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Phase 2 Study of Bosutinib in Japanese Patients With Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia

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BACKGROUND

- Bosutinib, a Src/Abl tyrosine kinase inhibitor, is approved at a starting dose of 500 mg once daily (QD) in many countries, including Japan, for patients with Philadelphia chromosome–positive (Ph+) chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) after prior therapy.[1-3]
- The indication for bosutinib was expanded to patients with newly diagnosed CP CML, at a starting dose of 400 mg QD, in 2017 by the US Food and Drug Administration[1] and in 2018 by the European Medicines Agency.[2]
- Approval of first-line bosutinib for CP CML was based on data from the global phase 3 BFORE trial, which demonstrated a significantly higher major molecular response (MMR) rate at Month 12 with bosutinib vs imatinib in patients with Ph+ CP CML and e13a2/e14a2 transcripts (primary endpoint; 47.2% vs 36.9%; 2-sided *P*=0.02).[4]
- Although the efficacy and safety of first-line bosutinib has been established in a global population, regional populations have not been fully investigated.

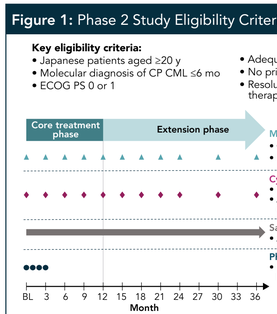
OBJECTIVES

- To evaluate the efficacy, safety, and pharmacokinetics (PK) of bosutinib in Japanese patients with newly diagnosed CP CML in a phase 2 study.

METHODS

- This is an ongoing, open-label, single-arm, phase 2 study (NCT03128411).
- Key eligibility criteria and assessments are shown in **Figure 1**.

Figure 1: Phase 2 Study Eligibility Criteria and Assessments



* Hydoxyurea (hydroxycarbamide) within 6 months was permitted.
† AEs of special interest analyzed by selecting MedDRA higher-level group terms, preferred terms, and standardized MedDRA queries to generate TEAE clusters.
AE=adverse event; BL=baseline; CCyR=complete cytogenetic response (0 Ph+ of ≥20 metaphases or MMR); CP CML=chronic phase chronic myeloid leukemia; ECOG PS=Eastern Cooperative Oncology Group performance status; IS=international scale; MMR=major molecular response (≤0.1% *BCR-ABL* on IS); MedDRA=Medical Dictionary for Regulatory Activities; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03; Ph+=Philadelphia chromosome–positive; RT-PCR=reverse transcription polymerase chain reaction; TEAE=treatment-emergent adverse event

- Patients received bosutinib at a starting dose of 400 mg QD.
  - The dose was allowed to be escalated to a maximum of 600 mg QD in patients with unsatisfactory response.
  - The bosutinib dose was allowed to be interrupted or reduced to 300 mg QD and further to a minimum of 200 mg QD (with approval by the study sponsor) to manage toxicities.
- Bosutinib treatment was to continue for ~3 years after registration of the last patient (core treatment phase and the subsequent ≥24-month extension phase) or until end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.
- The data cutoff date for these analyses was March 12, 2019, after ≥12 months of follow-up of the last enrolled patient.
- Primary endpoint was MMR at Month 12 in the modified as-treated population, which included patients who were Ph+ and had e13a2/e14a2 transcripts.
  - 60 patients were required in the modified as-treated population for the study to have >82% power to reject the null hypothesis (25% MMR rate at Month 12) and accept the alternative hypothesis (40% MMR rate at Month 12) with a 1-sided α-level of 5%.
- Secondary endpoints included MMR and complete cytogenetic response (CCyR) by Month 12, event-free survival (EFS), overall survival (OS), safety, and PK.
- Exploratory endpoints included MMR at Months 3, 6, and 9; MR[4] and MR[4.5] at Months 3, 6, 9, and 12; MR[1] at Month 3; and MR[2] at Month 6.

RESULTS

Patients and Treatment

- In all, 60 Japanese patients with CP CML were treated with bosutinib (**Table 1**).
  - All patients were Ph+ and had e13a2/e14a2 transcripts and were included in the modified as-treated population analyzed for efficacy.

Table 1: Patient Demographics and Clinical Characteristics

	Bosutinib (N=60)
Age, median (range), years	55 (20–83)
Age group, n (%)	
<65 years	41 (68.3)
≥65 years	19 (31.7)
Sex, n (%)	
Male	36 (60.0)
Female	24 (40.0)
Weight, median (range), kg	59.8 (34.5–102.6)
Body mass index, median (range), kg/m^2	23.0 (15.6–36.3)
Time from CML diagnosis, median (range), days	15 (1–153)
Prior CML therapy,* n (%)	28 (46.7)
Sokal risk group, n (%)	
Low	27 (45.0)
Intermediate	26 (43.3)
High	7 (11.7)
ECOG PS, n (%)	
0	58 (96.7)
1	2 (3.3)

* Hydroxyurea (hydroxycarbamide) within 6 months.
CML=chronic myeloid leukemia; ECOG PS=Eastern Cooperative Oncology Group performance status

- At the data cutoff date, 41 (68.3%) patients remained on bosutinib (**Table 2**).
  - The most common adverse events (AEs) leading to bosutinib discontinuation were increased alanine aminotransferase (ALT; n=6) and increased aspartate aminotransferase (AST; n=5).
- 33 (55.0%) patients had ≥1 bosutinib dose reduction to manage AEs, most commonly increased ALT (n=13) and increased AST (n=8).

Table 2: Treatment Summary

	Bosutinib (N=60)
Duration of follow-up, median (range), months	16.6 (11.1–21.9)
Duration of treatment, median (range), months	15.3 (0.3–21.9)
Completed 12 months of treatment,* n (%)	42 (70.0)
Discontinued treatment within 12 months,* n (%)	18 (30.0)
Discontinued treatment, n (%)	19 (31.7)
Due to AEs	18 (30.0)
Physician's decision	1 (1.7)
Dose reduction due to AEs, n (%)	
400 mg QD to 300 mg QD	33 (55.0)
300 mg QD to 200 mg QD	8 (13.3)
Dose interruption due to AEs, n (%)	46 (76.7)
Dose escalation due to insufficient response, n (%)	
400 mg QD to 500 mg QD	6 (10.0)
500 mg QD to 600 mg QD	1 (1.7)
Dose intensity, median (range), mg/day	354.7 (95.3–494.1)

* Core treatment phase.
AE=adverse event; QD=once daily

Efficacy

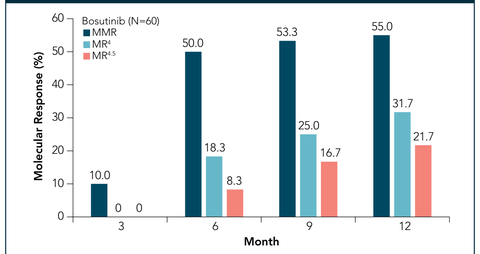
- The MMR rate at Month 12 was 55.0% (2-sided 90% CI: 44.4–65.6); the test of the null hypothesis was rejected (1-sided *P*<0.0001).
- Secondary and exploratory endpoints are shown in **Table 3** and **Figure 2**.
  - Deep molecular responses were attained starting at Month 6.
- The cumulative incidence of EFS events at Month 12 was 1.7% (90% CI: 0.2–6.4) although data for on-treatment EFS were not mature as of the data cutoff date.
- There were no on-treatment transformations to AP or BP CML.
- No patient died on treatment or within 28 days of the last dose of bosutinib.

Table 3: Efficacy Summary

% (90% CI)	Bosutinib (N=60)
Primary endpoint	
MMR at Month 12	55.0 (44.4–65.6)
Secondary endpoints	
MMR by Month 12	61.7 (51.3–72.0)
CCyR by Month 12	80.0 (71.5–88.5)
Exploratory endpoints	
MR[1] at Month 3	80.0 (71.5–88.5)
MR[2] at Month 6	66.7 (56.7–76.7)

CCyR=complete cytogenetic response (0 Philadelphia-positive chromosomes of ≥20 metaphases or MMR); IS=international scale; MMR=major molecular response (≤0.1% *BCR-ABL* on IS); MR[1]=molecular response 1 (≤10% *BCR-ABL* on IS); MR[2]=molecular response 2 (≤1% *BCR-ABL* on IS)

Figure 2: Molecular Response Rates at Months 3, 6, 9, and 12

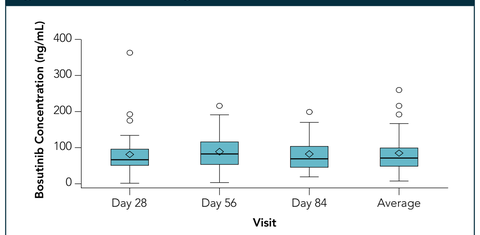


IS=international scale; MMR=major molecular response (≤0.1% *BCR-ABL* on IS); MR[4]=molecular response 4 (≤0.01% *BCR-ABL* on IS); MR[4.5]=molecular response 4.5 (≤0.0032% *BCR-ABL* on IS)

Pharmacokinetics

- The mean ± standard deviation of bosutinib concentration averaged over Days 28, 56, and 84 was 82.7 ± 48.0 ng/mL (**Figure 3**).

Figure 3: Box Plot of Trough Bosutinib Plasma Concentrations



Box plot bounds represent 25% and 75% quartiles; inside the box, solid line represents median, and diamond represents mean; circles represent outliers and whiskers to the last points within 1.5 times the interquartile range.
SD=standard deviation

Safety

- The most common treatment-emergent AEs (TEAEs) were diarrhea, increased ALT, and increased AST (**Table 4**).
  - Median (range) time to first event of diarrhea, increased ALT, and increased AST, respectively, was 1 (1–271), 15 (1–169), and 15 (1–57) days.
- Grade 3/4 TEAEs reported in ≥10% of patients were increased ALT (33.3%), increased AST (18.3%), diarrhea (15.0%), increased lipase (15.0%), lymphopenia (13.3%), and neutropenia (11.7%).
- When evaluated according to categories of special interest, the most frequently reported TEAEs of any grade were gastrointestinal (86.7%), liver function–related (80.0%), infection (65.0%), rash (55.0%), and myelosuppression (45.0%).
  - The incidence of cardiac, vascular, and hypertension TEAEs was low (5.0%, 1.7%, and 1.7%, respectively).
- The most common laboratory abnormalities, based on laboratory test values, were increased creatinine (95.0%), decreased lymphocyte count (91.7%), increased ALT (85.0%), increased AST (81.7%), and anemia (81.7%).

Table 4: Treatment-Emergent Adverse Events*

	Bosutinib (N=60)	
n (%)	Any Grade	Grade 3/4
Any treatment-emergent AE	60 (100)	45 (75.0)
Gastrointestinal	52 (86.7)	9 (15.0)
Diarrhea	52 (86.7)	9 (15.0)
Nausea	17 (28.3)	0
Vomiting	15 (25.0)	1 (1.7)
Constipation	7 (11.7)	0
Upper abdominal pain	6 (10.0)	0
Liver function	48 (80.0)	29 (48.3)
Increased ALT	33 (55.0)	20 (33.3)
Increased AST	28 (46.7)	11 (18.3)
Increased blood alkaline phosphatase	16 (26.7)	0
Liver disorder	7 (11.7)	5 (8.3)
Hematologic	27 (45.0)	16 (26.7)
Thrombocytopenia†	18 (30.0)	5 (8.3)
Lymphopenia‡	11 (18.3)	8 (13.3)
Neutropenia§	10 (16.7)	7 (11.7)
Anemia‖	10 (16.7)	0
Leukopenia¶	6 (10.0)	2 (3.3)
Infection	39 (65.0)	4 (6.7)
Nasopharyngitis	17 (28.3)	0
Upper respiratory tract infection	6 (10.0)	0
Rash	33 (55.0)	3 (5.0)
Rash	16 (26.7)	1 (1.7)
Maculopapular rash	8 (13.3)	1 (1.7)
Other		
Increased lipase	16 (26.7)	9 (15.0)
Pyrexia	14 (23.3)	1 (1.7)
Increased GGT	11 (18.3)	3 (5.0)
Increased amylase	9 (15.0)	1 (1.7)
Back pain	7 (11.7)	0
Headache	7 (11.7)	0

* Any grade AE reported in ≥10% of patients.
† Clustered terms were thrombocytopenia and platelet count decreased.
‡ Clustered terms were lymphopenia and lymphocyte count decreased.
§ Clustered terms were neutropenia and neutrophil count decreased.
‖ Clustered terms were anemia and hemoglobin decreased.
¶ Clustered terms were leukopenia and white blood cell count decreased.
AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase

CONCLUSIONS

- The primary objective of this phase 2 study was met, and the MMR rate at Month 12 in Japanese patients with newly diagnosed CP CML was similar to that reported in the bosutinib arm of the multinational BFORE trial (55.0% vs 47.2%).[4]
  - Other efficacy endpoints were also comparable or more favorable in this phase 2 study vs the bosutinib arm of BFORE,[4] eg, rates of MR[4] (31.7% vs 20.7%) and MR[4.5] (21.7% vs 8.1%) at Month 12.
- The safety profile of bosutinib was consistent with that reported in an earlier study of previously treated Japanese patients with CP CML[5] as well as global populations of previously treated or newly diagnosed patients with CP CML.[4,6-8]
- The average bosutinib plasma trough concentration in this study was ~1.12-fold higher than that observed in bosutinib-treated patients in the global BFORE trial (Pfizer, data on file).
  - A population PK model based on a combined dataset that includes this study is being conducted.
- These data suggest bosutinib is an effective first-line treatment option for Japanese patients with newly diagnosed CP CML.

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DISCLOSURES

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ABSTRACT PLAIN LANGUAGE SUMMARY

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