CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203469
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Drug Name:	Ponatinib
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Keywords:	

Link to keywords: Single arm, Open label, CML, Ph+ ALL, Major cytogenetic response, major hematologic response

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1 EXECUTIVE SUMMARY

This submission consists of the results of a phase 2 study for oral ponatinib (AP24534). This study is a multicenter, international, single arm, open-label trial to determine the efficacy of ponatinib in patients with chronic myeloid leukemia (CML) in chronic (CP), accelerated (AP) or blast phase (BP) or with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) who were either resistant or intolerant to either dasatinib or nilotinib (R/I) or had the (T)hreonine-315-(I)soleucine (T315I) mutation.

Patients were assigned to one of six cohorts according to disease diagnosis and presence of the T315I mutation: Cohort A (CP-CML R/I), Cohort B (CP-CML T315I), Cohort C (AP-CML R/I), Cohort D (AP-CML T315I), Cohort E (BP-CML/Ph+ ALL R/I), or Cohort F (BP-CML/Ph+ ALL T315I). All patients were tested mutation which was performed at a central laboratory (b) (4) to ensure uniformity in the testing procedure, and standardized analysis and reporting of the results to assign patients to a T315I cohort. A total of 444 patients were assigned, 267 patients to the CP-CML (203 to R/I, 64 to T315I), 83 patients to the AP-CML (65 to R/I, 18 to T315I), and 94 patients to the BP-CML/Ph+ ALL (48 to R/I 46 to T315I) cohorts.

The starting dose was oral 45 mg once daily until progression. This study was conducted North America, Europe/Australia, and Asia. The primary objective was to examine the efficacy of ponatinib for patients with resistant or intolerant to dasatinib or nilotinib (R/I) or those with the T315I mutation (T315I). The primary endpoints were the major cytogenetic response (MCyR) rates based on the null and alternative rates of 20% and 35%, respectively in the R/I CP-CML cohort and 10% and 35%, respectively in the T315I CP-CML cohort and major hematologic response rates based on the null and alternative rates of 10% and 30%, respectively in the AP-CML and BP-CML/Ph + ALL cohorts.

For R/I CP-CML, the study met its objective in ruling out MCyR rates of 20% and 10%, respectively for the R/I and T315I cohorts. For R/I AP-CML disease, the study met its objective in ruling out MaHR rates of 10% for all cohorts. Given the applicant's analyses (See Table 7) and the additional analyses performed by this reviewer (See Table 12), I conclude that the drug has shown activity in all the studied cohorts.

The key statistical issues and findings that impact demonstration of efficacy/safety were as follows:

- The primary endpoint of MCyR had a rate of 48.8 % in the R/I CP-CML patients (Cohort A) and 70.3% in the T315I CP-CML patients (Cohort B). The overall response rate for the CP-CML was 53.9% with an exact 95% CI of (47.8, 60.0). The complete cytogenetic response (CCyR) rate for the entire CP-CML cohort was 44.2% (95% CI: 38.1, 50.4), 37.8% in the R/I CP-CML cohort (95% CI: 30.8, 44.1) and 65.6% in the T315I CP-CML patients (95% CI: 52.7, 77.1), respectively (Table 7).

- The primary endpoint of MaHR had a rate of 60.0 % in the R/I AP-CML patients (Cohort C) and 50.0% in the T315I AP-CML patients (Cohort D). The overall response rate for the AP-

CML cohort was 57.8% with an exact 95 % CI of (46.5, 68.6). The complete hematologic response (CHR) rate for the AP-CML was 47.0% (95% CI: 35.9, 58.3), 46.2% in the R/I cohort (95% CI: 33.7, 59.0) and 50% in the T315I (95% CI: 26.0, 74.0), respectively (See Table 7). Based on FDA analyses, 43 patients (51.8%) had MaHR in the AP-CML. Among 43 MaHR, 36 (43.4%) had CHR and 7 patients (8.4%) had NEL. In the R/I cohort, 29 patients (44.6%) had CHR and 7 patients (10.8%) had NEL. In the T315I cohort, all 7 MaHR patients (38.9%) had CHR (See Table 12).

- The primary endpoint of MaHR had a rate of 35.4 % in the R/I BP-CML/Ph+ ALL patients (Cohort E) and 32.6% in the T315I BP-CML/Ph+ ALL patients (Cohort F). The overall response rate for the BP-CML/Ph+ ALL patients was 34.0 % with an exact 95 % CI of (24.6, 44.5). The CHR rate for the BP-CML/Ph+ ALL patients was 25.5% (95% CI: 17.1, 35.6), 27.1% in the R/I BP-CML/Ph+ ALL cohort (95% CI: 15.3, 41.9) and 23.9% in the T315I BP-CML/Ph+ ALL cohort (95% CI: 12.6, 38.8), respectively (See Table 13).

- The planned sample size of the AP-CML T315I cohort was 40 patients based on 10% of null MaHR rate and 30% of alternative MaHR rate with the power of 89% at an alpha of 0.05, but only 18 patients were used for analyses. Enrolling fewer patients into cohort AP-CML T315I than originally planned reduced the power/sensitivity to rule out a MaHR rate of 10%. However, the observed response rate in this cohort (and in the other cohorts) was much greater than the assumed response rate that was used to plan the sample size for the cohort. The 95% confidence interval for the MaHR rate in the AP-CML T315I cohort was (26%, 74%) easily ruling out a MaHR rate of 10%. Additionally, it should be noted that had the T315I cohort been fully enrolled to 40 patients without having any additional patients achieving a MaHR, the 95% confidence interval for MaHR rate would have been (11%, 38%) and thus, a 10% MaHR rate would have still been ruled out.

- As enrolment into the T315I cohort was still ongoing when enrolment into the R/I cohort had reached its planned sample size of 100, the sponsor continued enrolment into the R/I cohort. An additional analysis of MCyR was performed by the applicant based on the first 100 patients enrolled into the R/I cohort. The first 100 enrolled R/I CP-CML patients would have, on average, longer follow-up and would have had more time to achieve response. Recall that the data cutoff date was less than two months after the last patient was enrolled. The MCyR rate was 48.0% in the R/I CP-CML cohort based on the first 100 enrolled in the CP-CML R/I cohort. An analysis based on the planned sample size in an open-label setting can help verify the integrity of the results.

- An additional analysis of MaHR was performed by the applicant based on the first 40 patients enrolled into the R/I cohort and T315I BP-CML/Ph+ ALL cohort. An analysis based on the planned sample size in an open-label setting can help verify the integrity of the results. The first 40 enrolled into the cohort patients would have, on average, longer follow-up and would have had more time to achieve response. The MaHR rate was 60% in the R/I AP-CML cohort, 40% in the R/I BP-CML/Ph+ALL cohort and 30% in the T315I BP-CML/Ph+ALL cohorts, respectively. The sensitivity analysis results for 6 cohorts based on per-protocol populations were similar to the primary analysis results.

- For duration of MCyR in the CP-CML cohort, among 144 MCyR patients, 6 patients (4.2%) had events (5 from R/I and 1 from T315I). The median duration of MCyR was not reached for the entire CP-CML cohort. For duration of MaHR, among 48 MaHR patients in the AP-CML cohort, 22 patients (45.8%) had events (17 from R/I and 5 from T315I) and the median duration of MaHR in the AP-CML cohort was 9.5 months (9.5 months for R/I and 5.7 months for T315I). Among 32 MaHR patients in the BP-CML/Ph+ ALL cohorts, 17 patients (53.1%) had events (7 from R/I and 10 from T315I) and the median duration of MaHR in the BP-CML/Ph+ ALL cohorts was 4.7 months (NA for R/I and 4.1 months for T315I).

- The duration of MaHR based on FDA analysis, among 43 MaHR patients, 21 patients (48.8%) had events in the AP-CML cohort. The median duration of MaHR was 9.5 months based on FDA analysis in the AP-CML cohort. Among 32 MaHR patients, 21 patients (65.6%) had events in the BP-CML/Ph+ ALL cohorts. The median duration of MaHR was 3.5 months based on FDA analysis in the BP-CML/Ph+ ALL cohorts. Among 19 MaHR patients in the BP-CML cohort, 9 patients (47.4%) had events. Among 13 MaHR patients, 12 patients (92.3%) had events. The median MaHR were 4.7 months and 3.2 months, for the BP-CML and Ph+ ALL cohorts, respectively.

2 INTRODUCTION

2.1 Overview

Ponatinib (AP24534) is product of a computational and structure-based approach to the design of a small-molecule TKI. Ponatinib is a kinase inhibitor indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy.

The ARIAD Pharmaceuticals, Inc. (ARIAD) designed ponatinib to inhibit all variants of breakpoint cluster region, Abelson complex (BCR-ABL), including those that confer resistance to first and second-generation TKIs to provide therapeutic benefit to Ph+ patients who have failed treatment with currently approved TKIs or for whom no treatments are available. The ponatinib is applicable for treatment of patients who have developed resistance due to the evolution of mutations, T315I or other, refractory to prior TKI therapy.

This an open-label, international, phase 2 study was designed to test ponatinib in patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL who were resistant or intolerant to either dasatinib or nilotinib (R/I), or who carried the T315I mutation after any TKI therapy. Patients were assigned to one of the following six cohorts in accordance with disease diagnosis and presence of the T315I mutation: Cohort A (CP-CML R/I), Cohort B (CP-CML T315I), Cohort C (AP-CML R/I), Cohort D (AP-CML T315I), Cohort E (BP-CML/Ph+ ALL R/I), or Cohort F (BP-CML/Ph+ ALL T315I). All patients were tested for the T315I mutation testing in a central

laboratory [redacted] (b) (4) There were five patients enrolled who did not have prior therapy with dasatinib or nilotinib and thus, were not eligible for any cohort. These five patients were continued on treatment and included only in the safety population, they were not included in any efficacy population.

FDA approved dasatinib for the treatment of resistant or intolerant CML in 2006 and for the treatment of adult patients with newly diagnosed Ph+ CP-CML in 2010. FDA approved nilotinib for the treatment of patients with CP-CML or AP-CML who are resistant or intolerant to imatinib in 2012.

The primary objective of this study was to examine the efficacy and safety of ponatinib. The ponatinib dose of 45 mg once daily based on a Phase 1 study was used for this phase 2 trial.

There were a total of 68 investigators/study sites from Australia, Belgium, Canada, France, Germany, Italy, South Korea, United Kingdom, United States, the Netherlands, Spain, and Sweden. Approximately 42% of subjects were enrolled from United States. The first patient was enrolled on September 21, 2010 and last patient was enrolledon March 2, 2012. The data cutoff date was April 27, 2012 and 252 patients (56.1%) are still ongoing for their follow-up, mostly CP-CML (n=185) or AP-CML (n=56).

Table 1 : List of all studies included in analysis

	Phase and Design	Treatment Period	Follow, up Period	# of Subjects per Arm	Study Population
AP24534, 10, 201	*Phase 2*	*Median 9.9 months (Range: 0.1, 18.4)*	*30days after end of treatment 8 years for survival*	*Cohort A(N=203)* *Cohort B(N=64)* *Cohort C(N=65)* *Cohort D(N=18)* *Cohort E(N=48)* *Cohort F(N=46)*	*CP-CML R/I* *CP-CML T315I* *AP-CML R/I* *AP-CML T315I* *BP-CML/Ph+ALL R/I* *T315I*

2.2 Data Sources

The study report and data were provided electronically, the location/names of study report, data sets and SAS programs are as follows;

Study reports,
\\Cdsesub1\evsprod\NDA203469\0000\m5\53, clin, stud, rep\535, rep, effic, safety, stud\chronic, myeloid, leukemia\5352, stud, rep, uncontr\ap24534, 10, 201
Data sets analyzed,
\\Cdsesub1\evsprod\NDA203469\0000\m5\datasets\ap24534, 10, 201\analysis\legacy\datasets
SAS Program,
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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

It was possible to reproduce the primary analysis dataset, and in particular the primary endpoint, from the original data source.

3.2 Evaluation of Efficacy

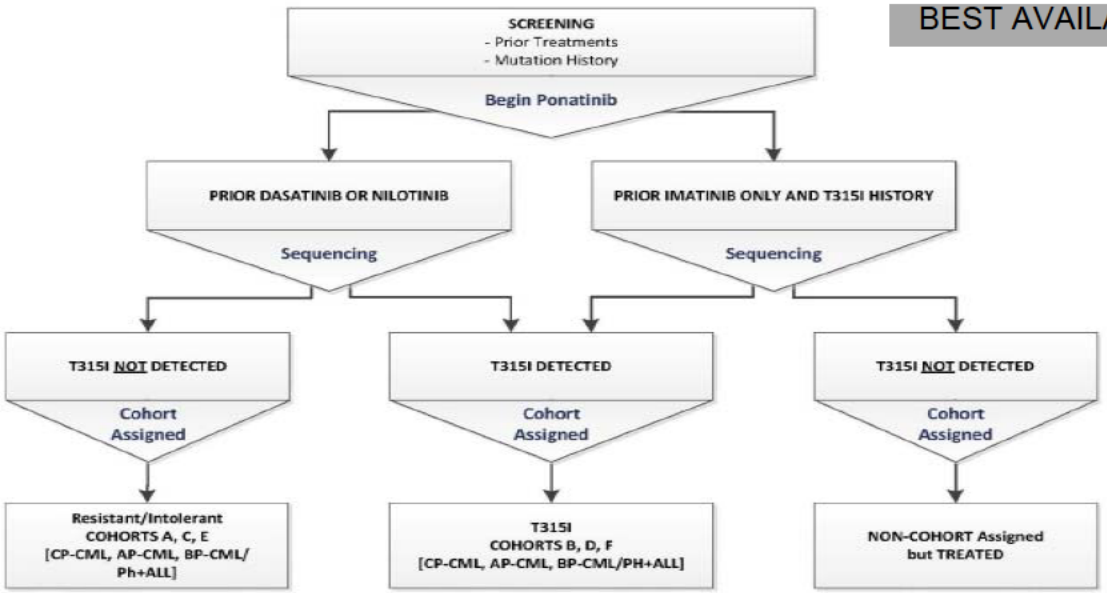
3.2.1 Study Design and Endpoints

This is a multicenter, international, phase 2, single-arm, open- label trial of oral ponatinib in patients with Ph+ disease. Eligible patients had CML in CP, AP, or BP, or Ph+ ALL and either: 1) disease that was resistant or intolerant to therapy with either dasatinib or nilotinib; or 2) BCR, ABL T315I mutation. This trial was designed with a separate T315I cohort within each disease group using six cohort groups. The six cohort groups are as follows;

	CP-CML	AP-CML	BP-CML /Ph+ ALL
Resistant or intolerant to dasatinib or nilotinib (R/I)	Cohort A	Cohort B	Cohort C
T315I mutation	Cohort D	Cohort E	Cohort F

All patients had mutation testing for a T315I cohort performing BCR-ABL mutational analysis. The process of assigning resistant/Intolerant (R/I) and T315I was explained in Figure 1.

Figure 1 : Process for Assigning Resistant/Intolerant and T315I Cohorts



The starting dose of ponatinib was 45 mg orally once daily based on the phase 1 study and remained during treatment until disease progression, development of intolerance, patient withdrawal of consent, or decision by the investigator.

Primary Endpoints

CP-CML in Cohorts A and B:
Major cytogenetic response (**MCyR**): The rate was defined as the proportion of patients who achieved a complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR) after the initiation of study treatment. Patients entering the trial already in PCyR had to achieve CCyR in order to be considered a success for MCyR. Patients in Cohorts A and B who did not respond by 12 months after the initiation of study treatment were analyzed as nonsuccesses.

A bone marrow (BM) aspirate for morphology and cytogenetics occurred every 3 cycles up to Cycle 27. After 27 cycles, patients without CCyR continued to require a BM aspirate and cytogenetic assessment every 6 cycles. Patients with CCyR and major molecular response (MMR) after the BM aspirate and cytogenetic assessment at Cycle 27 were not required to have any further BM aspirates unless there was loss of MMR and at least a 10-fold increase in BCR-ABL transcripts from the lowest point obtained on study, at which time BM aspirate and cytogenetics must have been obtained. Patients documented to be in CCyR but not in MMR after the BM aspirate and cytogenetics assessment at Cycle 27 were not required to have any further BM aspirates unless there was at least a 10-fold increase in BCR-ABL transcripts from the lowest point obtained on study, at which time BM aspirate and cytogenetics must have been obtained.

AP-CML or BP-CML or Ph+/ALL in Cohorts C through F:
Major hematologic response (**MaHR**): The rate was defined as the proportion of patients who achieved a complete hematologic response (CHR) or no evidence of leukemia (NEL) response after the initiation of study treatment, with 1 additional assessment, at least 28 days after the first assessment of response, at which CHR or NEL criteria were met. The MaHR determination required an assessment of extramedullary involvement by physical examination, a complete blood count (CBC) and differential and a BM aspirate.

A BM aspirate was required at Cycle 1 Day 28, Cycle 2 Day 28, and at the end of each even-numbered cycle thereafter, through Cycle 24, and then at the end of Cycle 27. After 27 cycles, patients without CCyR continued to require a BM aspirate and cytogenetic assessment every 3 cycles until Cycle 39, and subsequently every 6 cycles. Patients with CCyR and MMR after the BM aspirate and cytogenetic assessment at Cycle 27 and patients documented to be in CCyR but not in MMR after the BM aspirate and cytogenetics assessment at Cycle 27 (or later) were the same as above. The primary endpoints for the 6 cohorts are summarized as below.

	CP-CML	AP-CML	BP-CML/Ph+ ALL
Resistant or intolerant to dasatinib or nilotinib (R/I)	Cohort A **MCyR**	Cohort B **MaHR**	Cohort C **MaHR**
T315I mutation	Cohort D **MCyR**	Cohort E **MaHR**	Cohort F **MaHR**

Secondary Endpoints:

CP-CML in Cohorts A and B

a. Complete hematologic response (CHR): This rate was defined as the proportion of patients who achieved CHR that was confirmed by a CBC with differential at least 28 days after the initial criteria were met. Hematologic response determination occurred for CP-CML patients with each CBC and differential. The criteria for CHR also included the absence of extramedullary involvement, so an assessment of hepatosplenomegaly must have been recorded at each physical examination.
b. Cytogenetic responses (confirmed MCyR): This rate was defined the proportion of patients who achieved a confirmed CCyR or PCyR at 2 consecutive assessments at least 4 weeks apart (for patients not in PCyR at study entry), or the proportion of patients who achieved a confirmed CCyR at 2 consecutive assessments at least 4 weeks apart (for patients in PCyR at study entry).
c. Major molecular responses (MMR): This rate was defined as the proportion of patients who met the criteria for MMR at least once after the initiation of study treatment

AP-CML or BP-CML or Ph+/ALL in Cohorts C through F:

d. Cytogenetic responses: CCyR, PCyR, confirmed MCyR; and
e. Molecular responses: MMR

All Cohorts A through F:

f. Time to response was defined as the interval from the first dose of study treatment until the criteria for response are first met or censored at the last assessment of response
g. Duration of response was defined as the interval between the first assessment at which the criteria for response were met until the criteria for progression were met or censored at the last date at which the criteria for response were met.
h. Progression-free survival was defined as the interval from the first dose of study treatment until the criteria for progression were met or death or censored at the last response assessment
   Progression criteria:
   CP-CML: death, development of AP-CML or BP-CML, loss of CHR, confirmed by development in CBCs at least 4 weeks apart, or loss of MCyR;
   AP-CML: death, development of confirmed BP-CML, loss of previous major or minor hematologic response over a 2-week period, no decrease from baseline levels in % blasts in blood or BM on all assessments over a 4-week periods;
   BP-CML or PH+ALL: death or increasing blasts in peripheral blood or BM over a 4-week period

i. Overall survival was defined as the interval from the first dose of study treatment until death or censoring at the last date at which the patient was known to be alive.

3.2.2 Statistical Methodologies

The summary statistics and analyses were summarized by analysis population, by cohort, by diagnosis (i.e., CP-CML, AP-CML, BP-CML/Ph+ ALL), and where appropriate, overall. Three separate populations were used for analyses and three populations are summarized as follows:

Treated population:
Cohort A and B (CP-CML patients):
The treated population of Cohorts A or B included all patients who received at least 1 dose of study drug. Chronic phase patients with a negative baseline T315I mutation result and who were resistant or intolerant to either dasatinib or nilotinib were assigned to Cohort A. Chronic phase patients with a positive baseline T315I mutation result were assigned to Cohort B. Patients who were confirmed to have no detectable T315I mutation by direct sequencing, but who were not resistant or intolerant to dasatinib or nilotinib were not included in the treated population and were analyzed separately.

Cohorts C through F (AP-CML and BP-CML/Ph+ ALL Patients):
The treated population of Cohorts C through F included all patients who received at least 1 dose of study drug. AP-CML patients with a negative baseline T315I mutation result and who were resistant or intolerant to either dasatinib or nilotinib were assigned to Cohort C. AP-CML patients with a positive baseline T315I mutation result were assigned to Cohort D. BP-CML patients and Ph+ ALL patients with a negative baseline T315I mutation result and who were resistant or intolerant to either dasatinib or nilotinib were assigned to Cohort E. BP-CML patients and Ph+ ALL patients with a positive baseline T315I mutation result were assigned to Cohort F. Patients confirmed to have had no detectable T315I mutation by direct sequencing and who were not resistant or intolerant to dasatinib or nilotinib were not included in the treated population and were analyzed separately.
The Per Protocol Cytogenetic Population (PPP (Cytogenetic)) includes all patients in the treated population with a baseline cytogenetic assessment with at least 20 metaphases examined. Patients with <20 metaphases examined at baseline, CCyR at baseline, or missing baseline cytogenetic assessments were excluded.
The Per Protocol Hematologic Population (PPP (Hematologic)) includes all patients in the treated population in Cohorts C through F with a baseline BM assessment for which the percentage of BM blasts was determinable. Patients with missing baseline bone marrow blasts or MaHR at baseline were excluded.
Safety Population includes all patients who received at least 1 dose of ponatinib.

Sensitivity Analyses of the primary endpoint.

1. To assess the impact of the use of the per protocol population and the timing of when patients first demonstrated the criteria for success
   - All patients in the treated population were included for MCyR analyses, regardless of the number of metaphases examined for the baseline cytogenetic assessment, PCyR status at

baseline was based on the percentage of Ph+ cells, regardless of the number of metaphases examined and success/not a success was based on all available data in the database, regardless of when the criteria for success were met.

2. To assess the impact of patients for whom the baseline T315I direct sequencing result was not received until after the first bone marrow assessment
   - Patients for whom a positive baseline T315I direct sequencing result was received after the first cytogenetic response assessment (CP-CML patients) or BM assessment (AP-CML, BP-CML, or Ph+ ALL patients) were considered as T315I-negative, patients for whom a negative baseline T315I direct sequencing result was received after the first cytogenetic response assessment (CP-CML patients) or BM assessment (AP-CML, BP-CML, or Ph+ ALL patients) were considered as T315I-positive, and sensitivity analysis 1.

Sample size determination

MCyR

The sample sizes for cohort A and B were based on data used second-generation TKIs in patients who had failed dasatinib and nilotinib from several small studies (Garg et al, 2009; Giles et al, 2007; Quintas-Cardama et al, 2007). These 3 studies demonstrated an approximately 30% MCyR in these patients. However, these were highly selected patient populations without patients who had failed more than 2 agents, and with a short duration of response. Thus, the null or uninteresting MCyR rate was set at 20% for Cohort A (R/I CP-CML patients).

Cohort A: With null MCyR rate of 20% and 35% of alternative MCyR rate in the Cohort A (R/I CP-CML), 100 patients was planned. This provided 85% power at an overall alpha of 0.05. A minimum of 29 responders are needed to observe exact 95% CI exceeding the lower bound of 20% and the upper bound of 35%. The sample size of 100 patients provides at least 98% power to distinguish between 20% and 40% with a minimum 29 responders and at least 78 % power to distinguish between 30% and 45 % with a minimum 40 responders.

Cohort B: With null MCyR rate of 10% and 35% of alternative MCyR rate in the Cohort B (R/I CP-CML), 60 patients was planned. This provided 98% power at an overall alpha of 0.05. A minimum of 14 responders are needed to observe exact 95% CI exceeding the lower bound of 10% and the upper bound of 35%.

MaHR

Cohorts C through F: The sample sizes for cohorts c through F were based on similar considerations for each cohort (Garg et al, 2009). With null MaHR rate of 10% and 30% of alternative MaHR rate, 40 patients /Cohort was planned. This provided 89% power at an overall alpha of 0.05. A minimum of 9 responders are needed to observe exact 95% CI exceeding the lower bound of 10% and the upper bound of 30%.

For enrollment of patients, more patients who were resistant or intolerant to therapy were expected and a faster rate of enrollment than patients who had the T5131 mutation. The overall enrollment was determined by the number of the T315I cohorts.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The patient enrollment period was from September 21, 2010 to March 2, 2012. The data cutoff date was April 27, 2012. There were 449 patients in the safety population which included 5 patients who were not treated. The study population is summarized in Table 2.

Table 2 : Study Population by Cohorts

Study Population (n) Cohort	A	B	C	D	E	F	Total
Treated Population	203	64	65	18	48	46	444
PPP (Cytogenetic)	201	64	62	17	41	41	426
PPP (Hematologic)	202	64	53	15	46	44	424

The patient disposition is summarized by cohorts in Table 3.

Table 3 : Patient Disposition by Cohorts

	CP-CML	AP-CML	BP-CML /Ph+ ALL
Resistant or intolerant to dasatinib or nilotinib (R/I)	Cohort A (N=203) n (%)	Cohort B (N=64) n (%)	Cohort C (N=65) n (%)
Discontinued	136 (67.0)	46 (71.9)	44 (67.7)
Progressive Disease	67 (33.0)	18 (28.1)	21 (32.3)
Adverse Event	11 (5.4)	6 (9.4)	8 (12.3)
Death	27 (13.3)	4 (6.3)	7 (10.8)
Withdrawal by subject	3 (1.5)	2 (3.1)	1 (1.5)
Other	12 (5.9)	1 (1.6)	0
Lack of efficacy	1 (0.5)	3 (4.7)	3 (4.6)
Physician decision	6 (3.0)	0	1 (1.5)
Noncompliance with study drug	6 (3.0)	2 (3.1)	1 (1.5)
	1 (1.5)	0	0
T315I mutation	Cohort D (N=18) n (%)	Cohort E (N=48) n (%)	Cohort F (N=46) n (%)
Discontinued	10 (55.6)	9 (18.8)	2 (4.3)
Progressive Disease	8 (44.4)	39 (81.3)	44 (95.7)
Adverse Event	5 (27.8)	22 (45.8)	26 (56.5)
Death	2 (11.1)	5 (10.4)	5 (10.9)
Withdrawal by subject	1 (5.6)	6 (12.5)	5 (10.9)
Other	0	1 (2.1)	2 (4.3)
Lack of efficacy	0	3 (6.3)	3 (6.5)
Physician decision	0	1 (2.1)	3 (6.5)
Noncompliance with study drug	0	1 (2.1)	0
	0	0	0

Among 449 safety patients, 252 patients (56.1%) remained on therapy and197 patients (43.9%) discontinued treatment. The median duration of follow-up on efficacy endpoints for all patients was 9.9 months. Total of 78 patients (17.4%) were discontinued due to progressive disease, 50 patients (11.1%) discontinued due to adverse events (AEs), 18 patients (4.0%) discontinued due to death.

Five patients with prior imatinib therapy and a history of T3151 who do not have T3151 detected on pre-trial screening in the "Non-Cohort Assigned, but treated" group were included in the safety evaluation only.

Demographic and disease characteristics are summarized by treated population in Table 4.

Table 4 : Demographic and Disease Characteristics for CP-CML and AP-CML

	CP-CML		AP-CML	
	R/I N=203 n (%)	T315I N=64 n (%)	R/I N=65 n (%)	T315I N=18 n (%)
Age				
Median (yrs)	61	51	60	54
18- 44	31 (15.3)	24 (37.5)	16 (24.6)	5 (27.8)
45- 64	90 (44.3)	22 (34.4)	28 (43.1)	8 (44.4)
≥65	82 (40.3)	18 (28.1)	21 (32.3)	5 (27.8)
Gender				
Female	108 (53.2)	16 (25)	40 (61.5)	7 (38.9)
Male	95 (46.8)	48 (75)	25 (38.5)	11 (61.1)
Race				
White	174 (85.7)	42 (65.6)	47 (72.3)	9 (50.0)
Asian	17 (8.4)	14 (21.9)	8 (12.3)	3 (16.7)
Black/African American	7 (3.4)	4 (6.3)	7 (10.8)	5 (27.8)
Other (Unknown , other)	5 (2.5)	4 (6.3)	3 (4.6)	1 (5.6)
Region				
North America	85 (41.9)	26 (40.6)	30 (46.2)	6 (33.3)
US	77 (37.9)	23 (35.9)	29 (44.6)	6 (33.3)
Europe/Australia	104 (51.2)	26 (40.6)	30 (46.2)	10 (55.6)
Asia	14 (6.9)	12 (18.8)	5 (7.7)	2 (11.1)
ECOG				
0	139 (68.5)	47 (73.4)	33 (50.8)	12 (66.7)
1	60 (29.6)	17 (26.6)	25 (38.5)	6 (33.3)
2	4 (2.0)	0	7 (10.8)	0
Time since Diagnosis				
Median (yrs)	7.8	4.8	7.1	6.6
0-<5	71 (35.0)	33 (51.6)	23 (35.4)	5 (27.8)
5-<10	49 (24.1)	22 (34.4)	16 (24,6)	8 (44.4)
≥ 10	83 (40.9)	9 (14.1)	26 (40.0)	5 (27.8)

Resistant to prior TKI	164 (80.8)	50 (78.1)	60 (92.3)	14 (77.8)
Number of Prior TKI				
1	4 (2.0)	11 (17.2)	1 (1.5)	3 (16.7)
2	64 (31.5)	27 (42.2)	22 (33.8)	6 (33.3)
≥ 3	135 (66.5)	26 (40.6)	42 (64.6)	9 (50.0)
BCR-ABL Mutation at Entry				
0	136 (67.0)	0	39 (61.9)	0
1	53 (26.1)	50 (78.1)	20 (31.8)	16 (88.9)
≥2	14 (6.9)	14 (21.9)	4 (6.4)	2 (11.1)
No sequencing data			2 (3.1)	

The median ages in the T315I cohorts for both CP-CML and AP-CML (51 for CP-CML and 54 for AP-CML) were younger than in the R/I cohorts (61 for CP-CML and 60 for AP-CML). Female patients were 53.2% in the R/I CP-CML cohort and 61.5% in the R/I AP-CML cohort, while 25% in the T315I CP-CML cohort and 38.9 % in the T315I AP-CML cohort. The median time since diagnosis was longer in the R/I cohorts than in the T315I cohorts in both CP-CML and AP-CML. There were more patients with ECOG score of 0 than patients with ECOG scores of 1 or 2. Patients with resistant to prior TKI were the majority in the CP-CML and AP-CML cohorts. Patients with 2 or more prior TKI were the majority. The BCR-ABL mutation at entry was 67% in the R/I CP-CML cohort and 62% in the R/I AP-CML cohort. There were more patients with one BCR-ABL mutation than two or more BCR-ABL mutations in the CP-CML T315I and AP-CML T315I cohorts.

The demographic and disease characteristics for BP-CML/Ph+ ALL and all pooled 6 cohorts are summarized in Table 5.

Table 5 : Demographic and Disease Characteristics for BP-CML/Ph+ ALL and Total of 6 Cohorts: Treated Population

	BP-CML/Ph+ ALL		Total 6 cohorts
	R/I (N=48) n (%)	T315I (N=46) n (%)	Total (N=444) n (%)
Age			
Median (yrs)	54	56	59
18-44	16 (33.3)	17 (37.0)	109 (24.6)
45-64	18 (37.5)	16 (34.8)	182 (41.0)
≥65	14 (29.2)	13 (28.3)	153 (34.5)
Gender			
Female	17 (35.4)	20 (43.5)	208 (46.9)
Male	31 (64.6)	26 (56.5)	236 (53.2)
Race			
White	39 (81.3)	38 (82.6)	349 (78.6)
Asian	8 (16.7)	7 (15.2)	57 (12.8)
Black/African American	1 (2.1)	1 (2.2)	25 (5.6)
Other (Unknown , other)	0	0	13 (2.9)

Region			
North America	35 (72.9)	24 (52.2)	206 (46.4)
US	32 (66.7)	20 (43.5)	187 (41.7)
Europe/Australia	6 (12.5)	20 (43.5)	196 (44.1)
Asia	7 (14.6)	2 (4.4)	42 (9.5)
ECOG			
0	15 (31.9)	16 (34.8)	262 (59.0)
1	20 (42.6)	19 (41.3)	147 (33.1)
2	12 (25.5)	11 (23.9)	34 (7.7)
Missing			1 (0.2)
Time since Diagnose			
Median (yrs)	4.0	4.8	6.1
0- <5	27 (56.3)	35 (76.1)	194 (43.7)
5- <10	11 (22.9)	7 (15.2)	113 (25.5)
≥ 10	10 (20.8)	4 (8.7)	137 (30.9)
Resistant to Prior TKI	46 (95.8)	40 (87.0)	374 (84.2)
Number of Prior TKI			
1	2 (4.2)	7 (15.2)	29 (6.5)
2	13 (27.1)	22 (47.8)	166 (37.4)
≥ 3	33 (68.8)	17 (37.0)	249 (56.1)
BCR-ABL Mutation at Entry			
0	20 (44.4)	0	195 (44.4)
1	16 (35.6)	36 (78.3)	191 (43.5)
≥2	9 (20.0)	10 (21.7)	53 (12.1)
No sequencing data	3 (6.3)		

The median age was 54 years in the R/I cohort and 56 years in the T315I for BP-CML/Ph+ ALL. There were more Female patients. Patients were enrolled mostly from North America (72.9%) in the R/I cohort, but 52.2% patients were enrolled from North America and 43.5% were enrolled from Europe/Australia in the T315I cohort. There were more patients with ECOG score of 1 than ECOG score of 0 or 2. The median time since diagnosis was 4 years in the R/I cohort and 4.8 years in the T315I BP-CML/Ph+ ALL cohorts. Patients with resistant to prior TKI were majority in the BP-CML/Ph+ ALL cohorts. Patients with 2 or more prior TKIs were majority. For BCR-ABL mutation at entry, 44.4% patients in the R/I cohort had 0 mutation and 78.3% patients in the T315I cohort had one mutation in the BP-CML/Ph+ ALL cohorts.

Overall, majority was White patients and 41.7% patients were enrolled in the US sites. In the CP-CML and AP-CML cohorts, R/I patients had older median age, more Female patients and longer time since diagnosis than T315I patients. Patients' ECOG score of 0 were greater in the CP-CML and AP-CML cohorts, but patients' ECOG score of 1 were greater in the BP-CML/Ph+ ALL cohorts. The median time since diagnosis was 6.1 years overall. Majority were resistant to prior TKI. Majority had 2 or more prior TKIs. For BCR-ABL mutation at entry, more patients in the R/I cohort had 0 mutation but all patients in the T315I cohort had more than one mutation in the BP-CML/Ph+ ALL cohorts. The demographic characteristics of BP-CML and Ph+ ALL patients are summarized separately in Table 6.

Table 6 : Demographic and Disease Characteristics for BP-CML and Ph+ ALL Cohorts Separately: Treated Population

	BP-CML(N=62) n (%)	Ph+ ALL (N=32) n (%)
Age		
Median (yrs)	53	61
18-44	23 (37.1)	10 (31.3)
45-64	25 (40.3)	9 (28.1)
≥65	14 (22.6)	13 (40.6)
Gender		
Female	25 (40.3)	12 (37.5)
Male	37 (59.7)	20 (62.5)
Race		
White	46 (74.2)	31 (96.9)
Asian	14 (22.6)	1 (3.1)
Black/African American	2 (3.2)	0
Other (Unknown , other)	0	0
Region		
North America	41 (72.9)	18 (56.3)
US	39 (62.9)	14 (43.8)
Europe/Australia	12 (12.5)	14 (43.8)
Asia	9 (14.6)	0
ECOG		
0	20 (32.3)	11 (34.4)
1	22 (35.5)	17 (53.1)
2	19 (30.6)	4 (12.5)
Missing	1 (1.6)	
Time since Diagnose		
Median (yrs)	4.0	1.5
0-<5	34 (54.8)	28 (87.5)
5-<10	14 (22.6)	4 (12.5)
≥ 10	14 (22.6)	0
Resistant to Prior TKI	59 (95.2)	27 (84.4)
Number of Prior TKI		
1	3 (4.8)	6 (18.8)
2	22 (35.5)	13 (40.6)
≥ 3	37 (59.7)	13 (40.6)
BCR-ABL Mutation at Entry		
0	17 (28.3)	3 (9.7)
1	33 (55.0)	19 (61.3)
≥2	10 (16.7)	9 (29.0)

There were more BP-CML patients than Ph+ ALL patients. The median age was older in the Ph+ALL cohort than in the BP-CML cohort. The time since diagnosis was only 1.5 years for the Ph+ ALL cohort compared to 4 years in the BP-CML cohort.

3.2.4 Results and Conclusions

The primary endpoint results of MCyR in the CP-CML cohort and MaHR in the AP-CML and BP-CML/Ph+ ALL cohorts are summarized in Table 7.

Table 7 : Sponsor's Primary Endpoints Results by Cohort: Treated Population

	CP-CML		AP-CML		BP-CML/Ph+ALL	
	MCyR		MaHR		MaHR	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
R/I	99/203 (48.8)	41.7, 55.9	39/65 (60.0)	47.1, 72.0	17/48 (35.4)	22.2, 50.5
T315I	45/64 (70.3)	57.6, 81.1	9/18 (50.0)	26.0, 74.0	15/46 (32.6)	19.5, 48.0
Total	144/267 (53.9)	47.8, 60.0	48/83 (57.8)	46.5, 68.6	32/94 (34.0)	24.6, 44.5

In the CP-CML cohort, MCyR rate of 70.3% was higher in the T315I mutation cohort than in the R/I cohort of 48.8%. MaHR rates were 57.8% in the AP-CML and 34% in the BP-CML/Ph+ALL cohorts.

Reviewer's comments:
The sample size of Cohort AP-CML T315I was only 18 patients. This provides the power of approximately 46% based on 0.1 of null MaHR and 0.3 of alternative MaHR. Enrolling fewer patients into cohort AP-CML T315I than originally planned reduced the power/sensitivity to rule out a MaHR rate of 10%. However, the observed response rate in this cohort (and in the other cohorts) was much greater than the assumed response rate that was used to plan the sample size for the cohort. The 95% confidence interval for the MaHR rate in the AP-CML T315I cohort was (26%, 74%) easily ruling out a MaHR rate of 10%. Additionally, it should be noted that had the T315I cohort been fully enrolled to 40 patients without having any additional patients achieving a MaHR, the 95% confidence interval for MaHR rate would have been (11%, 38%) and thus, a 10% MaHR rate would have still been ruled out.

The number of patients achieved CCyR and PCyR in the CP-CML cohort are summarized in Table 8.

Table 8 : CCyR and PCyR Rates and Time to MCyR in CP-CML Patients: Treated Population

	Total (N=267) n (%)	R/I (N=203) n (%)	T315I (N=64) n (%)
MCyR	144 (53.9)	99 (48.8)	45 (70.3)
95% CI	47.8, 60.0	41.7, 55.9	57.6, 81.1
CCyR	118 (44.2)	76 (37.4)	42 (65.6)
95% CI	38.1, 50.4	30.8, 44.1	52.7, 77.1
PCyR	26 (9.7)	23 (11.3)	3 (4.7)
95% CI	6.5, 13.9	7.3, 16.5	1.0, 17.1
Time to MCyR			
Median (95% CI), month	5.5 (3.0, 5.7)	5.7 (4.4, 8.3)	2.8 (2.8, 3.0)

One hundred and eighteen patients (44.2%) had CCyR and 26 patients (9.7%) had PCyR in the CP-CML cohort. In the T315I cohort, 42 patients (65.6%) had CCyR and 3 patients (4.7%) had PCyR. In the R/I cohort 76 patients (37.4%) had CCyR and 23 patients (11.3%) had PCyR. The patient in the T315I cohort had greater CCyR than patients in the R/I cohort. The median time to MCyR was 5.5 months for the CP-CML cohort.

Sensitivity Analysis for the primary endpoints

Sensitivity Analysis 1:

The sensitivity analysis results using per-protocol population are summarized in Table 9.

Table 9 : Sensitivity Analyses 1: Using Per-Protocol Population

	CP-CML		AP-CML		BP-CML/Ph+ALL	
	MCyR		MaHR		MaHR	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
R/I	99/201 (49.3)	42.1, 56.4	39/53 (73.6)	59.7, 84.7	17/46 (37.0)	23.2, 52.5
T315I	45/64 (70.3)	57.6, 81.1	9/15 (60.0)	32.3, 83.7	15/44 (34.1)	20.5, 49.9
Total	144/265 (54.3)	48.1, 60.4	48/68 (70.6)	58.3, 81.0	32/90 (35.6)	25.7, 46.3

The analysis results using the per protocol population were similar to the primary analysis results.

Sensitivity Analysis 2:

The sensitivity analyses was performed on the original planned sample size i.e., the first 100 CP-CML R/I patients, the first 40 AP-CML R/I patients, the first 40 BP-CML/Ph+ALL R/I patients and the first 40 BP-CML/Ph+ALL T315I patients enrolled into the trial.

Table 10: Sensitivity Analyses 2: Using Original Planned Sample Size

	CP-CML		AP-CML		BP-CML/Ph+ALL	
	MCyR		MaHR		MaHR	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
R/I	48/100 (48.0)	37.9, 58.2	25/40 (60.0)	45.8,77.3	16/40 (40.0)	24.9, 56.7
T315I					12/40 (30.0)	16.6, 46.5

The MCyR rate was 48.0% in the R/I CP-CML cohort. The MaHR rate was 60% in the R/I AP-CML cohort, 40% in the R/I BP-CML/Ph+ALL cohort and 30% in the T315I BP-CML/Ph+ALL cohorts. The analysis results based on original planned sample size were similar to the primary analysis results.

Reviewer's comment: As enrolment into the T315I cohort was still ongoing when enrolment into the R/I cohort had reached its planned sample size of 100, the sponsor continued enrolment into the R/I cohort. An additional analysis of MCyR was performed by the applicant based on the first 100 patients enrolled into the R/I cohort. The first originally planned patients in the sensitivity analysis would have, on average, longer follow-up and would have had more time to achieve response. Recall that the data cutoff date was less than two months after the last patient was enrolled. It was the same for the AP-CML and BP-CML/Ph+ ALL cohorts.

The results of CHR and NEL rates and time to MaHR are summarized in Table 11.

Table 11: CHR and NEL Rate and Time to MaHR in the AP-CML Patients: Treated Population

	Total (N=83)	R/I (N=65)	T315I (N=18)
MaHR	48 (57.8)	39 (60.0)	9 (50.0)
95% CI	46.5, 68.6	47.1, 72.0	26.0, 74.0
CHR	39 (47.0)	30 (46.2)	9 (50.0)
95% CI	35.9, 58.3	33.7, 59.0	26.0, 74.0
NEL	9 (10.8)	9 (13.8)	0
95% CI	5.1, 19.6	6.5, 24.7	
Time to MaHR			
Median (95% CI), month	1.5 (0.9, 3.2)	1.5 (0.7, 3.2)	2.3 (0.5, ∞)

Thirty nine patients (47%) had CHR and 9 patients (10.8%) had NEL in the AP-CML cohort. In the R/I cohort, 30 patients (46.2%) had CHR and 9 patients (13.8%) had NEL. In the T315I cohort, all 9 MaHR patients (50%) had CHR. The median time to MaHR was 1.5 months in the AP-CML cohort.

Reviewer's comment: The clinical reviewer had discrepancy with the sponsor's MaHR for these 5 subjects in the AP-CML patients.

SUBJID	Cohort	Applicant's analysis	FDA analysis	Justification
938-012	AP R/I	MaHR (NEL)	Non-responder	MaHR at baseline
955-002	AP R/I	MaHR (NEL)	Non-responder	MaHR at baseline
956-001	AP R/I	MaHR (CHR)	Non-responder	MaHR at baseline
948-007	AP T315I	MaHR (CHR)	Non-responder	No labs or bone marrow prior to first dose.
957-010	AP T315I	MaHR (CHR)	Non-responder	No labs or bone marrow prior to first dose.

The results of MaHR, CHR and NEL based on FDA analyses are summarized in Table 12.

Table 12: CHR and NEL Rate and Time to MaHR in the AP-CML Patients by FDA Adjudication: Treated Population

	Total (N=83)	R/I (N=65)	T315I (N=18)
MaHR	43 (51.8)	36 (55.4)	7 (38.9)
95% CI	40.6, 62.9	42.5, 67.7	17.3, 64.3
CHR	36 (43.4)	29 (44.6)	7 (38.9)
95% CI	32.5, 54.7	32.3, 57.5	17.3, 64.3
NEL	7 (8.4)	7 (10.8)	0
95% CI	3.5,16.6	4.4, 20.9	
Time to MaHR			
Median (95% CI)	2.3 (0.9, 3.6)	1.8 (0.7, 3.6)	5.7 (0.6, ∞)

Forty three patients (51.8%) had MaHR in the AP-CML. Among 43 MaHR, 36 (43.4%) had CHR and 7 patients (8.4%) had NEL. In the R/I cohort, 29 patients (44.6%) had CHR and 7 patients (10.8%) had NEL. In the T315I cohort, all 7 MaHR patients (38.9%) had CHR.

Table 13: CHR and NEL Rates and Time to MaHR in the BP-CML/Ph+ALL Patients: Treated Population

	Total (N=94)	R/I (N=48)	T315I (N=46)
MaHR	32 (34.0)	17 (35.4)	15 (32.6)
95% CI	24.6, 44.5	22.2, 50.5	19.5, 48.0
CHR	24 (25.5)	13 (27.1)	11 (23.9)
95% CI	17.1, 35.6	15.3, 41.9	12.6, 38.8
NEL	8 (8.5)	4 (8.3)	4 (8.7)
95% CI	3.8, 16.1	2.3, 20.0	2.4, 20.8
Time to MaHR			
Median (95% CI), month	5.5 (3.6, ∞)	3.7 (3.3, ∞)	NA (1.4, ∞)

Twenty four patients (25.5%) had CHR and 8 patients (8.5%) had NEL in the BP-CML/PH+ALL cohort. In the R/I cohort, 13 patients (27.1%) had CHR and 4 patients (48.3%) had NEL. In the T315I cohort, 11 patients (23.9%) had CHR and 4 patients (8.7%) had NEL. The median time to MaHR was 5.5 months in the BP-CML/Ph+ ALL cohorts.

The CHR and NEL rates and time to MaHR for BP-CML and Ph+ ALL cohorts are summarized separately in Table 14.

Table 14: MaHR, CHR and NEL Rates and Time to MaHR: BP-CML and Ph+ALL Separately: Treated Population

	BP-CML (N=62)			Ph+ ALL (N=32)		
	Total n (%)	R/I (N= 38) n (%)	T315I (N=24) n (%)	Total n (%)	R/I (N=10) n (%)	T315I (N=22) n (%)
MaHR	19 (30.7)	12 (31.6)	7 (29.5)	13 (40.6)	5 (50.0)	8 (36.4)
95% CI	19.6, 43.7	17.5, 41.6	12.6, 51.1	23.7, 59.4	18.7, 81.3	17.2, 59.3
CHR	13 (21.0)	9 (23.7)	4 (16.7)	11 (34.4)	4 (40.0)	7 (31.8)
95% CI	11.7, 33.2	11.4, 40.2	4.7, 37.4	18.6, 53.2	12.2, 73.8	13.9, 54.9
NEL	6 (9.7)	3 (7.9)	3 (12.5)	2 (6.3)	1 (10.0)	1 (4.5)
95% CI	3.6, 19.9	1.7, 21.4	2.7, 32.4	0.8, 20.8	0.3, 44.5	0.1,22.8
Time to MaHR						
Median (95% CI)	NA(3.3, ∞)	3.7(3.3, ∞)	NA(1.4, ∞)	5.5(0.9, ∞)	5.5(0.5, 5.5)	NA(0.8,∞)

The MaHR rate was 30.7% in the BP-CML cohort (31.6% in R/I and 29.5% in T315I) and 40.6 % in the Ph+ALL cohort (50% in R/I and 36.4% in T315I). The CHR rate was 21% in the BP-CML cohort (23.7% in R/I and 16.7% T315I) and 34.4% in the Ph+ ALL cohort (40% in R/I and 31.8% in T315I). Higher MaHR and CHR rates were observed in the Ph+ ALL cohort than in the BP-CML cohort. The median time to MaHR was not reached in the BP-CML cohort and 5.5 months in the Ph+ ALL cohort.

Secondary Endpoints:
The secondary endpoints of confirmed MCyR, CHR, and MMR results in the CP-CML cohorts are summarized in Table 15.

Table 15: Confirmed MCyR, confirmed CHR and confirmed MMR in the CP-CML Cohort (Cohorts A and B): Treated Population

	Total (N=267) n (%)	R/I (N=203) n (%)	T315I (N=64) n (%)
Confirmed MCyR	110 (41.2)	72 (35.5)	38 (59.4)
95% CI	35.2, 47.4	28.9, 42.5	46.4, 71.5
CHR	249 (93.3)	191 (94.1)	58 (90.6)
95% CI	89.6, 96.0	89.9, 96.9	80.7, 96.5
Aduste CHR	146/154 (94.8)	109/114 (95.6)	37/40 (92.5)
95% CI	90.0, 97.7	90.1, 98.6	79.6, 98.4

MMR	79 (29.6)	47 (23.2)	32 (50.0)
95% CI	24.2, 35.5	17.5, 29.6	37.2, 62.8
Best MMR			
MMR	36 (13.4)	20 (9.9)	16 (25.0)
MMR4	18 (6.7)	11 (5.4)	7 (10.9)
CHR	25 (9.4)	16 (7.9)	9 (14.1)

The definition of the confirmed MCyR was that patients entering the trial in PCyR must have achieved 2 consecutive assessments of CCyR no fewer than 28 days apart and patients entering the trial in less than PCyR must have achieved 2 consecutive assessments of PCyR or CCyR no fewer than 28 days apart. Fifty one patients in the CP-CML R/I group had 2 cytogenetic assessments and 15 patients in the CP-CML T315I cohort had 2 cytogenetic assessments. The confirmed MCyR, CHR, and MMR rates were 35.5%, 94.1% and 23.2%, respectively, in the CP-CML R/I cohort and 59.4%, 57.8%, and 50%, respectively, in the CP-CML T315I cohort.

The secondary endpoints of MCyR, confirmed MCyR, and MMR results in the AP-CML and in the BP-CML/PH+ALL cohorts are summarized in Table 16.

Table 16: MCyR Rate in the AP-CML or BP-CML/Ph+ALL Cohorts: Treated Population

AP-CML	Total (N=83) n (%)	R/I (N=65) n (%)	T315I (N=18) n (%)
MCyR	32 (38.6)	22 (33.9)	10 (55.6)
95% CI	28.1, 49.9	22.6, 46.7	30.8, 78.5
CCyR	19 (22.9)	13 (20.0)	6 (33.3)
PCyR	13 (15.7)	9 (13.9)	4 (22.2)
BP-CML/Ph+ALL	Total (N=94) n (%)	R/I (N=48) n (%)	T315I (N=46) n (%)
MCyR	29 (30.9)	13 (27.1)	16 (34.8)
95% CI	21.7, 41.2	15.3, 41.9	21.4, 50.3
CCyR	23 (24.5)	11 (22.9)	12 (26.1)
PCyR	6 (6.4)	2 (4.4)	4 (8.9)

In the AP-CML cohort, MCyR rate of 55.6% in the T315I mutation cohort was higher than in the R/I cohort of 33.9%. In the BP-CML/Ph+ALL cohorts, MCyR rate was 27.1% in the R/I cohort and 34.8% in the T315I mutation cohort.

The MCyR rates for the BP-CML and Ph+ ALL cohorts are summarized separately in Table 17.

Table 17: MCyR Rate for the BP-CML and Ph+ ALL Separately: Treated Population

	BP-CML (N=62)			Ph+ ALL (N=32)		
	Total n (%)	R/I (N=38) n (%)	T315I (N=24) n (%)	Total n (%)	R/I (N=10) n (%)	T315I (N=22) n (%)
MCyR	14 (22.6)	7 (18.8)	7 (29.2)	15 (46.9)	6 (60.0)	9 (40.9)
95% CI	12.9, 35.0	7.7, 34.3	12.6, 51.1	29.1, 65.3	26.2, 87.8	20.7, 63.7
CCyR	11 (17.7)	6 (15.8)	5 (20.8)	12 (37.5)	5 (50.0)	7 (31.8)
PCyR	3 (4.8)	1 (2.6)	2 (8.3)	3 (9.4)	1 (10.0)	2 (9.1)

The MCyR rate in the Ph+ ALL cohort (46.9%) was higher than in the BP-CML cohort (22.6%). In the Ph+ ALL cohort, MCyR rate was higher in the R/I cohort than in the T315I cohort, but MCyR rate was higher in the T315I cohort than in the R/I cohort in the overall BP-CML patients.

The confirmed MCyR rate and MMR rate in the AP-CML and BP-CML/Ph+ ALL cohorts are summarized in Table 18.

Table 18: Confirmed MCyR and MMR Rates in the AP-CML and BP-CML/Ph+ALL: Treated Population

AP-CML	Total (N=83) n (%)	R/I (N=65) n (%)	T315I (N=18) n (%)
Confirmed MCyR	21 (25.3)	15 (23.1)	6 (33.3)
95% CI	16.4, 36.0	13.5, 35.2	13.3, 59.0
MMR	9 (10.8)	6 (9.2)	3 (16.7)
95% CI	5.1, 19.6	3.5, 19.0	3.6, 41.4
Best MMR			
MMR	6 (7.2)	3 (6.3)	3 (6.3)
MMR4	0	0	0
CHR	3 (3.6)	3 (9.4)	0
BP-CML/Ph+ALL	Total (N=94) n (%)	R/I (N=48) n (%)	T315I (N=46) n (%)
Confirmed MCyR	17 (18.1)	10 (20.8)	7 (15.2)
95% CI	10.9, 27.4	10.5, 35.0	6.3, 28.9
MMR	11 (11.7)	9 (18.8)	2 (4.3)
95% CI	6.0, 20.0	8.9, 32.6	0.5, 14.8
Best MMR			
MMR	6 (7.2)	5 (10.4)	1 (5.3)
MMR4	1 (1.2)	1 (2.1)	0
CMR	4 (4.8)	3 (9.4)	1 (5.3)

The confirmed MCyR, and MMR rates were 23.3% and 9.2%, respectively, in the AP-CML R/I cohort and 33.3% and 16.7%, respectively, in the AP-CML T315I cohort.

The confirmed MCyR, and MMR rates were 20.8% and 18.8%, respectively, in the BP-CML/Ph+ALL R/I cohorts and 15.2% and 4.4%, respectively, in the BP-CML/Ph+ALL T315I cohorts.

The confirmed MCyR rate and MMR rate are summarized for the BP-CML cohort and Ph+ ALL cohort separately in Table 19.

Table 19: Confirmed MCyR and MMR Rates for the BP-CML and Ph+ ALL Cohorts Separately: Treated Population

	BP-CML (N=62)			Ph+ ALL (N=32)		
	Total n (%)	R/I (N=38) n (%)	T315I (N=24) n (%)	Total n (%)	R/I (N=10) n (%)	T315I (N=22) n (%)
Confirmed MCyR	10 (16.1)	6 (15.8)	4 (16.7)	7 (21.9)	4 (40.0)	3 (13.6)
95% CI	8.0, 27.7	6.0, 31.3	4.7, 37.4	9.3, 40.0	12.2, 73.8	2.9, 34.9
MMR	8 (12.9)	7 (18.4)	1 (4.2)	3 (9.4)	2 (20.0)	1 (4.6)
95% CI	5.7, 23.9	7.7, 34.3	0.1, 21.1	2.0, 25.0	2.5, 55.6	0.1, 22.8
Best MMR						
MMR	5 (8.1)	4 (10.5)	1 (4.2)	1 (3.1)	1 (0.1)	0
MMR4	0	0	0	1 (3.1)	1 (0.1)	0
CMR	3 (4.8)	3 (7.9)	0	1 (3.1)	0	1 (4.5)

The confirmed MCyR was 10 patients (16.1%) among 62 patients in the BP-CML cohort and 7 patients (21.9%) among 32 patients in the Ph+ ALL cohort. The MMR was 8 patients (12.9%) among 62 patients in the BP-CML cohort and 3 patients (9.4%) among 32 patients in the Ph+ ALL cohort.

The time to response for MCyR, CHR, and MMR in the CP-CML cohort are summarized in Table 20.

Table 20: Time to response for MCyR, CHR, MMR in the CP-CML Cohort: Treated Population

	Total (N=267)	R/I (N=203)	T315I (N=64)
MCyR			
Median (95% CI) (Months)	5.5 (3.0, 5.7)	5.7 (4.4, 8.3)	2.8 (2.8, 3.0)
By 3 months	102 (38.2)	64 (31.5)	38 (59.4)
By 6 months	130 (48.7)	86 (42.4)	44 (68.8)
By 9 months	142 (53.2)	98 (48.3)	44 (68.8)
CHR			
Median (95% CI) (Months)	3.2 (2.3, 3.2)	3.2 (2.8, 3.2)	3.0 (1.6, 3.2)
MMR			
Median (95% CI) (Months)	NA (13.7, ∞)	NA (13.8, ∞)	8.2 (5.5, 11.0)

The median time to MCyR was 5.5 months in the entire CP-CML cohort. The median time to MCyR in the R/I and T315I cohorts was 2.8 months and 5.7 months, respectively.

Duration of Responses

The duration of MCyR, CHR, and MMR for CP-CML are summarized in Table 21.

Table 21: Duration of MCyR, CHR, MMR in the CP-CML Cohort: Treated Population

	Total (N=267)	R/I (N=203)	T315I (N=64)
MCyR			
# Events/ #Responses (%)	6/144 (4.2)	5/99 (5.1)	1/45 (1.1)
Median (95% CI) (Months)	NA	NA	NA
6 months	93.3	91.6	96.7
12 months	93.3	91.6	
CHR			
# Events/# Responses (%)	40/249 (16.1)	30/191 (15.7)	10/58 (17.2)
Median (95% CI) (Months)	NA	NA	NA
MMR			
# Events/# Responses (%)	9/79 (11.4)	7/47 (14.9)	2/32 (6.3)
Median (95% CI)	NA	NA	NA

Among 144 MCyR patients, 6 patients (4.2%) had events. The median duration of MCyR was not reached for the entire CP-CML cohort. The Kaplan- Meier (KM) probability of remaining in MCyR was 93.3% at both 6 months and 12 months. Among 244 CHR patients, 40 patients (16.1%) had events. Among 79 MMR patients, 9 patients (11.4%) had events. The median durations of CHR and MMR were not reached.

The duration of MaHR, MCyR and MMR in the AP-CML and BP-CML/Ph+ ALL cohorts are summarized in Tables 22 through 29.

Table 22: Duration of responses for MaHR, MCyR and MMR in the AP-CML Cohort: Treated Population

	Total (N=83)	R/I (N=65)	T315I (N=18)
MaHR			
# Events/# Responses (%)	22/48 (45.8)	17/39 (43.6)	5/9 (55.6)
Median (95% CI) (Months)	9.5 (6.8, 17.7)	9.5 (6.9, 17.7)	5.7 (1.4, ∞)
6 months	67.7	73.3	41.7
12 months	46.9	49.0	NA
MCyR			
# Events/# Responses (%)	10/32 (31.3)	7/22 (31.8)	3/10 (30.0)
Median (95% CI) (Months)	NA (3.4, ∞)	5.5 (1.8, ∞)	NA (0.2, ∞)

MMR # Events/# Responses (%) Median (95% CI)	1/9 (11.1) NA	1/6 (16.7) NA	0/3 NA

Among 48 MaHR patients, 22 patients (45.8%) had events. The median duration of MaHR was 9.5 months. The KM probability of remaining in MaHR was 67.7% and 46.9% at 6 months and 12 months, respectively in the entire AP-CML cohort. Among 32 MCyR patients, 10 patients (31.3%) had events and 1 event among 9 MMR patients in the entire AP-CML cohort. The median durations for MCyR and MMR were reached.

Reviewer's comment: The duration of MaHR based on FDA analysis results in the AP-CML cohort are summarized in Table 23.

Table 23 Duration of responses for MaHR in the AP-CML Cohort by FDA Analysis: Treated Population

	Total (N=83) n (%)	R/I (N=65) n (%)	T315I (N=18) n (%)
MaHR # Events/# Responses (%) Median (95% CI) (Months)	21/43 (48.8) 9.5 (5.5,17.7)	17/36 (47.2) 9.5 (6.9, 17.7)	4/7 (57.1) 4.2 (1.4, ∞)

Among 48 MaHR patients, 21 patients (48.8%) had events. The median duration of MaHR was 9.5 months based on FDA analysis.

Table 24: Duration of responses for MaHR, MCyR and MMR in the BP-CML/Ph+ALL Cohorts: Treated Population

	Total (N=94)	R/I (N=48)	T315I (N=46)
MaHR # Events/# Responses (%) Median (95% CI) (Months) 6 months 12 months	17/32 (53.1) 4.7 (3.2, ∞) 44.7 35.2	7/17 (41.2) NA (3.2, ∞) 67.7 51.6	10/15 (66.7) 4.1 (2.3, 4.7) 17.4 NA
MCyR # Events/# Responses (%) Median (95% CI) (Months)	17/29 (58.6) 4.3 (1.6, 6.4)	4/13 (30.8) NA (6.0, ∞)	13/16 (81.2) 1.6 (0.9, 4.0)
MMR # Events/# Responses (%) Median (95% CI)	6/12 (50.0) 3.7 (1.3, ∞)	4/10 (40.0) NA (1.3, ∞)	2/2 (100) 2.1 (1.1, 3.2)

Among 32 MaHR patients, 17 patients (53.1%) had events. The median duration of MaHR was 4.7 months. The KM probability of remaining in MaHR was 44.7% and 35.2% at 6 months and 12 months, respectively in the combined BP-CML/Ph+ ALL cohorts. Among 29 MCyR patients,

17 patients (58.6%) had events and 6 events among 12 MMR patients in the combined BP-CML/Ph+ ALL cohorts. The median durations for MCyR and MMR were 4.3 months and 3.7 months, respectively.

Reviewer's comment: The duration of MaHR based on FDA analysis results in the BP-CML/PH+ ALL cohorts are summarized in Table 25.

Table 25: Duration of responses for MaHR in the BP-CML/Ph+ALL Cohorts by FDA Analysis: Treated Population

	Total (N=94)	R/I (N=48)	T315I (N=46)
MaHR			
# Events/# Responses (%)	21/32 (65.6)	9/17 (52.9)	12/15 (80.0)
Median (95% CI) (Months)	3.5 (2.7, 6.4)	6.9 (2.7, ∞)	3.4 (1.8, 4.3)

Among 32 MaHR patients, 21 patients (65.6%) had events. The median duration of MaHR was 3.5 months based on FDA analysis.

The duration of MaHR, MCyR, and MMR in the BP-CML and Ph+ ALL cohorts are summarized separately in Tables 26 and 28.

Table 26: Duration of MaHR, MCyR and MMR for BP-CML Cohort: Treated Population

BP-CML	Total (N=62)	R/I (N=38)	T315I (N=24)
MaHR			
# Events/# Responses (%)	7/19 (36.8)	3/12 (25.0)	4/7 (57.1)
Median (95% CI) (Months)	NA (3.2, ∞)	NA (2.8, ∞)	4.1 (2.7, 4.7)
MCyR			
# Events/# Responses (%)	5/14 (58.6)	0/7	5/7 (81.2)
Median (95% CI) (Months)	NA (2.3, ∞)	NA	3.5 (1.6, 5.0)
MMR			
# Events/# Responses (%)	4/9 (44.4)	3/8 (37.5)	1/1 (100)
Median (95% CI)	NA (1.3, ∞)	NA (1.3, ∞)	NA

Among 19 MaHR patients in the BP-CML cohort, 7 patients (36.8%) had events. The median duration of MaHR was not reached yet (4.1 months in T315I).

Reviewer's comment: The duration of MaHR based on FDA analysis results in the BP-CML cohort are summarized in Table 27.

Table 27: Duration of MaHR for BP-CML Cohort by FDA Analysis: Treated Population

BP-CML	Total (N=62)	R/I (N=38)	T315I (N=24)
MaHR			
# Events/# Responses (%)	9/19 (47.4)	4/12 (33.3)	5/7 (71.4)
Median (95% CI) (Months)	4.7 (2.7, ∞)	NA (2.0, ∞)	3.5 (1.8, 4.7)

Among 19 MaHR patients, 9 patients (47.4%) had events. The median duration of MaHR was 4.7 months based on FDA analysis

Table 28: Duration of MaHR, MCyR and MMR for Ph+ ALL Cohort: Treated Population

Ph+ ALL	Total (N=32)	R/I (N=10)	T315I (N=22)
MaHR			
# Events/# Responses (%)	10/13 (76.9)	4/5 (80.0)	6/8 (75.0)
Median (95% CI) (Months)	4.3 (2.2, 7.4)	6.4 (1.8, 7.4)	3.8 (1.8, ∞)
6 months	35.9	30.0	25.0
12 months	12.0	NA	NA
MCyR			
# Events/# Responses (%)	12/15 (80.0)	4/6 (66.7)	8/9 (88.9)
Median (95% CI) (Months)	1.8 (0.9, 6.0)	6.4 (1.8, 6.4)	0.9 (0.7, 4.3)
6 months	23.1	53.3	11.1
12 months	NA	NA	NA
MMR			
# Events/# Responses (%)	2/3 (66.7)	1/2 (50.0)	1/1 (100)
Median (95% CI)	2.4 (1.1, 3.7)	3.7	1.1
6 months	50.0	NA	NA
12 months	NA	NA	NA

Among 13 MaHR patients in the Ph+ ALL cohort, 10 patients (76.9%) had events. The median duration of MaHR was 4.3 months (6.4 months in R/I and 3.8 months in T315I).
There were more events for MaHR, MCyR and MMR in the Ph+ALL cohort than in the BP-CML cohort.

Reviewer's comment: The duration of MaHR based on FDA analysis results in the Ph+ ALL cohort are summarized in Table 29.

Table 29: Duration of MaHR for Ph+ ALL Cohort by FDA Analysis: Treated Population

Ph+ ALL	Total (N=32)	R/I (N=10)	T315I (N=22)
MaHR # Events/# Responses (%) Median (95% CI) (Months)	 12/13 (92.3) 3.2 (1.8, 4.7)	 5/5 (100) 3.2 (1.8, 7.4)	 7/8 (87.5) 3.3 (1.8, 4.7)

Among 13 MaHR patients, 12 patients (92.3%) had events. The duration of MaHR was 3.2 months based on FDA analysis.

The Kaplan-Meier survival proportion for duration of MCyR in the CP-CML cohort and MaHR in the AP-CML and BP-CML/Ph+ ALL cohorts are plotted in Figures 2 through 4.

Figure 2 : Duration of MCyR in the CP-CML Cohort

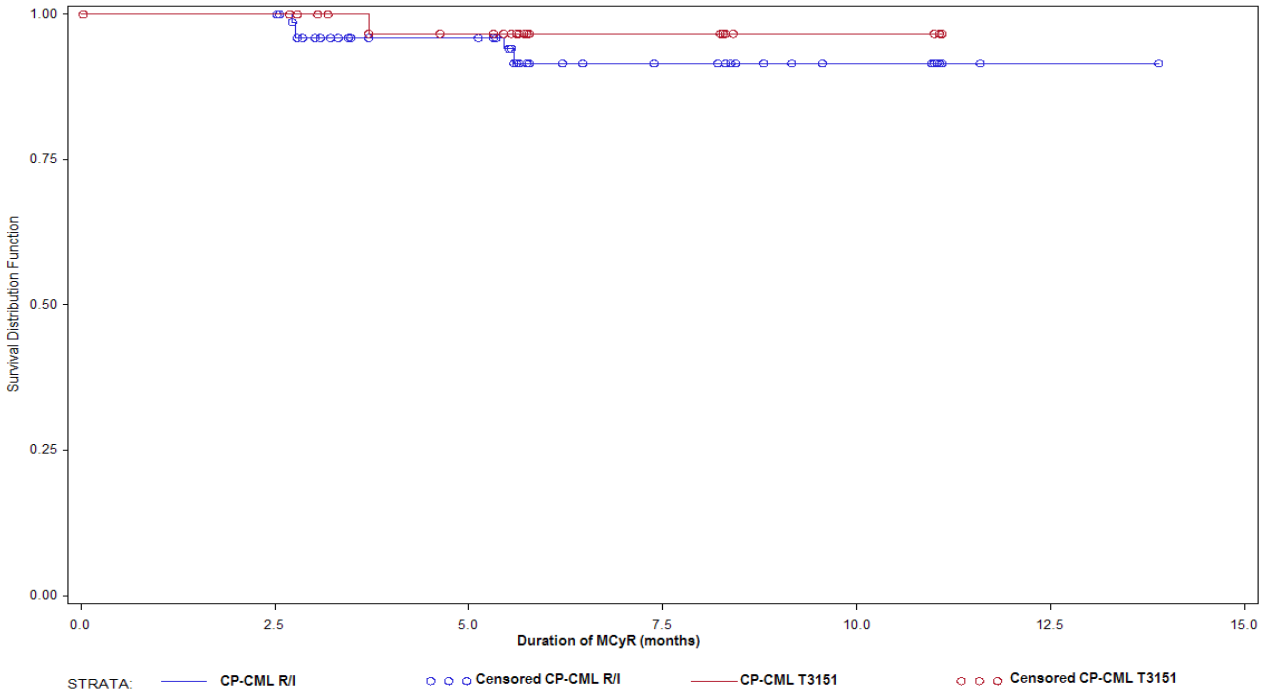


Figure 3 : Duration of MaHR in the AP-CML Cohort

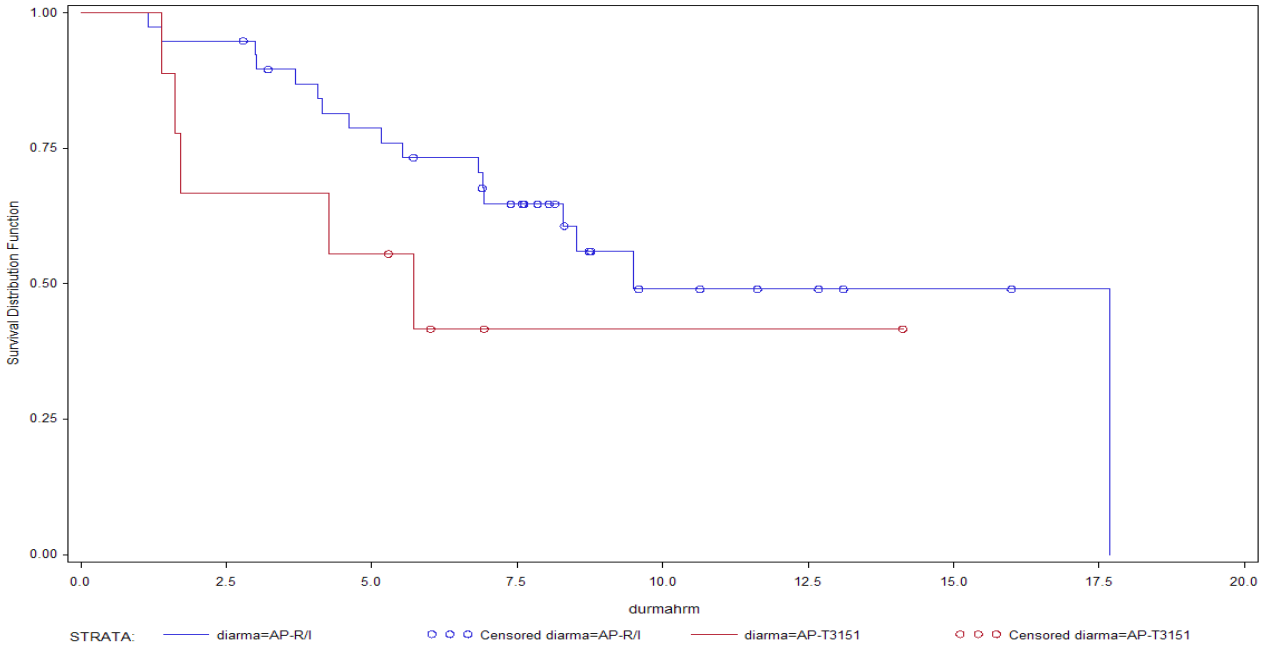
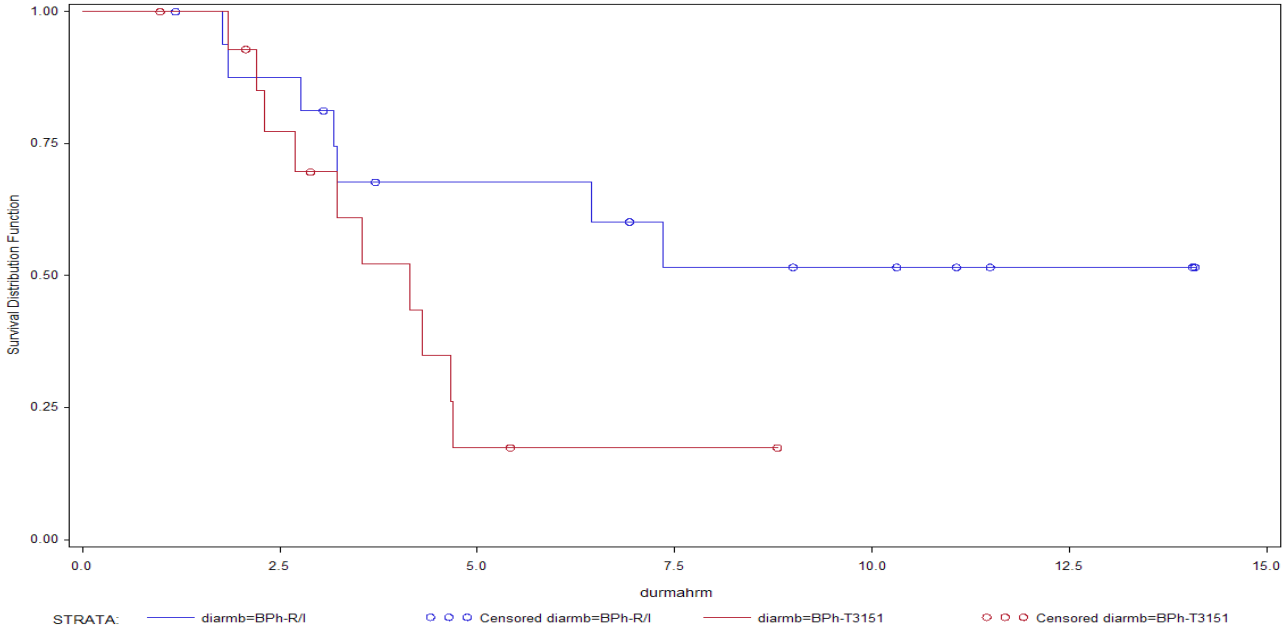


Figure 4 : Duration of MaHR in the BP-CML/Ph+ ALL Cohorts



PFS and OS
The results of PFS and OS in the CP- CML, AP-CML, and BP-CML/Ph+ ALL cohorts are summarized in Tables 30 through 33.

Table 30: PFS and OS in the CP-CML Cohort: Treated Population

	Total (N=267)	R/I (N=203)	T315I (N=64)
PFS*			
# Events/# Responses (%)	35 (13.1)	28 (13.8)	7 (10.9)
Median (95% CI) (Months)	NA (13.9, ∞)	NA (13.9, ∞)	NA
PFS**			
# Events/# Responses (%)	44 (16.5)	34 (16.7)	10 (15.4)
Median (95% CI) (Months)	NA (13.9, ∞)	NA (13.9, ∞)	NA
OS			
# Events/# Responses (%)	17 (6.4)	12 (5.9)	5 (7.8)
Median (95% CI) (Months)	NA	NA	NA

*:Treatment discontinuation due to progressive disease according to the investigator is not considered
**: Treatment discontinuation due to progressive disease according to the investigator is also considered.

Reviewer's comment: The patient who discontinued the treatment due to progression disease (PD) according to the investigator was not included in the sponsor's PFS. FDA included these patients in the PFS analyses.

There were 44 events (16.5%), 34 events from the R/I cohort and 10 events from the T315I cohort among 267 CP-CML patients including treatment discontinuation due to PD according to the investigator. The median PFS in the CP-CML cohort was not reached.

There were 17 deaths (6.4%), 12 deaths from the R/I cohort and 5 deaths from the T315I cohort among 267 CP-CML patients. The median OS in the CP-CML cohort was not reached.

Table 31: PFS and OS in the AP- CML: Treated Population

	Total (N=83)	R/I (N=65)	T315I (N=18)
PFS*			
# Events/# Responses (%)	30 (36.1)	24 (36.9)	6 (33.3)
Median (95% CI) (Months)	18.4 (10.1, ∞)	18.4 (10.1, 18.4)	NA (6.2, ∞)
PFS**			
# Events/# Responses (%)	33 (39.8)	27 (41.5)	6 (33.3)
Median (95% CI) (Months)	18.4 (9.2, ∞)	18.4 (9.1, 18.4)	NA (6.2, ∞)
OS			
# Events/# Responses (%)	12 (14.5)	8 (12.3)	4 (22.2)
Median (95% CI) (Months)	NA	NA	NA (9.2, ∞)

*:Treatment discontinuation due to progressive disease according to the investigator is not considered
**: Treatment discontinuation due to progressive disease according to the investigator is also considered.

There were 33 events (39.8%), 27 events from the R/I cohort and 6 events from the T315I cohort among 83 AP-CML patients including treatment discontinuation due to PD according to the investigator. The median PFS in the AP-CML cohort was 18.4 months.

There were 12 deaths (14.5%), 8 deaths from the R/I cohort and 4 deaths from the T315I cohort among 83 AP-CML patients. The median OS in the AP-CML cohort was not reached.

Table 32: PFS and OS for BP-CML/Ph+ALL: Treated Population

	Total (N=94)	R/I (N=48)	T315I (N=46)
PFS*			
# Events/# Responses (%)	60 (63.8)	27 (56.2)	33 (71.7)
Median (95% CI) (Months)	4.1 (2.7, 5.5)	5.6 (2.7, 8.3)	3.2 (1.9, 5.1)
PFS**			
# Events/# Responses (%)	67 (71.3)	31 (64.6)	36 (78.3)
Median (95% CI) (Months)	3.7 (2.6, 5.0)	3.9 (2.7, 7.3)	3.2 (1.8, 5.0)
OS			
# Events/# Responses (%)	60 (63.8)	31 (64.6)	29 (63.0)
Median (95% CI) (Months)	6.9 (5.0, 9.4)	6.9 (3.9, 12.5)	6.6 (4.9, 9.2)

*:Treatment discontinuation due to progressive disease according to the investigator is not considered
**: Treatment discontinuation due to progressive disease according to the investigator is also considered.

There were 67 events (71.3%), 31 events from the R/I cohort and 36 events from the T315I cohort among 94 BP-CML/Ph+ ALL patients including treatment discontinuation due to PD according to the investigator. The median PFS in the BP-CML/Ph+ ALL cohorts was 3.7 months.

There were 60 deaths (63.8%), 31 deaths from the R/I cohort and 29 deaths from the T315I cohort among 94 BP-CML/Ph+ ALL patients. The median OS was 6.9 months (6.9 months in R/I and 6.6 months in T315I).

Table 33: PFS and OS for BP-CML and Ph+ ALL Separately: Treated Population.

	Total (N=94)	BP-CML (N=62)	Ph+ ALL (N=32)
PFS*			
# Events/# Responses (%)	60 (63.8)	37 (59.7)	23 (71.9)
Median (95% CI) (Months)	4.1 (2.7, 5.5)	4.9 (2.4, 6.6)	3.2 (2.0, 5.1)
PFS**			
# Events/# Responses (%)	67 (71.3)	42 (67.7)	25 (78.1)
Median (95% CI) (Months)	3.7 (2.6, 5.0)	3.9 (1.9, 5.6)	3.2 (2.0, 5.0)
R/I	31/48 (64.6)	22/38 (57.9)	9/10 (90.0)
Median (95% CI)	3.9 (2.7, 7.3)	4.1 (2.4, 9.5)	3.9 (1.0, 7.3)
T315I	36/46 (78.3)	20/24 (83.3)	16/22 (72.7)
Median (95% CI)	3.2 (1.8, 5.0)	3.3 (1.5, 5.5)	2.9 (1.8, 5.0)

OS			
# Events/# Responses (%)	60 (63.8)	43 (59.3)	17 (53.1)
Median (95% CI) (Months)	6.9 (5.0, 9.3)	6.9 (3.9, 9.3)	9.0 (4.4, ∞)
R/I	31/48 (64.6)	26/38 (68.4)	5/10 (50.0)
Median (95% CI)	6.9 (3.9, 12.5)	6.1 (3.3, 12.5)	NA (1.8, ∞)
T315I	29/46 (63.0)	17/24 (70.8)	12/22 (54.5)
Median (95% CI)	6.6 (4.9, 9.2)	6.9 (3.4, 10.6)	6.5 (3.9, ∞)

*:Treatment discontinuation due to progressive disease according to the investigator is not considered
**: Treatment discontinuation due to progressive disease according to the investigator is also considered.

There were 42 events (67.7 %), 22 events from the R/I cohort and 20 events from the T315I cohort among 62 BP-CML patients including treatment discontinuation due to PD according to the investigator. The median PFS in the BP-CML was 3.9 months.

There were 25 events (78.1 %), 9 events from the R/I cohort and 16 events from the T315I cohort among 32 Ph+ ALL patients including treatment discontinuation due to PD according to the investigator. The median PFS in the Ph+ ALL was 3.2 months.

A total of 60 deaths (63.8%) were observed. More deaths were observed in the BP-CML cohort (43 deaths) than in the Ph+ALL cohort (17 deaths). The OS median was 6.9 months and 9.0 months in the BP-CML cohort and in the Ph+ ALL cohort, respectively.

Reviewer's Comment:
The median PFS including treatment discontinuation due to PD according to the investigator was similar or a little shorter than that of sponsor.

Lost to follow-up was examined by calculating the difference between the cutoff date of April 27, 2012 and the censoring dates for censored patients based on the disease assessment schedule of every 12 weeks. The time between censoring date and the cutoff date for MCyR, MaHR and OS are summarized in Table 34.

Table 34: Time between Censoring Date and the Data Cutoff Date (April 27, 2012) for MCyR, MaHR and OS Duration

	≤12 weeks	13, 24 weeks	25, 36 weeks	>36 weeks
Duration of MCyR	167	2	1	3
Duration of MaHR	39	0	1	1
Duration of OS	307	24	12	12

There are 6 MCyR patients and 2 MaHR patients who missed their most recent disease assessments, 4 MCyR and 2 MaHR patients who missed their two most recent disease assessments prior to the data cutoff date.

There are 48 patients with OS who missed their most recent disease assessments, 24 patients with OS who missed their two most recent disease assessments prior to the data cutoff date.

Conclusion for Efficacy Endpoints:

The primary endpoint of MCyR was 144 patients out of 267 CP-CML patients (53.9%: 95% CI: 47.8, 60.0), 99 patients out of 203 CP-CML R/I cohort patients (48.8%: 95% CI: 41.7, 55.9) and 45 patients out of 64 T315I CP-CML patients (70.3%: 95% CI: 57.6, 81.1).

The primary endpoint of MaHR was 48 patients out of 83 AP-CML patients (57.8%: 95% CI: 46.5, 68.6), 39 patients out of 65 AP-CML R/I cohort patients (60.0%: 95% CI: 47.1, 72.0) and 9 patients out of 18 T315I AP-CML cohort patients (50.0 %: 95% CI: 26.0, 74.0). Based on FDA analyses, 43 patients (51.8%) had MaHR in the AP-CML. Among 43 MaHR, 36 (43.4%) had CHR and 7 patients (8.4%) had NEL. In the R/I cohort, 29 patients (44.6%) had CHR and 7 patients (10.8%) had NEL. In the T315I cohort, all 7 MaHR patients (38.9%) had CHR.

The primary endpoint of MaHR was 32 patients out of 94 BP-CML/Ph+ ALL cohort patients (34.0%: 95% CI: 24.6, 44.5), 17 patients out of 48 BP-CML/PH+ ALL R/I cohort patients (35.4%: 95% CI: 22.2, 50.5) and 15 patients out of 46 T315I BP-CML/Ph+ ALL cohorts patients (32.6 %: 95% CI: 19.5, 48.0).

- The MaHR rate was 30.7% in the BP-CML cohort (31.6% in R/I and 29.5% in T315I) and 40.6 % in the Ph+ ALL cohort (50% in R/I and 36.4% in T315I).

The secondary endpoint of CCyR was 118 patients out of 267 CP-CML cohort patients (44.2%: 95% CI: 38.1, 50.4), 76 patients out of 203 CP-CML R/I cohort patients (37.4%: 95% CI: 30.8, 44.1) and 42 patients out of 64 T315I CP-CML cohort patients (65.6%: 95% CI: 52.7, 77.1).

The secondary endpoint of CHR was 39 patients out of 83 AP-CML cohort patients (47.0%: 95% CI: 35.9, 58.3), 30 patients out of 65 AP-CML R/I cohort patients (46.2%: 95% CI: 33.7, 59.0) and 9 patients out of 18 T315I CP-CML cohort patients (50.0%: 95% CI: 26.0, 74.0).

The secondary endpoint of CHR was 24 patients out of 94 BP-CML/Ph+ ALL cohort patients (25.5%: 95% CI: 17.1, 35.6), 13 patients out of 48 BP-CML/Ph+ ALL R/I cohort patients (27.1%: 95% CI: 15.3, 41.9) and 11 patients out of 46 T315I BP-CML/Ph+ ALL cohorts patients (23.9%: 95% CI: 12.6, 38.8).

- The CHR rate was 21% in BP-CML (23.7% in R/I and 16.7% T315I) and 34.4% in Ph+ ALL (40% in R/I and 31.8% in T315I). Higher MaHR and CHR rates were observed in the Ph+ ALL than BP-CML cohort.

For duration of MCyR in the CP-CML cohort, among 144 MCyR patients, 6 patients (4.2%) had events (5 from R/I and 1 form T315I). The median duration of MCyR was not reached for the entire CP-CML cohort.

For duration of MaHR in the AP-CML cohort, among 48 MaHR patients, 22 patients (45.8%) had events (17 from R/I and 5 from T315I) and the median duration of MaHR was 9.5 months (9.5 months for R/I and 5.7 months for T315I).

The duration of MaHR based on FDA analysis results in the AP-CML cohort are as follows: Among 43 MaHR patients, 21 patients (48.8%) had events. The median duration of MaHR was 9.5 months based on FDA analysis.

For duration of MaHR in the BP-CML/Ph+ ALL cohorts, among 32 MaHR patients, 17 patients (53.1%) had events (7 from R/I and 10 from T315I) and the median duration of MaHR was 4.7 months (NA for R/I and 4.1 months for T315I).

- Among 19 MaHR patients in the BP-CML cohort, 7 patients (36.8%) had events and the median duration of MaHR was not reached (4.1 months in T315I). Among 13 MaHR patients in the Ph+ ALL cohort, 10 patients (76.9%) had events and the median duration of MaHR was 4.3 months (6.4 months in R/I and 3.8 months in T315I).

The duration of MaHR based on FDA analysis results in the BP-CML/Ph+ ALL cohorts are as follows: Among 32 MaHR patients, 21 patients (65.5%) had events. The median duration of MaHR was 3.5 months based on FDA analysis.

- Among 19 MaHR patients in the BP-CML cohort, 9 patients (47.4%) had events. The median duration of MaHR was 4.7 months based on FDA analysis.
- Among 13 MaHR patients, 12 patients (92.3%) had events. The duration of MaHR was 3.2 months based on FDA analysis.

There were 44 events (16.5%), 34 events from the R/I cohort and 10 events from the T315I cohort among 267 CP-CML patients including treatment discontinuation due to PD according to the investigator. The median PFS in the CP-CML cohort was not reached

There were 33 events (39.8%), 27 events from the R/I cohort and 6 events from the T315I cohort among 83 AP-CML patients including treatment discontinuation due to PD according to the investigator. The median PFS in the AP-CML cohort was 18.4 months.

There were 67 events (71.3%), 31 events from the R/I cohort and 36 events from the T315I cohort among 94 BP-CML/Ph+ ALL patients including treatment discontinuation due to PD according to the investigator. The median PFS in the BP-CML/Ph+ ALL cohorts was 3.7 months.

- For the BP-CML cohort, there were 42 events (67.7 %), 22 events from the R/I cohort and 20 events from the T315I cohort among 62 BP-CML patients including treatment discontinuation due to PD according to the investigator. The median PFS was 3.9 months. For the Ph+ ALL cohort, there were 25 events (78.1 %), 9 events from the R/I cohort and 16 events from the T315I cohort among 32 Ph+ ALL patients treatment discontinuation due to PD according to the investigator. The median PFS was 3.2 months.

For overall survival in the CP-CML cohort, there were 17 deaths (6.4%), 12 deaths from the R/I cohort and 5 deaths from the T315I cohort among 267 CP-CML cohort patients. The median OS for the CP-CML was not reached.

For overall survival in the AP-CML, there were 12 deaths (14.5%), 8 deaths from the R/I cohort and 4 deaths from the T315I cohort among 83 AP-CML cohort patients and the median OS in the AP-CML cohort was not reached.

For overall survival in the BP-CML/Ph+ ALL cohorts, there were 60 deaths (63.8%), 31 deaths from the R/I cohort and 29 deaths from the T315I cohort among 94 BP-CML/Ph+ ALL cohorts' patients. The median OS was 6.9 months (6.9 months in R/I and 6.6 months in T315I).

- For the BP-CML cohort, there were 43 deaths, 26 deaths from the R/I and 17 deaths from T315I. The median OS in the BP-CML cohort was 6.9 months (6.1 months in R/I and 6.9 months in T315I). For the Ph+ ALL cohort, there were 17 deaths, 5 deaths from the R/I and 12 deaths from T315I. The median OS in the Ph+ ALL cohort was 9 months (NA in R/I and 6.5 months in T315I).

3.3 Evaluation of Safety

For a detailed summary of the evaluation of safety refer to the review by Dr. Angelo De Claro.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The study was designed to address a question about the effects in the entire population, not to address questions about subgroups. These subgroup analyses should be considered with caution.

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses for gender, race, age groups (<65 years versus ≥ 65 years) and graphic regions of the primary endpoint of MCyR in the CP-CML and MaHR in the AP-CML and BP-CML/Ph+ ALL cohorts are summarized in Tables below.

Table 35: Subgroup Analyses of MCyR for Age, Gender, Race and Geographic Region: CP-CML: Treated Population

CP-CML	R/I (N=203)		T315I (N=64)		Total (N=267)	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
Age						
< 65	70/121 (57.9)	48.5, 66.8	36/46 (78.3)	63.6, 89.1	106/167 (63.5)	55.7, 70.8
≥ 65	29/82 (35.4)	25.1, 46.7	9/18 (50.0)	26.0, 74.0	38/100 (38.0)	28.5, 48.3
Sex						
Female	48/108 (44.4)	34.9, 54.3	13/16 (81.2)	54.4, 96.0	61/124 (49.2)	40.1, 58.3
Male	51/95 (53.7)	43.2, 64.0	32/48 (66.7)	51.6, 79.6	83/143 (58.0)	49.5, 66.2
Race						
White	82/174 (47.1)	39.5, 54.8	27/42 (64.3)	48.0, 78.5	109/216 (50.5)	43.6, 57.3
Non-White	17/29 (58.6)	38.9, 76.5	18/22 (81.8)	59.7, 94.8	35/51 (68.6)	54.1, 80.9
Geographic Region						
US	46/81 (56.8)	45,3, 67.8	17/25 (68.0)	46.5, 85.1	63/106 (59.4)	49.5, 68.9
Non-US	53/122 (43.4)	34.5, 52.7	28/39 (71.8)	55.1, 85.0	81/161 (50.3)	42.3, 58.3

Age <65 years old, Male, Non-White or US patients demonstrated better MCyR responses in the CP-CML cohort.

Table 36: Subgroup Analyses of MaHR for Age, Gender, Race and Geographic Region: AP-CML: Treated Population

AP- CML	R/I (N=65)		T315I (N=18)		Total (N=83)	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
Age						
< 65	27/44 (61.4)	45.5, 75.6	7/13 (53.9)	25.1, 80.8	34/57 (59.7)	45.8, 72.4
≥ 65	12/21 (57.1)	34.0, 78.2	2/5 (40.0)	5.3, 85.3	14/26 (53.9)	33.4, 73.4
Sex						
Female	26/40 (65.0)	48.3, 79.4	4/7 (57.1)	18.4, 90.1	30/47 (63.8)	48.5, 77.3
Male	13/25 (52.0)	31.3, 72.2	5/11 (45.5)	16.8, 76.6	18/36 (50.0)	32.9, 67.1
Race						
White	27/47 (57.5)	42.2, 71.7	4/9 (44.4)	13.7, 78.8	31/56 (55.4)	41.5, 68.7
Non-White	12/18 (66.7)	40.9, 86.7	5/9 (55.6)	21.2, 86.3	17/27 (63.0)	42.4, 80.6
Geographic Region						
US	15/30 (50.0)	31.3, 68.7	3/7 (42.9)	9.9, 81.6	18/37 (48.7)	31.9, 65.6
Non-US	24/35 (68.6)	50.7, 83.2	6/11 (54.6)	23.4, 83.3	30/46 (65.2)	49.8, 78.7

Age <65 years old, Female, Non-White, or Non-US patients demonstrated better MaHR responses in the AP-CML cohort.

Reviewer's comment: Subgroup results based on FDA analysis (excluding 5 MaHR responders after FDA adjudication) are summarized in Table 37.

Table 37: Subgroup Analyses of MaHR for Age, Gender, Race and Geographic Region: AP-CML by FDA Analysis: Treated Population

AP- CML	R/I (N=65)		T315I (N=18)		Total (N=83)	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
Age						
< 65	24/44 (54.6)	38.9, 69.6	5/13 (38.5)	13.9, 68.4	29/57 (50.9)	37.3, 64.4
≥ 65	12/21 (57.1)	34.0, 78.2	2/5 (40.0)	5.3, 85.3	14/26 (53.9)	33.4, 73.4
Sex						
Female	24/40 (60.0)	43.3, 75.1	3/7 (42.9)	9.9, 81.6	27/47 (57.5)	42.2, 71.7
Male	12/25 (48.0)	27.8, 68.7	4/11 (36.4)	10.9, 69.2	16/36 (44.4)	27.9, 61.9
Race						
White	25/47 (53.2)	38.1, 67.9	4/9 (44.4)	13.7, 78.8	29/56 (51.8)	38.0, 65.3
Non-White	11/18 (61.1)	40.9, 86.7	3/9 (33.3)	7.5, 70.1	14/27 (51.9)	32.0, 71.3
Geographic Region						
US	15/30 (50.0)	31.3, 68.7	3/7 (42.9)	9.9, 81.6	18/37 (48.7)	31.9, 65.6
Non-US	21/35 (60.0)	42.1, 76.1	4/11 (36.4)	10.9, 69.2	25/46 (54.4)	39.0, 69.1

Table 38: Subgroup Analyses of MaHR for Gender Race and Geographic Region: BP-CML/Ph+ ALL: Treated Population

BP-CML/ Ph+ ALL	R/I (N=48)		T315I (N=46)		Total (N=94)	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
Age						
< 65	13/34 (38.2)	22.2, 56.4	8/33 (24.2)	11.1, 42.3	21/67 (31.3)	20.6, 43.8
≥ 65	4/14 (28.6)	8.4, 58.1	7/13 (53.9)	25.1, 80.8	11/27 (40.7)	22.4, 61.2
Sex						
Female	8/17 (47.1)	23.0, 72.2	7/20 (35.0)	15.4, 59.2	15/22 (40.5)	24.8, 57.9
Male	9/31 (29.0)	14.2, 48.0	8/26 (30.8)	14.3, 51.8	17/57 (29.8)	18.4, 43.4
Race						
White	13/39 (33.3)	19.1, 50.2	12/38 (31.6)	17.5, 48.9	25/77 (32.5)	22.2, 44.1
Non-White	4/9 (44.4)	13.7, 78.8	3/8 (37.5)	8.5, 75.5	7/17 (41.2)	18.4, 67.1
Geographic Region						
US	13/33 (39.4)	22.9, 57.9	7/20 (35.0)	15.4, 59.2	20/53 (48.7)	24.8, 52.1
Non-US	4/15 (26.7)	7.8, 55.1	8/26 (30.8)	14.3, 51.8	12/41 (29.3)	16.1, 45.5

Age ≥ 65 years old, Female, Non-White, or US patients demonstrated better MaHR responses in the BP-CML/Ph+ ALL cohorts.

4.2 Other Special/Subgroup Populations

Other subgroups analyses results for baseline disease characteristics are summarized in Tables 39 through 42.

Table 39: Subgroup Analyses for Disease Characteristics at Baseline: CP-CML: Treated Population

CP-CML	R/I (N=203)		T315I (N=64)		Total (N=267)	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
ECOG						
0	72/139 (51.8)	43.2, 60.4	36/47 (76.6)	62.0, 87.7	108/186 (58.1)	50.6, 65.2
≥ 1	27/64 (42.2)	29.9, 55.2	9/17 (52.9)	27.8, 77.0	36/81 (44.4)	33.4, 55.9
Time since Diagnosis (years)						
<10	67/120 (55.8)	46.5, 65.9	42/55 (76.4)	63.0, 86.8	109/175 (62.3)	54.7, 69.5
≥10	32/83 (38.6)	28.1, 49.0	3/9 (33.3)	7.5, 70.1	35/92 (38.0)	28.1, 48.8
Resistant to TKI						
Yes	80/164 (48.8)	40.9, 56.7	33/50 (66.0)	51.2, 78.8	113/214 (52.8)	45.9, 59.7
Number of Prior TKI						
≤3	40/68 (58.8)	46.2, 70.6	31/38 (81.6)	65.7, 92.3	71/106 (67.0)	57.2, 75.8
>3	59/135 (43.7)	35.2, 52.5	14/26 (53.9)	33.4, 73.4	73/161 (45.3)	37.5, 53.4
BCR-ABL Mutation at Entry						
0	63/136 (46.3)	37.7, 55.1	0		63/136 (46.3)	37.7, 55.1
≥1	36/67 (53.7)	41.1, 66.0	45/64 (70.3)	57.6, 81.1	81/131 (61.8)	52.9, 70.2

The patients with ECOG score 0, time since diagnosis <10 years, or number of prior TKI ≤ 3 demonstrated better MCyR rates in the CP-CML cohort. The patients' BCR-ABL mutation at entry ≥ 1 had better MCyR rate than no mutation in the R/I CP+CML cohort. The patients' BCR-ABL mutation at entry was all ≥ 1 in the T315I CP-CML cohort with MCyR rate of 61.8%.

Table 40: Subgroup Analyses for Disease Characteristics at Baseline: AP-CML: Treated Population

AP-CML	R/I (N=65)		T315I (N=18)		Total (N=83)	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
ECOG						
0	23/33 (69.7)	51.3, 84.4	7/12 (58.3)	27.7, 84.8	30/45 (66.7)	51.1, 80.0
≥ 1	16/32 (50.0)	31.9, 68.1	2/6 (33.3)	4.3, 77.7	18/38 (47.4)	31.0, 64.2
Time since Diagnosis (years)						
<10	25/39 (64.1)	47.2, 78.8	6/13 (46.2)	19.2, 74.9	31/52 (59.6)	45.1, 73.0
≥10	14/26 (53.9)	33.4, 73.4	3/5 (60.0)	14.7, 94.7	17/31 (54.8)	36.0, 72.7

Resistant to TKI						
Yes	34/60 (56.7)	43.2, 69.4	7/14 (66.0)	23.0, 77.0	41/74 (55.4)	43.4, 67.0
Number of Prior TKI						
≤3	15/23 (65.2)	42.7, 83.6	4/9 (44.4)	13.7, 78.8	19/32 (59.4)	40.6, 76.3
>3	24/42 (57.1)	41.0, 72.3	5/9 (55.6)	21.2, 86.3	29/51 (56.9)	42.3, 70.7
BCR-ABL Mutation at Entry						
0	22/39 (56.4)	39.6, 72.2	0		22/39 (56.4)	39.6, 72.2
≥1	17/26 (65.4)	44.3, 82.8	9/18 (50)	26.0, 74.0	26/44 (59.1)	43.3, 73.7

The patients with ECOG score 0, time since diagnosis <10 years demonstrated better MaHR rates in the AP-CML cohort. The patients' BCR-ABL mutation at entry ≥ 1 had better MaHR rates than no mutation in the R/I AP-CML cohort. The patients' BCR-ABL mutation at entry was all ≥ 1 in the T315I AP-CML cohort with MaHR rate of 59.1%.

Reviewer's comment: Subgroup results based on FDA MaHR after deleting 5 MaHR responders by clinical reviewer's adjudication are summarized in Table 41.

Table 41: Subgroup Analyses for Disease Characteristics at Baseline: AP-CML by FDA Analysis: Treated Population

AP-CML	R/I (N=65)		T315I (N=18)		Total (N=83)	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
ECOG						
0	21/33 (63.6)	45.1, 79.6	6/12 (50.0)	21.1, 78.9	27/45 (60.0)	44.3, 74.3
≥ 1	15/32 (46.9)	29.1, 65.3	1/6 (16.7)	0.4, 64.1	16/38 (42.1)	26.3, 59.2
Time since Diagnosis (years)						
<10	23/39 (59.0)	42.1, 74.4	4/13 (46.2)	9.1, 61.4	27/52 (51.9)	37.6, 66.0
≥10	13/26 (50.0)	29.9, 70.1	3/5 (60.0)	14.7, 94.7	16/31 (51.6)	33.1, 69.9
Resistant to TKI						
Yes	32/60 (53.3)	40.0, 66.3	5/14 (35.7)	12.8, 64.9	37/74 (50.0)	38.1, 61.9
Number of Prior TKI						
≤3	15/23 (65.2)	42.7, 83.6	4/9 (44.4)	13.7, 78.8	19/32 (59.4)	40.6, 76.3
>3	21/42 (50.0)	34.2, 65.8	3/9 (33.3)	7.5, 70.1	24/51 (47.1)	32.9, 61.5
BCR-ABL Mutation at Entry						
0	21/39 (53.9)	37.2, 69.9	0		21/39 (53.9)	37.2, 69.9
≥1	15/26 (57.7)	36.9, 76.7	7/18 (38.9)	17.3, 64.3	22/44 (50.0)	34.6, 65.4

The other subgroup results were similar to the sponsor's results.

Table 42: Subgroup Analyses for Disease Characteristics at Baseline: BP-CML/Ph+ ALL: Treated Population

BP-CML/ Ph+ ALL	R/I (N=48)		T315I (N=46)		Total (N=94)	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
ECOG						
0	7/15 (46.7)	21.3, 73.4	6/16 (37.5)	15.2, 64.6	13/31 (41.9)	24.6, 60.9
≥ 1	10/33 (30.3)	15.6, 48.7	9/30 (30.0)	14.7, 49.4	19/63 (30.2)	19.2, 43.0
Time since Diagnosis (years)						
<10	14/38 (36.8)	21.8, 54.0	13/42 (31.0)	17.6, 47.1	27/80 (33.8)	23.6, 45.2
≥10	3/10 (30.0)	6.7, 65.3	2/4 (50.0)	6.8, 93.2	5/14 (35.7)	12.8, 64.9
Resistant to TKI						
Yes	16/46 (34.8)	21.4, 50.3	13/40 (32.5)	18.6, 49.1	29/86 (33.7)	23.9, 44.7
Number of Prior TKI						
≤3	8/15 (53.3)	26.6, 78.7	10/29 (34.5)	17.9, 54.3	18/44 (40.9)	26.3, 56.8
>3	9/33 (27.3)	13.3, 45.5	5/17 (29.4)	10.3, 56.0	14/50 (28.0)	16.2, 42.5
BCR-ABL Mutation at Entry						
0	5/20 (25.0)	8.7, 49.1	0		5/20 (25.0)	8.7, 49.1
≥1	12/28 (42.9)	24.5, 62.8	15/46 (32.6)	19.5, 48.0	27/74 (36.5)	25.6, 48.5

The patients with ECOG score 0 or number of prior TKI ≤3 demonstrated better MaHR rates in the BP-CML/Ph+ ALL cohorts. The patients' BCR-ABL mutation at entry ≥ 1 had better MaHR rate than no mutation in the R/I BP-CML/Ph+ ALL cohorts. The patients' BCR-ABL mutation at entry was all ≥ 1 in the T315I BP-CML/Ph+ ALL cohorts with MaHR rate of 36.5%.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The planned sample size of Cohort AP-CML T315I was 40 patients based on 0.1 for the null MaHR rate and 0.3 for the alternative MaHR rate with the power of 89% at an alpha of 0.05, but only 18 patients were used for analyses. Enrolling fewer patients into cohort AP-CML T315I than originally planned reduced the power/sensitivity to rule out a MaHR rate of 10%. However, the observed response rate in this cohort (and in the other cohorts) was much greater than the assumed response rate that was used to plan the sample size for the cohort. The 95% confidence interval for the MaHR rate in the AP-CML T315I cohort was (26%, 74%) easily ruling out a MaHR rate of 10%. Additionally, it should be noted that had the T315I cohort been fully enrolled to 40 patients without having any additional patients achieving a MaHR, the 95%

confidence interval for MaHR rate would have been (11%, 38%) and thus, a 10% MaHR rate would have still been ruled out.

The planned sample size of R/I in the CP-CML cohort was 100 based on null MCyR rate of 20% in the Cohort A (R/I CP-CML) and 35% of alternative MCyR rate in the Cohort A with 85% power at an alpha of 0.05, but 203 patients were used for analyses. As enrolment into the T315I cohort was still ongoing when enrolment into the R/I cohort had reached its planned sample size of 100, the sponsor continued enrolment into the R/I cohort. An additional analysis of MCyR was performed by the applicant based on the first 100 patients enrolled into the R/I cohort. The first 100 enrolled R/I CP-CML patients in the sensitivity analysis would have, on average, longer follow-up and would have had more time to achieve response. Recall that the data cutoff date was less than two months after the last patient was enrolled. The MCyR rate was 48.0% in the R/I CP-CML cohort based on the first 100 enrolled in the CP-CML R/I cohort. An analysis based on the planned sample size in an open-label setting can help verify the integrity of the results.

The follow-up of the study is still ongoing.

5.2 Collective Evidence

- The primary endpoint of MCyR rate in the CP-CML patients and MaHR rate in the AP-CML (including FDA analysis) and BP-CML/Ph+ ALL cohorts were above the pre-specified rates.

- The planned sample size of R/I in the CP-CML cohort was 100 based on null MCyR rate of 20% for Cohort A (R/I CP-CML) and 35% of alternative MCyR rate in the Cohort A with 85% power at an alpha of 0.05, but 203 patients were used for analyses. The sensitivity analysis was performed on the original planned sample size, the first 100 CP-CML R/I patients and the MCyR rate was 48.0% in the R/I CP-CML cohort. The first 100 enrolled R/I CP-CML patients would have, on average, longer follow-up and would have had more time to achieve response. Recall that the data cutoff date was less than two months after the last patient was enrolled. An analysis based on the planned sample size in an open-label setting can help verify the integrity of the results

- For the sensitivity analysis of MaHR based on planned sample sizes for the first 40 BP-CML/Ph+ALL R/I patients and the first 40 BP-CML/Ph+ALL T315I patients enrolled into the trial, the MaHR rate was 60% in the R/I AP-CML cohort, 40% in the R/I BP-CML/Ph+ALL cohorts and 30% in the T315I BP-CML/Ph+ALL cohorts. An analysis based on the planned sample size in an open-label setting can help verify the integrity of the results. The first 40 enrolled into the cohort patients would have, on average, longer follow-up and would have had more time to achieve response. The sensitivity analysis results for 6 cohorts based on per-protocol populations were similar to the primary analysis results. In addition, the sensitivity analyses results based on per-protocol populations for 6 cohorts were similar to the primary analyses results.

- For duration of MCyR in the CP-CML cohort, among 144 MCyR patients, 6 patients (4.2%) had events (5 from R/I and 1 form T315I). The median duration of MCyR was not reached for the entire CP-CML cohort. For duration of MaHR, among 48 MaHR patients in the AP-CML cohort, 22 patients (45.8%) had events (17 from R/I and 5 from T315I) and the median duration of MaHR in the AP-CML cohort was 9.5 months (9.5 months for R/I and 5.7 months for T315I). Among 32 MaHR patients in the BP-CML/Ph+ ALL cohorts, 17 patients (53.1%) had events (7 from R/I and 10 from T315I) and the median duration of MaHR in the BP-CML/Ph+ ALL cohorts was 4.7 months (NA for R/I and 4.1 months for T315I).

- The duration of MaHR based on FDA analysis results, among 43 MaHR patients, 21 patients (48.8%) had events in the AP-CML cohort. The median duration of MaHR was 9.5 months based on FDA analysis in the AP-CML cohort. Among 32 MaHR patients, 21 patients (65.6%) had events in the BP-CML/Ph+ ALL cohorts. The median duration of MaHR was 3.5 months based on FDA analysis in the BP-CML/Ph+ ALL cohorts.
  - Among 19 MaHR patients in the BP-CML cohort, 9 patients (47.4%) had events. The median duration of MaHR was 4.7 months based on FDA analysis.
  - Among 13 MaHR patients, 12 patients (92.3%) had events. The duration of MaHR was 3.2 months based on FDA analysis.

- As this is a single arm study without the control group, it is impossible to assess the treatment effect. Caution should be taken when interpreting the results of PFS and overall survival analyses. There were 44 events (16.5%), 34 events from the R/I cohort and 10 events from the T315I cohort among 267 CP-CML patients including treatment discontinuation due to PD according to the investigator. The median PFS in the CP-CML cohort was not reached. There were 33 events (39.8%), 27 events from the R/I cohort and 6 events from the T315I cohort among 83 AP-CML patients including treatment discontinuation due to PD according to the investigator. The median PFS in the AP-CML cohort was 18.4 months. There were 67 events (71.3%), 31 events from the R/I cohort and 36 events from the T315I cohort among 94 BP-CML/Ph+ ALL patients including treatment discontinuation due to PD according to the investigator. The median PFS in the BP-CML/Ph+ ALL cohorts was 3.7 months.

- For overall survival in the CP-CML cohort, there were 17 deaths (6.4%), 12 deaths from the R/I cohort and 5 deaths from the T315I cohort among 267 CP-CML patients. The median OS for CP-CML was not reached. There were 12 deaths (14.5%), 8 deaths from the R/I cohort and 4 deaths from the T315I cohort among 83 AP-CML patients and the median OS for AP-CML was not reached. There were 60 deaths (63.8%), 31 deaths from the R/I cohort and 29 deaths from the T315I cohort among 94 BP-CML/Ph+ ALL patients. The median OS for BP-CML/Ph+ ALL was 6.9 months (6.9 months in R/I and 6.6 months in T315I).

5.3 Conclusions and Recommendations

For R/I CP-CML, the study met its objective in ruling out MCyR rates of 20% and 10%, respectively for the R/I and T315I cohorts. For R/I AP-CML disease, the study met its objective in ruling out MaHR rates of 10% for all cohorts. Given the applicant's analyses (See Table 7) and

the additional analyses performed by this reviewer (See Tables 9 and 13), I conclude that the drug has shown activity in all the studied cohorts.

5.4 Labeling Recommendations

Based on FDA adjudication, 5 patients who had for MaHR, the primary endpoint in the AP-CML cohort were not responders. The primary endpoint results for the AP-CML cohort have changed to the FDA analysis results. (b) (4)

There were major safety issues. Warnings and precautions section were revised to provide more granular data regarding clinical course for pancreatitis and lipase elevation. Dose modification criteria were modified to reflect actual practice observed in the clinical trial.

References:

Garg RJ, Kantarjian H, O'Brien S, Quintas-Cardama A, Faderl S, Estrov Z, et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. Blood. 2009 Nov 12;114(20):4361-8.

Giles FJ, le Coutre P, Bhalia KN, Ossenkoppele G, Alimena G, Haque A, et al. Nilotinib therapy after dasatinib failure in patients with imatinib-resistant chronic myeloid leukemia (CML) in chronic phase (CP), accelerated phase (AP) or blast crisis (BC). Blood. 2007;110(11):Abstract 1029.

Quintas-Cardama A, Kantarjian H, Jones D, Nicaise C, O'Brien S, Giles F, et al. Dasatinib (BMS-354825) is active in Philadelphia chromosome-positive chronic myelogenous leukemia after imatinib and nilotinib (AMN107) therapy failure. Blood. 2007 Jan 15;109(2):497-9.

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/s/

KYUNG Y LEE
11/16/2012

MARK D ROTHMANN
11/16/2012
I concur

THOMAS E GWISE
11/17/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203469 **Applicant:** **Stamp Date: 8/29/2012**

ARIAD Pharmaceuticals Inc.

Drug Name: **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

File name: 5_Statistics Filing Checklist for a NDA022291

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Kyung Yul Lee, Ph.D.

Reviewing Statistician Date

Mark Rothmann, Ph.D.

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a NDA022291

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/s/

KYUNG Y LEE
11/14/2012

MARK D ROTHMANN
11/14/2012