0
Arthralgia	10 (20.4)	0
Lipase increased	10 (20.4)	7 (14.3)
Dyspnoea	9 (18.4)	3 (6.1)
Pruritus	9 (18.4)	0
Pain in extremity	9 (18.4)	0
Pyrexia	8 (16.3)	2 (4.1)
Abdominal pain	8 (16.3)	2 (4.1)
Alanine aminotransferase increased	8 (16.3)	3 (6.1)
Leukopenia	8 (16.3)	2 (4.1)
Nasopharyngitis	8 (16.3)	0
Back pain	8 (16.3)	2 (4.1)
Muscle spasms	8 (16.3)	0

Preferred Term	CML-CP with prior imatinib and other TKI (Group B E8) All grades N = 49 n (%)	CML-CP with prior imatinib and other TKI (Group B E8) Grade 3 or 4 N = 49 n (%)
Dyspepsia	7 (14.3)	0
Hypokalaemia	7 (14.3)	3 (6.1)
Decreased appetite	7 (14.3)	1 (2.0)
Myalgia	7 (14.3)	1 (2.0)
Vomiting	7 (14.3)	0
Diarrhoea	6 (12.2)	1 (2.0)
Hypomagnesaemia	6 (12.2)	0
Abdominal pain upper	6 (12.2)	0
Upper respiratory tract infection	5 (10.2)	0
Cough	5 (10.2)	0
Dizziness	5 (10.2)	0
Oedema peripheral	5 (10.2)	0
Hypophosphataemia	5 (10.2)	2 (4.1)
Pneumonia	5 (10.2)	2 (4.1)
Hypertension	5 (10.2)	0
Sinusitis	5 (10.2)	0
Weight increased	5 (10.2)	1 (2.0)
Aspartate aminotransferase increased	5 (10.2)	1 (2.0)

CML=chronic myeloid/myelogenous leukemia; CP=chronic phase; TKI=tyrosine kinase inhibitor

CML-AP with prior imatinib only (Group A E1)

Adverse events in at least 5% of patients regardless of study drug relationship by primary system organ class

	CML-AP with prior imatinib only (Group A E1) N = 137 n (%)
-Any primary system organ class	**136 (99.3)**
Blood and lymphatic system disorders	92 (67.2)
General disorders and administration site conditions	86 (62.8)
Infections and infestations	83 (60.6)
Gastrointestinal disorders	82 (59.9)
Musculoskeletal and connective tissue disorders	74 (54.0)
Skin and subcutaneous tissue disorders	72 (52.6)
Investigations	69 (50.4)
Metabolism and nutrition disorders	67 (48.9)
Respiratory, thoracic and mediastinal disorders	58 (42.3)
Nervous system disorders	48 (35.0)
Eye disorders	28 (20.4)
Vascular disorders	34 (24.8)
Cardiac disorders	26 (19.0)
Psychiatric disorders	24 (17.5)
Injury, poisoning and procedural complications	19 (13.9)
Renal and urinary disorders	19 (13.9)
Hepatobiliary disorders	21 (15.3)
Reproductive system and breast disorders	13 (9.5)
Ear and labyrinth disorders	9 (6.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (5.8)

CML=chronic myeloid/myelogenous leukemia; CP=chronic phase

Most frequent adverse events (at least 10%) by preferred term

Preferred Term	CML-AP with prior imatinib only (Group A E1) All grades N = 137 n (%)	CML-AP with prior imatinib only (Group A E1) Grade 3 or 4 N = 137 n (%)
-Any event	136 (99.3)	105 (76.6)
Thrombocytopenia	64 (46.7)	55 (40.1)
Anaemia	47 (34.3)	23 (16.8)
Rash	40 (29.2)	0
Pyrexia	38 (27.7)	3 (2.2)
Neutropenia	35 (25.5)	32 (23.4)
Diarrhoea	34 (24.8)	3 (2.2)
Fatigue	31 (22.6)	1 (0.7)
Nausea	30 (21.9)	1 (0.7)
Pruritus	28 (20.4)	0 (0.0)
Headache	27 (19.7)	2 (1.5)
Constipation	26 (19.0)	0
Cough	25 (18.2)	0
Pain in extremity	24 (17.5)	2 (1.5)
Abdominal pain	23 (16.8)	4 (2.9)
Decreased appetite	23 (16.8)	1 (0.7)
Arthralgia	22 (16.1)	0
Myalgia	22 (16.1)	2 (1.5)
Bone pain	21 (15.3)	4 (2.9)
Lipase increased	21 (15.3)	11 (8.0)
Nasopharyngitis	21 (15.3)	0
Back pain	20 (14.6)	1 (0.7)
Muscle spasms	20 (14.6)	0
Asthenia	19 (13.9)	2 (1.5)
Vomiting	18 (13.1)	0
Musculoskeletal pain	17 (12.4)	2 (1.5)
Oedema peripheral	16 (11.7)	0
Abdominal pain upper	16 (11.7)	1 (0.7)
Alopecia	16 (11.7)	0
Hypertension	16 (11.7)	1 (0.7)
Leukopenia	16 (11.7)	11 (8.0)
Hyperbilirubinaemia	14 (10.2)	5 (3.6)

AP=accelerated phase; CML=chronic myeloid/myelogenous leukemia

CML-AP with prior imatinib and other TKI (Group B E7)

Adverse events which are not SAEs and SAEs in at least 5% of patients regardless of study drug relationship by primary system organ class

Primary System Organ Class	CML-AP with prior imatinib & other TKI (Group B E7) AEs which are not SAEs N = 25 n(%)	CML-AP with prior imatinib & other TKI (Group B E7) SAEs N = 25 n(%)
Any primary system organ class	25 (100.0)	13 (52.0)
Blood and lymphatic system disorders	17 (68.0)	6 (24.0)
Cardiac disorders	3 (12.0)	0 (0.0)
Gastrointestinal disorders	17 (68.0)	4 (16.0)
General disorders and administration site conditions	17 (68.0)	5 (20.0)
Infections and infestations	11 (44.0)	3 (12.0)
Investigations	13 (52.0)	1 (4.0)
Metabolism and nutrition disorders	8 (32.0)	1 (4.0)
Musculoskeletal and connective tissue disorders	14 (56.0)	1 (4.0)
Nervous system disorders	9 (36.0)	2 (8.0)
Psychiatric disorders	4 (16.0)	0 (0.0)
Renal and urinary disorders	4 (16.0)	1 (4.0)
Reproductive system and breast disorders	4 (16.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	11 (44.0)	3 (12.0)
Skin and subcutaneous tissue disorders	17 (68.0)	0 (0.0)
Vascular disorders	2 (8.0)	1 (4.0)

Most frequent adverse events which are not SAEs and SAEs (at least 10%) by preferred term

Preferred Term	CML-AP with prior imatinib & other TKI (Group B E7) AEs which are not SAEs N = 25 n (%)	CML-AP with prior imatinib & other TKI (Group B E7) SAEs N = 25 n (%)
-Any event	25 (100.0)	13 (52.0)
Neutropenia	8 (32.0)	1 (4.0)
Nausea	8 (32.0)	0 (0.0)
Rash	9 (36.0)	0 (0.0)
Thrombocytopenia	6 (24.0)	1 (4.0)
Fatigue	6 (24.0)	0 (0.0)
Vomiting	6 (24.0)	1 (4.0)
Diarrhoea	6 (24.0)	0 (0.0)
Nasopharyngitis	5 (20.0)	0 (0.0)
Pyrexia	9 (36.0)	2 (8.0)
Anaemia	8 (32.0)	0 (0.0)
Leukopenia	5 (20.0)	0 (0.0)
Headache	5 (20.0)	0 (0.0)
Cough	6 (24.0)	0 (0.0)
Dyspnoea	4 (16.0)	1 (4.0)
Asthenia	4 (16.0)	1 (4.0)
Stomatitis	3 (12.0)	0 (0.0)
Abdominal pain	3 (12.0)	1 (4.0)
Bone pain	5 (20.0)	0 (0.0)
Muscle spasms	3 (12.0)	0 (0.0)
Alanine aminotransferase increased	5 (20.0)	0 (0.0)
Pain in extremity	5 (20.0)	0 (0.0)
Pruritus	4 (16.0)	0 (0.0)
Musculoskeletal chest pain	4 (16.0)	0 (0.0)
Hypocalcaemia	4 (16.0)	0 (0.0)
Dyspepsia	4 (16.0)	0 (0.0)
Erythema	3 (12.0)	0 (0.0)
Dry skin	3 (12.0)	0 (0.0)
Night sweats	3 (12.0)	0 (0.0)
Toothache	3 (12.0)	0 (0.0)
Hypomagnesaemia	3 (12.0)	0 (0.0)
Hypokalaemia	3 (12.0)	0 (0.0)

CML-BC with prior imatinib only (Group A E3)

AEs which are not SAEs and SAEs in at least 5% of patients regardless of study drug relationship by primary system organ class

Primary System Organ Class	CML-BC with prior imatinib only (Group A E3) AEs which are not SAEs N = 136 n (%)	CML-BC with prior imatinib only (Group A E3) SAEs N = 136 n (%)
Any primary system organ class	135 (99.3)	84 (61.8)
Blood and lymphatic system disorders	97 (71.3)	39 (28.7)
Cardiac disorders	18 (13.2)	3 (2.2)
Gastrointestinal disorders	95 (69.9)	24 (17.6)
General disorders and administration site conditions	90 (66.2)	22 (16.2)
Hepatobiliary disorders	17 (12.5)	2 (1.5)
Infections and infestations	66 (48.5)	31 (22.8)
Investigations	65 (47.8)	10 (7.4)
Metabolism and nutrition disorders	57 (41.9)	7 (5.1)
Musculoskeletal and connective tissue disorders	68 (50.0)	10 (7.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.01)	9 (6.6)
Nervous system disorders	52 (38.2)	11 (8.1)
Psychiatric disorders	27 (19.9)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	61 (44.9)	16 (11.8)
Skin and subcutaneous tissue disorders	79 (58.1)	0 (0.0)
Vascular disorders	28 (20.6)	6 (4.4)

- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
- Includes all adverse events on study and up to 28 days after last dose.

Most frequent adverse events which are not SAEs and SAEs (at least 10%) by preferred term

Preferred Term	CML-BC with prior imatinib only (Group A E3) AEs which are not SAEs N = 136 n (%)	CML-BC with prior imatinib only (Group A E3) SAEs N = 136 n (%)
-Any event	135 (99.3)	84 (61.8)
Febrile neutropenia	7 (5.1)	13 (9.6)

Preferred Term	CML-BC with prior imatinib only (Group A E3) AEs which are not SAEs N = 136 n (%)	CML-BC with prior imatinib only (Group A E3) SAEs N = 136 n (%)
Neutropenia	39 (28.7)	8 (5.9)
Nausea	41 (30.1)	9 (6.6)
Rash	39 (28.7)	0 (0.0)
Thrombocytopenia	60 (44.1)	14(10.3)
Fatigue	28 (20.6)	3 (2.2)
Vomiting	30 (22.1)	8 (5.9)
Diarrhoea	34 (25.0)	2 (1.5)
Pneumonia	7 (5.1)	15 (11.0)
Pyrexia	49 (36.0)	14(10.3)
Anaemia	61 (44.9)	6 (4.4)
Oedema peripheral	27 (19.9)	1 (0.7)
Arthralgia	20 (14.7)	2 (1.5)
Headache	26 (19.1)	2 (1.5)
Cough	21 (15.4)	0 (0.0)
Stomatitis	14 (10.3)	1 (0.7)
Dyspnoea	14 (10.3)	5 (3.7)
Asthenia	24 (17.6)	2 (1.5)
Abdominal pain upper	21 (15.4)	1 (0.7)
Back pain	19 (14.0)	3 (2.2)
Abdominal pain	17 (12.5)	4 (2.9)
Bone pain	14 (10.3)	4 (2.9)
Alanine aminotransferase increased	14 (10.3)	1 (0.7)
Blood bilirubin increased	14 (10.3)	1 (0.7)
Constipation	31 (22.8)	3 (2.2)
Chills	15 (11.0)	1 (0.7)
Weight decreased	15 (11.0)	0 (0.0)
Pain in extremity	18 (13.2)	2 (1.5)
Pruritus	18 (13.2)	0 (0.0)
Hypocalcaemia	15 (11.0)	1 (0.7)
Epistaxis	17 (12.5)	0 (0.0)
Oropharyngeal pain	16 (11.8)	1 (0.7)
Hypokalaemia	22 (16.2)	0 (0.0)

CML-BC with prior imatinib and other TKI (Group B E9)

AEs which are not SAEs and SAEs in at least 5% of patients regardless of study drug relationship by primary system organ class

Primary System Organ Class	CML-BC with prior imatinib & other TKI (Group B E9) AEs which are not SAEs N = 34 n (%)	CML-BC with prior imatinib & other TKI (Group B E9) SAEs N = 34 n (%)
Any primary system organ class	34 (100.0)	25 (73.5)
Blood and lymphatic system disorders	25 (73.5)	11 (32.4)
Cardiac disorders	4 (11.8)	1 (2.9)
Ear and labyrinth disorders	2 (5.9)	0 (0.0)
Gastrointestinal disorders	28 (82.4)	2 (5.9)
General disorders and administration site conditions	20 (58.8)	6 (17.6)
Hepatobiliary disorders	7 (20.6)	1 (2.9)
Infections and infestations	16 (47.1)	8 (23.5)
Injury, poisoning and procedural complications	0 (0.0)	2 (5.9)
Investigations	14 (41.2)	0 (0.0)
Metabolism and nutrition disorders	16 (47.1)	2 (5.9)
Musculoskeletal and connective tissue disorders	17 (50.0)	2 (5.9)
Nervous system disorders	13 (38.2)	6 (17.6)
Psychiatric disorders	9 (26.5)	0 (0.0)
Renal and urinary disorders	4 (11.8)	2 (5.9)
Reproductive system and breast disorders	4 (11.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	16 (47.1)	2 (5.9)
Skin and subcutaneous tissue disorders	12 (35.3)	1 (2.9)
Vascular disorders	5 (14.7)	1 (2.9)

Most frequent adverse events which are not SAEs and SAEs (at least 10%) by preferred term

Preferred Term	CML-BC with prior imatinib & other TKI (Group B E9) AEs which are not SAEs N = 34 n (%)	CML-BC with prior imatinib & other TKI (Group B E9) SAEs N = 34 n (%)
-Any event	34 (100.0)	25 (73.5)

Preferred Term	CML-BC with prior imatinib & other TKI (Group B E9) AEs which are not SAEs N = 34 n (%)	CML-BC with prior imatinib & other TKI (Group B E9) SAEs N = 34 n (%)
Febrile neutropenia	2 (5.9)	4 (11.8)
Neutropenia	18 (52.9)	3 (8.8)
Nausea	10 (29.4)	0 (0.0)
Rash	5 (14.7)	1 (2.9)
Thrombocytopenia	17 (50.0)	3 (8.8)
Fatigue	5 (14.7)	0 (0.0)
Vomiting	7 (20.6)	0 (0.0)
Diarrhoea	10 (29.4)	0 (0.0)
Pyrexia	11 (32.4)	5(14.7)
Anaemia	14 (41.2)	4(11.8)
Oedema peripheral	9 (26.5)	0 (0.0)
Arthralgia	9 (26.5)	0 (0.0)
Headache	6 (17.6)	1 (2.9)
Cough	5 (14.7)	0 (0.0)
Stomatitis	7 (20.6)	0 (0.0)
Leukopenia	6 (17.6)	0 (0.0)
Bone pain	4 (11.8)	1 (2.9)
Hyperbilirubinaemia	7 (20.6)	0 (0.0)
Constipation	6 (17.6)	0 (0.0)
Dysphagia	4 (11.8)	0 (0.0)
Pain in extremity	7 (20.6)	1 (2.9)
Decreased appetite	6 (17.6)	0 (0.0)
Hypophosphataemia	4 (11.8)	0 (0.0)
Hypomagnesaemia	4 (11.8)	0 (0.0)
Insomnia	5 (14.7)	0 (0.0)

Relapsed/refractory Ph+ ALL (E4)

AEs which are not SAEs and SAEs in at least 5% of patients regardless of study drug relationship by primary system organ class

Primary System Organ Class	Relapsed/refractory Ph+ ALL (E4) AEs which are not SAEs N = 41 n (%)	Relapsed/refractory Ph+ ALL (E4) SAEs N = 41 n (%)
Any primary system organ class	40 (97.6)	30 (73.2)
Blood and lymphatic system disorders	30 (73.2)	14 (34.1)
Cardiac disorders	12 (29.3)	3 (7.3)
Eye disorders	10 (24.4)	0 (0.0)
Gastrointestinal disorders	34 (82.9)	9 (22.0)
General disorders and administration site conditions	34 (82.9)	11 (26.8)
Hepatobiliary disorders	8 (19.5)	0 (0.0)
Infections and infestations	24 (58.5)	9 (22.0)
Investigations	32 (78.0)	8 (19.5)
Metabolism and nutrition disorders	24 (58.5)	2 (4.9)
Musculoskeletal and connective tissue disorders	28 (68.3)	8 (19.5)
Nervous system disorders	22 (53.7)	6 (14.6)
Psychiatric disorders	11 (26.8)	3 (7.3)
Renal and urinary disorders	6 (14.6)	3 (7.3)
Respiratory, thoracic and mediastinal disorders	22 (53.7)	6 (14.6)
Skin and subcutaneous tissue disorders	27 (65.9)	0 (0.0)
Vascular disorders	10 (24.4)	0 (0.0)

Most frequent adverse events which are not SAEs and SAEs (at least 10%) by preferred term

Preferred Term	Relapsed/refractory Ph+ ALL (E4) AEs which are not SAEs N = 41 n (%)	Relapsed/refractory Ph+ ALL (E4) SAEs N = 41 n (%)
-Any event	40 (97.6)	30 (73.2)
Nausea	20 (48.8)	1 (2.4)
Febrile neutropenia	3 (7.3)	5 (12.2)
Rash	10 (24.4)	0 (0.0)
Headache	15 (36.6)	1 (2.4)
Thrombocytopenia	15 (36.6)	1 (2.4)
Fatigue	12 (29.3)	0 (0.0)

Preferred Term	Relapsed/refractory Ph+ ALL (E4) AEs which are not SAEs N = 41 n (%)	Relapsed/refractory Ph+ ALL (E4) SAEs N = 41 n (%)
Pruritus	9 (22.0)	0 (0.0)
Vomiting	13 (31.7)	2 (4.9)
Diarrhoea	14 (34.1)	0 (0.0)
Neutropenia	12 (29.3)	3 (7.3)
Constipation	10 (24.4)	0 (0.0)
Arthralgia	10 (24.4)	2 (4.9)
Cough	8 (19.5)	0 (0.0)
Pyrexia	16 (39.0)	6(14.6)
Anaemia	16 (39.0)	0 (0.0)
Pain in extremity	5 (12.2)	2 (4.9)
Bone pain	8 (19.5)	1 (2.4)
Pain	5 (12.2)	2 (4.9)
Leukopenia	7 (17.1)	0 (0.0)
Dyspnoea	5 (12.2)	1 (2.4)
Oedema peripheral	7 (17.1)	0 (0.0)
Blood alkaline phosphatase increased	6 (14.6)	0 (0.0)
Dehydration	8 (19.5)	0 (0.0)
Asthenia	8 (19.5)	1 (2.4)
Decreased appetite	7 (17.1)	0 (0.0)
Abdominal pain	5 (12.2)	2 (4.9)
Abdominal pain upper	7 (17.1)	2 (4.9)
Alopecia	6 (14.6)	0 (0.0)
Stomatitis	5 (12.2)	0 (0.0)
Alanine aminotransferase increased	8 (19.5)	0 (0.0)
Aspartate aminotransferase increased	6 (14.6)	0 (0.0)
Blood bilirubin increased	6 (14.6)	0 (0.0)
Musculoskeletal pain	6 (14.6)	0 (0.0)
Tachycardia	6 (14.6)	0 (0.0)
Back pain	6 (14.6)	2 (4.9)
Myalgia	8 (19.5)	0 (0.0)
Anxiety	6 (14.6)	0 (0.0)
Hypokalaemia	7 (17.1)	0 (0.0)
Hypocalcaemia	5 (12.2)	0 (0.0)
Hypophosphataemia	5 (12.2)	1 (2.4)
Dizziness	5 (12.2)	0 (0.0)

Preferred Term	Relapsed/refractory Ph+ ALL (E4) AEs which are not SAEs N = 41 n (%)	Relapsed/refractory Ph+ ALL (E4) SAEs N = 41 n (%)
Hyperbilirubinaemia	5 (12.2)	0 (0.0)
Lethargy	5 (12.2)	0 (0.0)
Tremor	5 (12.2)	0 (0.0)
Epistaxis	5 (12.2)	1 (2.4)
Erythema	5 (12.2)	0 (0.0)
Hypotension	5 (12.2)	0 (0.0)

HES/CEL (E5)

AEs which are not SAEs and SAEs in at least 5% of patients regardless of study drug relationship by primary system organ class

Primary System Organ Class	HES/CEL (E5) AEs which are not SAES N = 16 n (%)	HES/CEL (E5) SAES N = 16 n (%)
Any primary system organ class	16(100.0)	11 (68.8)
Blood and lymphatic system disorders	3 (18.8)	1 (6.3)
Cardiac disorders	7 (43.8)	3 (18.8)
Ear and labyrinth disorders	1 (6.3)	0 (0.0)
Endocrine disorders	1 (6.3)	0 (0.0)
Eye Disorders	4 (25.0)	0 (0.0)
Gastrointestinal disorders	12 (75.0)	1 (6.3)
General disorders and administration site conditions	13 (81.3)	1 (6.3)
Hepatobiliary disorders	1 (6.3)	0 (0.0)
Immune system disorders	3 (18.8)	1 (6.3)
Infections and infestations	6 (37.5)	3 (18.8)
Injury, poisoning and procedural complications	5 (31.3)	1 (6.3)
Investigations	7 (43.8)	1 (6.3)
Metabolism and nutrition disorders	5 (31.3)	1 (6.3)
Musculoskeletal and connective tissue disorders	8 (50.0)	2 (12.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (6.3)
Nervous system disorders	6 (37.5)	0 (0.0)
Psychiatric disorders	4 (25.0)	0 (0.0)
Renal and urinary disorders	1 (6.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	10 (62.5)	2 (12.5)

Primary System Organ Class	HES/CEL (E5) AEs which are not SAES N = 16 n (%)	HES/CEL (E5) SAES N = 16 n (%)
Skin and subcutaneous tissue disorders	13 (81.3)	1 (6.3)
Vascular disorders	5 (31.3)	1 (6.3)

CEL=chronic eosinophilic leukemia; HES=hypereosinophilic syndrome.

Most frequent adverse events which are not SAEs and SAEs (at least 10%) by preferred term

Preferred Term	HES/CEL (E5) AEs which are not SAES N = 16 n (%)	HES/CEL (E5) SAES N = 16 n (%)
-Any event	16 (100.0)	11 (68.8)
Nausea	6 (37.5)	0 (0.0)
Rash	6 (37.5)	1 (6.3)
Headache	6 (37.5)	0 (0.0)
Fatigue	6 (37.5)	0 (0.0)
Pruritus	9 (56.3)	0 (0.0)
Diarrhoea	6 (37.5)	0 (0.0)
Dyspepsia	3 (18.8)	0 (0.0)
Oedema peripheral	5 (31.3)	0 (0.0)
Cough	3 (18.8)	0 (0.0)
Anaemia	2 (12.5)	0 (0.0)
Conjunctivitis	2 (12.5)	0 (0.0)
Insomnia	4 (25.0)	0 (0.0)
Dyspnoea	3 (18.8)	0 (0.0)
Abdominal distention	2 (12.5)	0 (0.0)
Abdominal pain	2 (12.5)	1 (6.3)
Abdominal pain upper	4 (25.0)	0 (0.0)
Constipation	2 (12.5)	0 (0.0)
Bone pain	2 (12.5)	0 (0.0)
Arthralgia	3 (18.8)	0 (0.0)
Myalgia	3 (18.8)	0 (0.0)
Hypokalaemia	2 (12.5)	0 (0.0)
Productive cough	2 (12.5)	0 (0.0)
Seasonal allergy	2 (12.5)	0 (0.0)
Rhinorrhoea	2 (12.5)	0 (0.0)
Asthma	2 (12.5)	0 (0.0)

Preferred Term	HES/CEL (E5) AEs which are not SAES N = 16 n (%)	HES/CEL (E5) SAES N = 16 n (%)
Thermal burn	2 (12.5)	0 (0.0)
C-reactive protein increased	2 (12.5)	0 (0.0)
Papule	2 (12.5)	0 (0.0)
Urticaria	2 (12.5)	0 (0.0)
Hypotension	2 (12.5)	0 (0.0)

SM (E6)

AEs which are not SAEs and SAEs in at least 5% of patients regardless of study drug relationship by primary system organ class

Primary System Organ Class	SM (E6) AEs which are not SAEs N = 61 n (%)	SM (E6) SAEs N = 61 n (%)
Any primary system organ class	16 (100.0)	35 (57.4)
Blood and lymphatic system disorders	21 (34.4)	3 (4.9)
Cardiac disorders	12 (19.7)	6 (9.8)
Gastrointestinal disorders	51 (83.6)	11 (18.0)
General disorders and administration site conditions	51 (83.6)	10 (16.4)
Infections and infestations	37 (60.7)	4 (6.6)
Injury, poisoning and procedural complications	15 (24.6)	6 (9.8)
Investigations	37 (60.7)	1 (1.6)
Metabolism and nutrition disorders	27 (44.3)	4 (6.6)
Musculoskeletal and connective tissue disorders	39 (63.9)	6 (9.8)
Nervous system disorders	44 (72.1)	4 (6.6)
Psychiatric disorders	18 (29.5)	3 (4.9)
Renal and urinary disorders	10 (16.4)	3 (4.9)
Respiratory, thoracic and mediastinal disorders	36 (59.0)	2 (3.3)
Skin and subcutaneous tissue disorders	41 (67.2)	3 (3.3)
Vascular disorders	15 (24.6)	2 (3.3)

Most frequent adverse events which are not SAEs and SAEs (at least 10%) by preferred term

Preferred Term	SM (E6) AEs which are not SAEs N = 61 n (%)	SM (E6) SAEs N = 61 n (%)
-Any event	61 (100.0)	35 (57.4)
Nausea	30 (49.2)	2 (3.3)
Rash	14 (23.0)	1 (1.6)
Headache	30 (49.2)	0 (0.0)
Fatigue	27 (44.3)	1 (1.6)
Thrombocytopenia	9 (14.8)	0 (0.0)
Diarrhoea	23 (37.7)	4 (6.6)
Vomiting	28 (45.9)	3 (4.9)
Constipation	16 (26.2)	0 (0.0)
Bone pain	12 (19.7)	0 (0.0)
Anaemia	12 (19.7)	0 (0.0)
Pyrexia	11 (18.0)	0 (0.0)
Muscle spasms	18 (29.5)	0 (0.0)
Back pain	8 (13.1)	1 (1.6)
Oedema peripheral	11 (18.0)	1 (1.6)
Abdominal pain	10 (16.4)	1 (1.6)
Abdominal pain upper	13 (21.3)	2 (3.3)
Asthenia	9 (14.8)	1 (1.6)
Nasopharyngitia	12 (19.7)	0 (0.0)
Arthralgia	13 (21.3)	0 (0.0)
Myalgia	12 (19.7)	0 (0.0)
Blood bilirubin increased	7 (11.5)	0 (0.0)
Alanine aminotransferase increased	12 (19.7)	0 (0.0)
Weight decreased	8 (13.1)	0 (0.0)
Lipase increased	7 (11.5)	0 (0.0)
Decreased appetite	9 (14.8)	1 (1.6)
Dizziness	16 (26.2)	0 (0.0)
Tremor	7 (11.5)	0 (0.0)
Dyspnoea	12 (19.7)	1 (1.6)
Pruritus	20 (32.8)	0 (0.0)
Flushing	7 (11.5)	0 (0.0)
Cough	9 (14.8)	0 (0.0)

Summary of adverse event categories

Phase I

Safety Parameter	Initial Dose Cohort			All patients
	All QD[a]	400 mg b.i.d.	600 mg b.i.d.	
	N = 69	N = 32	N = 18	N = 119
	n (%)	n (%)	n (%)	n (%)
Patients with AE(s)	69 (100)	32 (100)	18 (100)	119 (100)
Serious or other significant events				
Death within 28 days after discontinuation	17 (24.6)	4 (12.5)	1 (5.6)	22 (18.5)
SAE(s)	55 (79.7)	26 (81.3)	13(72.2)	98 (82.4)
Study drug related SAEs	15 (21.7)	14 (43.8)	9 (50.0)	38 (31.9)
Discontinued due to SAE	12 (17.0)	5 (15.6)	1 (5.6%)	15 (12.6
Grade 4 AE(s)	44 (63.8)	15 (46.9)	9 (50.0)	68 (57.1)
Discontinued due to AE(s)	13 (18.8)	7 (21.9)	3 (16.7)	23 (19.3)
Discontinued due to study drug-related AE(s)	3 (4.3)	1 (3.1)	1 (5.6)	5 (4.2)
AE(s) requiring dose adjustment or dose interruption	37 (53.6)	22 (68.8)	13 (72.2)	72 (60.5)

a: All QD = All QD initial dose cohorts combined: includes 50, 100, 200, 400, 600, 800, and 1200 mg.
AE=adverse event; SAE=serious adverse event

Phase II & Extension

CML-CP with prior imatinib only (Group A E2) and CML-CP with prior imatinib and other TKI (Group B E8)

	CML-CP with prior imatinib only (Group A E2) Total N = 321 n (%)	CML-CP with prior imatinib and other TKI (Group B E8) Total N = 49 n (%)
Deaths reported within 28 days of last dose of study drug	13 (4.0)	0
SAEs (including deaths)	146 (45.5)	21 (42.9)
Drug-related SAEs	61 (19.0)	5 (10.2)
AEs leading to discontinuation*	75 (23.4)	9 (18.4)
Drug-related AEs leading to discontinuation	57 (17.8)	7 (14.3)
AEs requiring dose adjustment/interruption	207 (64.5)	33 (67.3)

AE=adverse events; AP=accelerated phase; CML=chronic myeloid/myelogenous leukemia; CP=chronic phase; SAE=serious adverse event; TKI=tyrosine kinase inhibitor

*One event (potassium increased) was reported as AEs leading to discontinuation but the primary reason for study discontinuation was reported as abnormal laboratory values.

CML-AP with prior imatinib only (Group A E1)

	CML-AP with prior imatinib only (Group A E1) Total N = 137 n (%)
Deaths reported within 28 days of last dose of study drug	14 (10.2)
SAEs (including deaths)	55 (40.1)
Drug-related SAEs	26 (19.0)
AEs leading to discontinuation*	28 (20.4)
Drug-related AEs leading to discontinuation	17 (12.4)
AEs requiring dose adjustment/interruption	84 (61.3)

AE=adverse events; AP=accelerated phase; CML=chronic myeloid/myelogenous leukemia; CP=chronic phase; SAE=serious adverse event; TKI=tyrosine kinase inhibitor

*Two events (neutropenia, lipase increase) were reported as AEs leading to discontinuation but the primary reason for study discontinuation was reported as abnormal laboratory values.

CML-CP with prior imatinib & other TKI (Group B E7), CML-BC with prior imatinib only (Group A E3), CML-BC with prior imatinib & other TKI (Group E9), Ph+ALL (E4), HES/CEL (E5) and SM (E6)

	CML-CP with prior imatinib & other TKI (Group B E7) Total N = 25 n (%)	CML-BC with prior imatinib only (Group A E3) Total N = 136 n (%)	CML-BC with prior imatinib & other TKI (Group B E9) Total N = 34 n (%)	Relapsed/refractory Ph+ ALL (E4) Total N = 41 n (%)	HES/CEL (E5) Total N = 16 n (%)	SM (E6) Total N = 61 n (%)
Deaths reported within 28 days of last dose of study drug	4 (16.0)	34 (25.0)	14 (41.2)	13 (31.7)	1 (6.3)	4 (6.6)
SAEs	13 (52.0)	84 (61.8)	25 (73.5)	30 (73.2)	11 (68.8)	35 (57.4)

Other Relevant Findings

Not applicable.

Date of Clinical Trial Report

16-Sep-2013

Date Inclusion on Novartis Clinical Trial Results Database

18-Sep-2013

Date of Latest Update