CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc

Investigational Product: Bosutinib

Clinical Study Report Synopsis: Protocol B1871040

Protocol Title: An Open-Label Bosutinib Treatment Extension Study for Subjects With Chronic Myeloid Leukemia (CML) who Have Previously Participated in Bosutinib Studies B1871006 or B1871008

Investigators: Appendix 16.1.4.1 has a list of investigators involved in this study.

Study Center(s): 85 sites 30 countries participated in this study. Appendix 16.1.4.1 has a list of sites involved in this study.

Publications Based on the Study: A list of publications is provided in Appendix 16.1.11.

Study Initiation Date: 28 Aug 2013 (First Subject First Visit)

Study Completion Date: 05 Jun 2020

Report Date: 27 May 2021

Previous Report Date(s): 29 Mar 2021

Phase of Development: NA

Primary and Secondary Study Objectives and Endpoints:

Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint
	To allow long-term bosutinib treatment in patients with chronic or advanced phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) and Ph+ acute lymphoblastic leukemia (ALL)[a] who received bosutinib in a previous Pfizer sponsored study (ie, studies B1871006 and B1871008) and who had the potential, as judged by the investigator, to derive clinical benefit from continued treatment with bosutinib.	

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Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint
Efficacy	• To collect long-term efficacy data for bosutinib. • To assess the duration of clinical benefit for Ph+ CML participants treated with bosutinib.	• Duration of major/complete cytogenetic response (MCyR/CCyR) for B1871006 patients only • Duration of major/deep molecular response (MMR/MR^4) for B1871006 patients only • Duration of complete hematologic response (CHR) for B1871006 patients only • Duration of overall hematologic response (OHR) for B1871006 advanced patients only • Progression-free survival (PFS) for B1871006 patients only • Transformation to accelerated or blast phase for B1871006 patients only • BCR-ABL1 mutations present at treatment discontinuation[b] • Overall Survival (OS)
Safety	• To collect long-term safety data for bosutinib. • To fulfill the European Medicines Agency (EMA) post approval requirement for the collection and analysis of safety data about diarrhea incidence after a switch from clinical study to commercial bosutinib formulation.	• Long-term safety of bosutinib, including type, incidence, severity, timing, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities, as well as reason for treatment discontinuation. • Diarrhoea incidence after switch from clinical study to commercial bosutinib formulation.
PK	• To fulfill the EMA post-approval requirement for the analysis of the pharmacokinetics (PK) of bosutinib administered once daily.	• Compare the trough concentration (C_{trough}) of bosutinib in this study to C_{trough} of previous studies.

a. Both Ph+ CML and Ph+ ALL participants were included in this study.
b. After Protocol Amendment 2, B1871040 participants enrolled in China did not have the centralized BCR-ABL1 kinase domain mutational analysis and pharmacokinetic analysis performed due to the lack of local laboratory resources in China.

Source: Appendix 16.1.1 Protocol Section 2; and Appendix 16.1.9 SAP Section 2.2 and Section 6.

METHODS

Study Design: This was an open-label bosutinib treatment extension protocol which enrolled bosutinib participants who were previously enrolled in one of the two previous bosutinib parent studies: B1871006 or B1871008.

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Diagnosis and Main Criteria for Inclusion: Participants enrolled included those who, at the time of this protocol approval were still receiving bosutinib in either one of the parent studies (B1871006 and B1871008) and were benefiting from bosutinib treatment as judged by the investigator, as well as those participants who had already discontinued bosutinib as part of the parent studies and were in long-term follow-up for survival or had completed the parent study. The former group continued to receive bosutinib as part of the extension study; the latter group only entered into the long-term survival follow-up part of the extension study.

Study Treatment: Participants received the same bosutinib dose administered at the time of completion of the parent study. Dosing was continuous until disease progression, unacceptable toxicity, death, withdrawal of consent, or Sponsor study discontinuation. Central supply or locally obtained commercial supplies of bosutinib were used for this study. Lots used in the study are shown in Table S2.

Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Bosutinib (SKI-606) 100 mg Oval Yellow Film Coated Tablet Commercial Formulation	1109640	11-009651	100 mg	Tablet
Bosutinib (SKI-606) 100 mg Oval Yellow Film Coated Tablet Commercial Formulation	1312057	14-000496	100 mg	Tablet
Bosutinib (SKI-606) 100 mg Oval Yellow Film Coated Tablet Commercial Formulation	1312063	14-000495	100 mg	Tablet
Bosutinib (SKI-606) 100 mg Oval Yellow Film Coated Tablet Commercial Formulation	9850133002	12-005962	100 mg	Tablet

Efficacy Evaluations: Efficacy was determined by physical examination, analysis of peripheral blood and bone marrow. Automated CBC, differential counts, bone marrow differential, molecular analysis for BCR-ABL1 transcripts, cytogenetics, physical examination, and mortality were used to determine the response to treatment.

Bone marrow aspirate or peripheral blood were used for cytogenetics using karyotyping or FISH and were performed locally. Molecular response monitoring using RT-qPCR for BCR-ABL1 copy number was performed on peripheral blood. In the parent study B1871006, molecular assessments were performed at a central laboratory, however the International Scale was not used. In the extension study, molecular assessments were performed locally.

Mutational analysis of BCR-ABL1 transcript was performed by direct sequencing using a peripheral blood sample collected at the end-of-treatment visit for all eligible participants.

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Pharmacokinetic Evaluations: PK evaluations were done using a single predose blood sample following at least 2 weeks of uninterrupted dosing with bosutinib at the same dose level. To fulfill the EMA post-approval requirement for the analysis of the PK of bosutinib administered once daily, trough concentrations (C_{trough}) of bosutinib in this study were compared with C_{trough} of previous studies. Concentrations of bosutinib were to be determined in plasma using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay.

Safety Evaluations: Safety evaluations included adverse events, and abnormalities in physical examinations, vital signs, clinical laboratory tests, electrocardiograms (ECGs) and echocardiogram and/or multiple-gated acquisition (MUGA) scans.

Based on clinical experience with bosutinib and other tyrosine-kinase inhibitors (TKIs), certain categories of adverse events of special interest (AESI) were selected for further analysis. These categories included cardiac, haemorrhage, effusion, oedema, myelosuppression, liver function, infection, rash, hypersensitivity, gastrointestinal, vascular, hypertension, and renal AEs.

Statistical Methods: This study did not include any formal sample size determination. Descriptive summaries and confidence intervals (if applicable) are provided; no inferential analyses are planned for this study.

Data from the 2 parent studies were combined with the data from this study for the analysis of efficacy and safety. The B1871040 data from the 21 participants from China (7 CP1L, 13 CP2L and 1 ADV; see Table S3 footnote) were excluded from the analyses due to inability to obtain timely approval to use data in accordance with the Human Genetic Resources Administration of China (HGRAC) regulations.

The population was analyzed in the following cohorts:

Table S3. Participant Populations from B1871006 and B1871008 used in this Study Analysis

Population	Definition
Chronic Phase CML (CP)	
CP1L (participants from B1871008)	Chronic phase CML 1st line (all participants in B1871008 study). Participants with newly-diagnosed CML.
CP2L (participants from B1871006)	Chronic phase CML 2nd line resistant or intolerant to imatinib (participants in B1871006 study)
CP3L (participants from B1871006)	Chronic phase CML 3rd (CP3L) / 4th (CP4L) line resistant or intolerant to imatinib and resistant or intolerant to dasatinib and/or nilotinib
Accelerated Phase CML (AP)	

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AP (participants from B1871006)	Accelerated phase CML resistant or intolerant to imatinib only (AP2L) or resistant or intolerant to imatinib and at least one additional TKI including dasatinib and/or nilotinib (AP3L/AP4L)
Blast Phase CML (BP)	
BP (participants from B1871006)	Blast phase CML resistant or intolerant to imatinib only (BP2L) or resistant or intolerant to imatinib and at least one additional TKI including dasatinib and/or nilotinib (BP3L/BP4L)
Ph+ ALL	
Ph+ ALL (participants from B1871006)	Ph+ acute lymphoblastic leukemia (ALL) resistant or intolerant to imatinib only or resistant or intolerant to imatinib and at least one additional TKI including dasatinib and/or nilotinib

Source: Appendix 16.1.9, SAP Section 2.1

For the presentation in this report, the following groups are used:

CP 2+ L: participants with previously treated chronic-phase CML, a combination of CP2L and CP3L

2+ L: participants with previously treated Ph+ leukemias, a combination of CP2L, CP3L, and ADV

ADV: participants with advanced leukemias, a combination of AP, BP, and Ph+ ALL

RESULTS

Subject Disposition and Demography: Overall, 820 participants were enrolled in the 2 parent studies, 250 newly diagnosed (CP1L) participants in study B1871008 and 570 previously treated (2+ L) participants in study B1871006 (Table S4). Of these, 248 and 570 were treated in the respective parent studies. A total of 281 participants enrolled in B1871040 in 85 sites in 30 countries. B1871040 data for participants enrolled in China were not included in the efficacy and safety analysis presented in this CSR. Of the remaining 260 participants enrolled in study B1871040, 124 were from parent study B1871008 and 136 were from parent study B1871006. Of the 260, 188 were treated in study B1871040, 98 and 90 in the CP1L and 2+ L cohorts respectively; the remaining 72 were in long-term follow-up for survival only.

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Table S4. Summary of Population Evaluation

	CP1L	CP2L	CP3L	AP	BP	ALL	ADV	Total 2+L	Total
Full Analysis Set[a]	250	284	119	79	64	24	167	570	820
Safety Analysis Set[b]	248	284	119	79	64	24	167	570	818
Screened in B1871040	124	90	28	15	2	1	18	136	260
Enrolled in B1871040[c]	124	90	28	15	2	1	18	136	260
Treated in B1871040	98	69	13	6	1	1	8	90	188
Molecular Population[d], n(%)	NA	197 (69.4)	107 (89.9)	54 (68.4)	48 (75.0)	24 (100.0)	126 (75.4)	430 (75.4)	430 (52.4)
Evaluable Analysis Set[e]									
Cytogenetic, n(%)	-	262 (92.3)	112 (94.1)	72 (91.1)	54 (84.4)	20 (83.3)	146 (87.4)	520 (91.2)	520 (63.4)
Hematologic, n(%)	-	283 (99.6)	117 (98.3)	72 (91.1)	60 (93.8)	22 (91.7)	154 (92.2)	554 (97.2)	554 (67.6)
Pharmacokinetics (PK) Analysis Set in B1871040[f]	75 (30.0)	46 (16.2)	9 (7.6)	4 (5.1)	0	1 (4.2)	5 (3.0)	60 (10.5)	135 (16.5)

Data cut-off date: 02SEP2020(7 CP1L, 13 CP2L and 1 ADV subjects from China were excluded)
Abbreviations: CP1L - Chronic phase first-line, CP2L - Chronic phase second-line, CP3L - Chronic phase third/fourth-line, AP - Accelerated phase, BP - Blast phase, ALL - Acute lymphoblastic Leukemia.
a. The full analysis set is all patients randomized to the bosutinib arm from B1871008(CP1L) and all dosed patients from B1871006(2+L), where 2+L=CP2L+CP3L+ADV and ADV=AP+BP+ALL.
b. The safety analyses set are those subjects who received at least one dose of bosutinib. For B1871006 subjects, this is the same as the full analysis set.
c. Enrolled is defined as having an informed consent date and meeting the inclusion/exclusion criteria required by the protocol.
d. All subjects in the Full Analysis Set are considered for Molecular response except for subjects from sites in China, India, Russia and South Africa since they were not assessed for molecular response.
e. The evaluable analysis set are those dosed subjects from B1871006 with a valid baseline efficacy assessment from B1871006 for the respective endpoint (i.e. [1] at least 20 metaphases or at least 1 Ph+ metaphase from the baseline bone marrow cytogenetic assessment or [2] a valid baseline hematologic assessment
f. The pharmacokinetic (PK) analysis set are those subjects who received at least one dose of bosutinib and have at least one sample of bosutinib concentration.
PFIZER CONFIDENTIAL. Source data: Table 16.2.1.1; Table 14.1.1.1 is for Pfizer internal use.
Report Name: pop4_fas. Date of Reporting Dataset Creation: 16SEP2020. Date of Table Generation: 26JAN2021 (13:14).

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Of the 818 participants treated with bosutinib, 13.2% were still on treatment at study completion after ≥ 10 years; 24.2% of the CP1L and 8.4% of the 2+ L cohort (13.4%, 5.0% and 2.4% in the CP2L, CP3L and ADV cohort, respectively) were still on treatment after ≥ 10 years. In the CP1L, CP2L, CP3L and ADV cohorts, 61.3%, 79.6%, 94.1% and 96.4% of participants, respectively, permanently discontinued bosutinib. The most frequent reasons for permanent treatment discontinuation were lack of efficacy (objective disease progression or relapse and unsatisfactory response) in 27.6% of participants and AEs in 26.9 %. The most frequent reasons for discontinuation differed across cohorts with AEs being the most common reason in newly diagnosed participants (CP1L; 32.3%) and lack of efficacy in pretreated participants (2+ L; 36.8%).

Of the 820 participants enrolled in studies B1871008, B1871006 and B1871040, 166 (20.2%) completed the extension study. Twenty two percent (22%) of CP1L and 32.8% of 2+ L completed the respective parent study but did not enroll in B1871040. The most common reason for study discontinuation was refusal for further follow-up (14.0%) in the CP1L cohort and death in the 2+ L cohort (31.9%).

Of the 820 participants, 45.2% were female and 54.8% were male; median age was 52.0 years. Participants in study B1871008 (CP1L) were younger than participants in study B1871006 (2+ L) with a median age of 49.0 and 53.0 years, respectively, 12.0% and 22.5% were ≥ 65 years in the CP1L and 2+ L cohorts, respectively. Most participants had an ECOG performance status of 0 (68.7%).

Among pretreated participants, all had received prior imatinib. In addition, 77.3% and 26.1%, of the CP3L cohort had prior dasatinib and nilotinib use respectively, and 32.9% and 16.2%, of the ADV cohort had prior dasatinib and nilotinib use, respectively.

Efficacy Results:

Cumulative responses:

Cytogenetic response:
In the CP2L cohort, 59.9% (95%CI: 53.7, 65.9) and 49.6% (95%CI: 43.4, 55.8) of participants attained or maintained MCyR and CCyR, respectively, while receiving bosutinib. Among participants without the respective response at baseline, 55.4% (95%CI: 48.3, 62.3) and 47.2% (95%CI: 40.8, 53.6) attained MCyR and CCyR, respectively.

In the CP3L cohort, 42.0% (95%CI: 32.7, 51.7) and 32.1% (95%CI: 23.6, 41.6), of participants attained or maintained MCyR and CCyR, respectively, while receiving bosutinib. Among participants without the respective response at baseline, 31.8% (95%CI: 22.3, 42.6) and 27.9% (95%CI: 19.5, 37.5) attained MCyR and CCyR, respectively.

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In the ADV cohort, 37.0% (95%CI: 29.2, 45.4) and 28.8% (95%CI: 21.6, 36.8) of participants attained or maintained MCyR and CCyR, respectively, while receiving bosutinib.

Molecular response:
In the CP2L cohort, 42.1% (95%CI: 35.1, 49.4) and 37.1% (95%CI: 30.3, 44.2) of the CP2L cohort attained or maintained MMR and MR^4, respectively, while receiving bosutinib. Among participants without the respective response at baseline, 40.7% (95%CI: 33.7, 48.1) and 35.8% (95%CI: 29.0, 43.0) attained MMR and MR^4, respectively.

In the CP3L cohort, 17.8% (95%CI: 11.0, 26.3) and 15.0% (95%CI: 8.8, 23.1) of the CP3L cohort attained or maintained MMR and MR^4, respectively while receiving bosutinib. Among participants without respective response at baseline 14.7% (95%CI: 8.5, 23.1) and 13.6% (95%CI: 7.6, 21.8) attained MMR and MR^4, respectively.

In the ADV cohort, 11.9% (95%CI: 6.8, 18.9) and 10.3% (95%CI: 5.6, 17.0) attained or maintained MMR and MR^4, respectively, while receiving bosutinib.

Complete Hematologic Response:
86.6% (95%CI: 82.0, 90.3), 73.5% (95%CI: 64.5%, 81.2%), and 23.4%; (95%CI: 16.9, 30.9) of participants in the CP2L, CP3L, and ADV cohorts, respectively, had CHR.

Overall Hematologic Response (Participants with Advanced Disease Only):
39.0%, (95%CI: 31.2, 47.1) of the participants in the ADV cohort had an OHR.

Duration of response:

Cytogenetic Response:
The Kaplan Meier (KM) estimate of maintaining MCyR at year 10 was 65.3% (95%CI: 56.6, 74.0), 55.3% (95%CI: 36.3, 74.4) and 30.6% (95%CI: 16.4, 44.7) in the CP2L, CP3L, and ADV responders, respectively. The median duration of response was not reached in the CP2L and CP3L cohorts and was 34.3 weeks (95%CI: 24.0, 84.0) in the ADV cohort.

The KM estimate of maintaining CCyR at year 10 was 63.4% (95%CI: 54.0, 72.8), 40.8% (95%CI: 22.0, 59.6), and 29.6% (95%CI: 14.6, 44.7) in the CP2L, CP3L, and ADV responders, respectively. The median duration of response was not reached in the CP2L cohort, and was 252.0 (95%CI: 24.0, not estimable) and 36.1 (95%CI: 16.9, 84.0) weeks, respectively, in the CP3L and ADV cohorts.

Molecular Response:
The KM estimate of maintaining MMR at year 10 was 63.4% (95%CI: 50.2, 76.6), 70.0% (95%CI: 47.5, 92.5), and 66.0% (95%CI: 41.7, 90.3) in the CP2L, CP3L, and ADV responders, respectively. The median duration of response was not reached for any of the 3 cohorts.

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The KM estimate of maintaining MR^4 at year 10 was 60.8% (95%CI: 46.1, 75.4) in the CP2L responders. The median duration of response was not reached. There were too few participants with MR^4 in the CP3L and ADV cohorts so the KM analysis was not performed.

Complete Hematologic Response:
The KM estimate of maintaining CHR at year 10 was 44.1% (95%CI: 35.2, 52.9) and 45.1% (95%CI: 29.3, 60.9) in the CP2L and CP3L responders. KM estimates in later years could not be assessed in the ADV cohort as the few participants (8) who enrolled in 1040 and were still on-treatment did not have a BM aspirate performed to assess BM blasts. Median duration of response was 432.6 (95%CI: 380.7, 521.4), 314.6 (95%CI: 289.0, not estimable), and 119.9 (95%CI: 34.9, not estimable) weeks in the CP2L, CP3L and ADV cohorts, respectively.

Overall Hematologic Response:
The KM estimate of maintaining OHR at year 10 was 40.1% (95%CI: 24.7, 55.5) in the ADV responders. Median duration of response was 78.0 weeks (95%CI: 48.3, not estimable).

Transformation to AP or BP CML:

5.3% (95%CI: 3.0, 8.6) and 4.2% (95%CI: 1.4, 9.5) of the participants in the CP2L and CP3L cohorts, respectively, progressed to accelerated or blast phase while on treatment with bosutinib, and 3.8% (95%CI: 0.8, 10.7) of the participants in the AP cohort progressed to blast phase.

PFS:

Cumulative incidence of on-treatment progression/death events at year 10 was 23.9% (95%CI: 19.5, 29.5), 26.9% (95%CI: 20.0, 36.2) and 55.7% (95%CI 48.6, 63.8) in the CP2L, CP3L and ADV cohorts, respectively.

BCR-ABL1 Mutations Present Post-Baseline:

Of the 231, 98 and 129 participants in the CP2L, CP3L, and ADV cohorts who were assessed for mutations at baseline, 174, 74, 68, respectively, had a post-baseline sample; 28, 13, and 14 participants had emergent mutations. Among participants with emergent mutations, the most common mutations across all cohorts (CP2L, CP3L and ADV) were T315I (35.7%, 23.1%, and 42.9%, respectively) and V299L (17.9%, 46.2%, and 35.7%, respectively).

Of the 208 participants in the CP1L cohort with a post-baseline sample, 7 had post-baseline mutations. Among participants with mutations, the most common mutations were T315I (42.9%) and V299L (42.9%).

Overall Survival:

OS at year 10 for the CP2L, CP3L, and ADV cohorts, respectively, was 71.5% (95%CI: 64.4, 78.7), 60.4% (95%CI: 47.2, 73.7), and 34.2% (95%CI: 25.0, 43.3) (Figure S1). In the AP cohort, OS at year 10 was 50.7% (95%CI: 36.5, 65.0). Median OS was not reached for the

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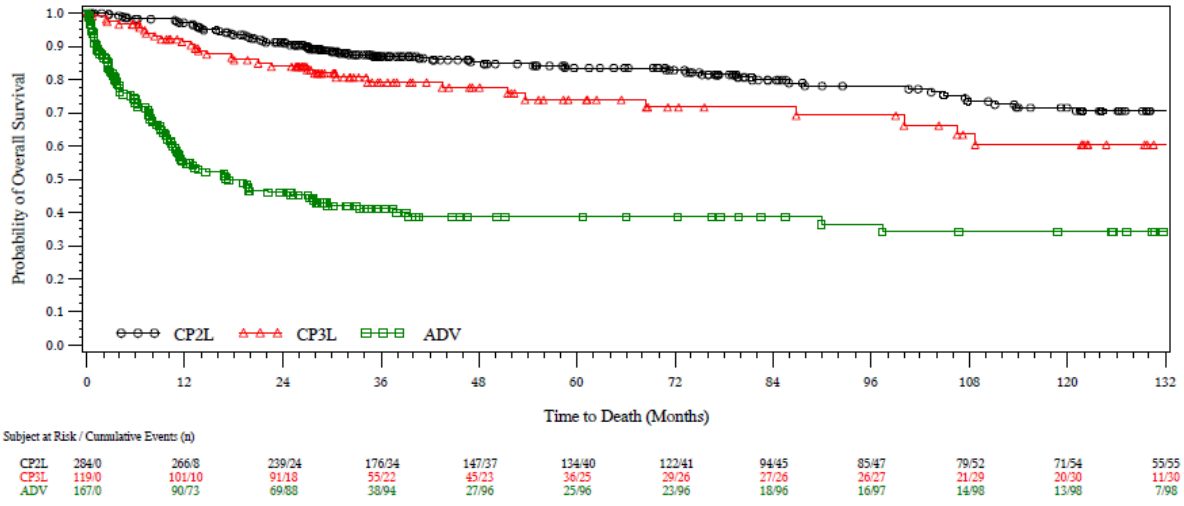
CP2L, CP3L, and AP cohorts, and was 17.4 (95%CI: 11.4, 29.5) months for the overall ADV cohort.

The median (range) duration of follow-up was 53.67 (0.53, 171.55), 34.14 (0.23, 165.16) and 13.72 (0.26, 162.63) months in the CP2L, CP3L, and ADV cohorts, respectively, and was 28.32 (0.26, 158.75) months in the AP cohort.

OS at year 10 for the CP1L cohort was 88.2% (95%CI: 83.3, 93.2). Median OS was not reached. The median (range) duration of follow-up was 73.34 (0.03, 147.83) months.

Figure S1 Kaplan-Meier Estimate of Overall Survival (OS) by CP2L, CP3L, and ADV – Full Analysis Set



Data cut-off date: 02SEP2020 (all subjects from China in study B1871040 were excluded)
PFIZER CONFIDENTIAL. Source data: Table 16.2.6.1. Report Name: FIG6_OS4_FAS_1006. Date of Reporting Dataset Creation: 24SEP2020. Date of Table Generation: 10NOV2020 (16:17).

Figure 14.2.2.4.3 for Pfizer internal use

Pharmacokinetic Results:

Following at least 2 weeks of uninterrupted dosing with bosutinib at the same dose level, the geometric mean steady-state C_{trough} of bosutinib ranged from 62.0 to 99.4 ng/mL for doses ranging from 200 mg to 600 mg. The geometric mean bosutinib C_{trough} values observed in this study were similar to previous studies for doses ranging from 300 mg to 600 mg.

Safety Results:

Exposure:

The overall median duration of treatment (range) was 17.04 (0.03 to 170.49) months. The median duration of treatment was longest in the CP1L cohort with 61.69 (0.03 to 145.86) months followed by the CP2L cohort with 25.59 (0.16 to 170.49) months. CP3L and ADV cohorts had a shorter median duration of treatment with 8.62 (0.23 to 164.28) and 3.95 (0.03

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to 161.51) months, respectively. Overall, the median (range) dose intensity was 448.36 (426.71 to 462.57) mg/day. Dose intensity was similar across cohorts.

Dose delays, reductions and escalations:

68.9% of participants had at least 1 dose delay and 48.3% of participants had at least 1 dose reduction. 13.9% of participants had at least one dose escalation.

Adverse Events:

Long-term safety was evaluated until the last participant reached 10 years of follow up, as calculated from the date of his/her first dose of bosutinib administered in the parent study.

Overall, 98.8% of participants had treatment-emergent AE (TEAEs); most had treatment-related TEAEs (97.4%), 78.5% had Grade 3 or 4 TEAEs, and 45.0% had treatment-emergent serious AE (SAEs) (Table S5).

Table S5. Brief Summary of Adverse Events – Safety Population

	CP1L (N=248) n (%)	CP2L (N=284) n (%)	CP3L (N=119) n (%)	ADV (N=167) n (%)	Total 2+L (N=570) n (%)	Total (N=818) n (%)
Any treatment-emergent adverse event (TEAE)	241 (97.2)	283 (99.6)	119 (100.0)	165 (98.8)	567 (99.5)	808 (98.8)
Grade 3 or 4 TEAEs	191 (77.0)	223 (78.5)	84 (70.6)	144 (86.2)	451 (79.1)	642 (78.5)
Treatment-emergent serious adverse events (SAEs)	102 (41.1)	124 (43.7)	44 (37.0)	98 (58.7)	266 (46.7)	368 (45.0)
Adverse events leading to treatment discontinuation	84 (33.9)	79 (27.8)	37 (31.1)	32 (19.2)	148 (26.0)	232 (28.4)
TEAEs leading to dose reduction	116 (46.8)	149 (52.5)	63 (52.9)	57 (34.1)	269 (47.2)	385 (47.1)
TEAEs leading to temporary stop	186 (75.0)	211 (74.3)	81 (68.1)	85 (50.9)	377 (66.1)	563 (68.8)
TEAEs related to study drug	235 (94.8)	282 (99.3)	119 (100.0)	161 (96.4)	562 (98.6)	797 (97.4)
TEAEs leading to death	9 (3.6)	18 (6.3)	6 (5.0)	32 (19.2)	56 (9.8)	65 (7.9)

Data cut-off date: 02SEP2020 (all subjects from China in study B1871040 were excluded)
Treatment-emergent adverse events (TEAE) were defined as any event increasing in severity from baseline or any new event starting during bosutinib therapy or up until the last date of test treatment + 28 days for B1871008; 30 days for B1871006 and B1871040.
Note: Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA version 23.0).
PFIZER CONFIDENTIAL. Source data: Table 16.2.7.1; Table 14.3.1 is for Pfizer internal use
Report Name: AE4_BSUM_SAFETY. Date of Reporting Dataset Creation: 16SEP2020.Date of Table Generation: 04MAR2021 (08:00).

TEAEs:

The most common TEAEs (occurring in ≥ 20% of participants) were diarrhoea (78.9%), nausea (43.9%), thrombocytopenia (38.9%), vomiting (38.4%), rash (31.9%), anaemia (31.3%), pyrexia (26.5%), alanine aminotransferase (ALT) increased (23.6%), abdominal pain (22.7%), and fatigue (21.6%).

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Grade 3 or 4 TEAEs:
The most common Grade 3 or 4 TEAEs (occurring in ≥ 10% of participants) were thrombocytopenia (24.6%), anaemia (13.9%), neutropenia (12.1%), and ALT increased (10.9%).

SAEs:
The most common treatment-emergent SAEs (occurring in ≥2% of participants) were pneumonia (5.4%), pleural effusion (5.3%), pyrexia (3.5%), diarrhoea (2.7%), and thrombocytopenia (2.4%).

Deaths:
Overall, 206 (25.2%) died during the study. The most common reason for death was disease under study (61.2%). 7.5% of participants died within 30 days of last dose. 3 participants died because of a TEAE considered related to study treatment: 1 participant in the CP3L cohort due to lower gastrointestinal bleeding, 1 participant in the ADV cohort due to acidosis, and 1 participant in the ADV cohort due to myocardial infarction.

Discontinuations due to AEs:
Overall, 28.4% of participants permanently discontinued study treatment because of an AE. The most frequent (occurring in ≥ 2% of participants) AEs leading to permanent discontinuation of study treatment were thrombocytopenia (4.6%), ALT increased (2.8%), and pleural effusion (2.2%). In newly diagnosed participants, the most common reason for discontinuation was ALT increased (4.4%) while in pretreated participants it was thrombocytopenia (5.3%). The majority of participants that discontinued due to AEs did so during the first year on treatment, fewer participants with longer exposure permanently discontinued treatment due to AEs.

Treatment-Emergent AEs of Special Interest (AESIs):
Gastrointestinal AESIs occurred in 85.5% of participants. Diarrhoea, nausea, and vomiting were reported in 78.9%, 43.9%, and 38.4% of participants, respectively. The frequency of gastrointestinal AESIs was lower in the CP1L cohort (77.4%) than in the 2+ L cohort (88.9%). Overall, 83.3% of participants had gastrointestinal AESIs related to study treatment and 3.7% had a gastrointestinal SAE. Of the participants with gastrointestinal AESIs, 15.0% had a history of prior gastrointestinal events.

While diarrhoea occurred frequently (78.9%), it occurred early on-treatment (median time to onset 2.0 days) and was generally short in duration (median duration of any event 2.0 days). Of the participants with diarrhoea AESIs, 19.7% required dose modifications to manage the AEs; 17.8% required dose interruptions and 8.2% required dose reductions. Of those participants with dose interruptions who got rechallenged, 98.2 % were successfully rechallenged. Overall, 0.9 % of participants permanently discontinued treatment due to diarrhoea AESIs. There were no deaths due to diarrhoea AESIs.

Liver function AESIs occurred in 34.0% of participants. The most frequent liver function AESIs (occurring in ≥ 2% of participants) were ALT increased (23.6%), AST increased

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(19.6%), blood alkaline phosphatase increased (5.5%), hyperbilirubinemia (3.1%), and blood bilirubin increased (2.2%). Liver function AESIs occurred at a higher frequency in CP1L participants (51.2%) compared to 2+ L participants (26.5%). Within the 2+ L cohort, liver related AESIs were more frequent in the CP2L (31.3%) cohort than in more heavily pretreated participants (CP3L, 23.5%) and participants with advanced leukemias (ADV, 20.4%). Overall, 29.6% of participants had liver function AESIs related to study treatment, and 1.8% had a liver function SAE. Of the participants with liver function AESIs, 8.6% had a history of prior liver function events.

Of the participants with liver function AESIs, 44.6% required dose modifications to manage the AEs; 44.2% required dose interruptions and 26.6% required dose reductions. Of those participants with dose interruptions who got rechallenged, 75.2% were successfully rechallenged. Overall, 4.4% of participants permanently discontinued treatment due to liver function AESIs. There were no deaths due to liver function AESIs.

Cardiac AESIs occurred in 14.4% of participants. The most frequent cardiac AESIs (occurring in ≥ 2% of participants) were pericardial effusion (4.4%), atrial fibrillation (2.6%), and cardiac failure congestive (2.3%). The frequency of cardiac AESIs was similar across cohorts (range: 13.3% to 16.0%). Overall, 7.3% of participants had cardiac AESIs related to study treatment and 6.4% had a cardiac SAE. Of the participants with cardiac AESIs, 22.0% had a history of prior cardiac events.

Of the participants with cardiac AESIs, 34.7% required dose modifications to manage the AEs; 32.2% required dose interruptions and 10.2% required dose reductions. Of those participants with dose interruptions who got rechallenged, 83.3% were successfully rechallenged. Overall, 2.3% of participants permanently discontinued treatment due to cardiac AESIs. There were 10 participants with fatal cardiac AESIs.

Vascular AESIs occurred in 8.7% of participants. The most frequent vascular AESIs (occurring in ≥ 1.0% of participants) were angina pectoris (1.5%) and coronary artery disease (1.5%). The frequency of vascular AESIs was similar across cohorts (range: 6.5% to 10.6%). Overall, 1.6% of participants had vascular AESIs related to study treatment, and 5.6% had a vascular SAE. Of the participants with vascular AESIs, 26.8% had a history of prior vascular events.

Of the participants with vascular AESIs, 25.4% required dose modifications to manage the AEs; 23.9% required dose interruptions and 7.0% required dose reductions. Of those participants with dose interruptions who got rechallenged, 93.8% were successfully rechallenged. Overall, 1.2% of participants permanently discontinued treatment due to vascular AESIs. There were 11 participants with fatal vascular AESIs.

Effusion AESIs occurred in 14.7% of participants. Pleural effusion occurred in 12.8% of participants and pericardial effusion in 4.4% of participants. Overall, the frequency of effusion AESIs was similar between the CP1L and 2+ L cohorts (13.7% and 15.1%, respectively), however, within the 2+ L cohort, the frequency of effusions was higher in the

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CP3L cohort (19.3%). Overall, 10.9% of participants had effusion AESIs related to study treatment, 6.0% had an effusion SAE. Of the participants with effusion AESIs, 23.3% had a history of prior effusion events.

Of the participants with effusion AESIs, 58.3% required dose modifications to manage the AEs; 55.0% required dose interruptions, and 27.5% required dose reductions. Of those participants with dose interruptions who got rechallenged, 78.3% were successfully rechallenged. Overall, 2.8% of participants permanently discontinued treatment due to effusion AESIs. There was 1 participant with a fatal effusion AESI (pleural and pericardial effusion [in addition to acute renal failure])

Renal AESIs occurred in 15.0% of participants. The most frequent renal AESI (occurring in ≥ 10% of participants) was blood creatinine increased (10.5%). The frequency of renal AESIs was similar across cohorts (range: 14.1% to 16.2%). Overall, 6.5% of participants had renal AESIs related to study treatment, and 2.9% had a renal SAE. Of the participants with renal AESIs, 11.4% had a history of prior renal events.

Of the participants with renal AESIs, 23.6% required dose modifications to manage the AEs; 22.0% required dose interruptions and 8.1% required dose reductions. Of those participants with dose interruptions who got rechallenged, 77.3% were successfully rechallenged. Overall, 1.1% of participants had renal AESIs that led to permanent discontinuation of treatment. There were 2 participants with fatal renal AESIs.

Haemorrhage AESIs occurred in 21.4% of participants. The most frequent haemorrhage AESI (occurring in ≥ 2% of participants) was epistaxis in 2.9% of participants, followed by contusion in 2.2% of participants.

Fluid retention/oedema AESIs occurred in 20.3% of participants. The most frequent fluid retention/oedema AESIs (occurring in ≥ 5 % of participants) were oedema peripheral (9.8%) and edema (5.6 %).

Myelosuppression AESIs occurred in 58.1% of participants. The most frequent myelosuppression AESIs (occurring in ≥ 10% of participants) were thrombocytopenia (32.6%), anaemia (28.7%), and neutropenia (15.8%).

Infection AESIs occurred in 55.0% of participants. The most frequent infection AESIs (occurring in ≥ 10% of participants) were upper respiratory tract infection (11.5%) and nasopharyngitis (11.4%).

Rash AESIs occurred in 39.6% of participants. The most frequent rash AESIs (occurring in ≥ 2 % of participants) were rash (31.9%), erythema (3.7%), acne (3.2%), and dermatitis (2.4%).

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Hypersensitivity AESIs occurred in 3.7% of participants. The most frequent hypersensitivity AESIs (occurring in ≥ 1% of participants) were drug hypersensitivity (1.3%) and seasonal allergy (1.0%).

Hypertension AESIs occurred in 10.1% of participants. The most frequent hypertension AESI (occurring in ≥ 5% of participants) was hypertension (9.4%).

Clinical Laboratory Results:

Overall, laboratory abnormalities (all grade) during the treatment period occurred in 99.4% of participants. Grade 1/2 and 3/4 abnormalities occurred in 46.3% and 53.1% of participants, respectively.

The most frequent (all grade and grade 3/4) blood chemistry laboratory abnormalities occurring on treatment were ALT increased (all grade 59.8%, Grade 3/4 14.1%), and aspartate aminotransferase (AST) increased (all grade 52.1%, Grade 3/4 7.0%).

The most frequent all grade hematologic laboratory abnormalities were low haemoglobin (88.8%) and low platelets (69.3%), the most frequent grade 3/4 hematologic laboratory abnormalities were low platelets (29.2%) and absolute neutrophil count (ANC) low (19.7%).

70.2% of participants had on-treatment clinical laboratory test results of potential clinical importance. The most frequent (occurring in ≥ 10% of participants) laboratory abnormalities were for hematology parameters: decreased platelet count (29.2%), decreased absolute neutrophil count (ANC) (19.7%), decreased haemoglobin (17.1%), decreased lymphocytes (15.2%), decreased leukocytes (11.0%), and for blood chemistry parameters: serum ALT increased (14.1%) and serum lipase increased (11.9%).

Overall, 23.2% of participants had an eGFR Grade of 3b, 4 or 5. A total of 167 (20.4%) participants had shifts from Grade ≤3a at baseline to Grade ≥3b on-treatment, of these, the majority already had an eGFR ≥Grade 2. There were 24 (2.9%) participants with Grade 3b at baseline, of these 2 (0.2%) had a shift to Grade ≤3a, 5 (0.6%) remained in Grade 3b, 15 (1.8%) had a shift to Grade 4 and 2 (0.2%) to Grade 5. One participant (0.1%) with Grade 4 at baseline had a shift to Grade 5 on treatment. Shifts to higher KDIGO eGFR grades were more frequent in the 2+ L cohort than in the CP1L cohort.

Vital Sign Results:

The most frequently reported changes were changes in body weight (≥ or ≤ 10% from baseline) in 27.5% of participants.

During the on-treatment period, the most frequent ECG abnormality across all cohorts was QRS interval ≥ 120 msec, occurring in 4.7% of participants. For QTcB, 1.0% of participants had QTcB > 500 msec and 1.8% of participants had an increase of >60 msec from baseline. For QTcF, 0.6% of participants had QTcF > 500 msec and 1.4% had an increase of > 60 msec from baseline.

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For QTcB, in the overall population, shifts from QTcB ≤500 at baseline to >500 msec on-treatment occurred in 8 (1.0%) participants. One (0.1%) participant with a QTcB > 500 msec at baseline had a shift to Grade 2 on-treatment. For QTcF, in the overall population, shifts from QTcF ≤500 at baseline to >500 msec on-treatment occurred in 5 (0.6%) participants. There were no participants with QTcF > 500 msec at baseline. The results were similar across cohorts.

In the overall population, 3 (0.4%) participants had shifts in left ventricular ejection fraction (LVEF) from Grade ≤2 at baseline to Grade ≥3 on-treatment, of these, 2 had a shift to Grade 3 and 1 to Grade 4. Three (0.4%) participants with Grade 3 at baseline remained on Grade 3 during treatment and 1 (0.1) with missing LVEF at baseline had a Grade 3 on-treatment. All on-treatment Grade 3 or 4 declines in LVEF occurred in the 2+ L cohort. No participants in the CP1L cohort had a decline in LVEF ≥ Grade 3.

CONCLUSION(S):

This study was a treatment extension protocol aimed to allow long term bosutinib treatment in participants with chronic or advanced phase Ph+ leukemias who received bosutinib in previous Pfizer sponsored Studies B1871006 or B1871008 and who were thought to have the potential, as judged by the investigator, to derive clinical benefit from continued treatment with bosutinib. Participants were followed for a minimum of 10 years.

The results of this extension study demonstrated that bosutinib administered orally at a starting dose of 500 mg QD showed efficacy in previously treated participants with Ph+ CML. This has been confirmed by long-term data showing durable responses, few on-treatment progressions to AP or BP and long-term overall survival. High OS rates were observed in CP1L, CP2L and CP3L participants who were treated with bosutinib. Similar clinically meaningful OS rates were seen in the AP cohort despite the advanced nature of the disease.

The safety profile was acceptable and consistent with what has been described previously in other CML trials. Overall, bosutinib was well-tolerated with toxicities that were manageable by dose interruption, dose reduction, and/or standard medical therapy and were mostly reversible. No new safety signals were identified after long-term follow-up.

The geometric mean bosutinib C_{trough} values observed in this study were similar to previous studies for doses ranging from 300 mg to 600 mg.

Based on the overall efficacy and safety data, bosutinib continues to show a positive risk/benefit profile and represents an alternative treatment option in patients with Ph+ CML who are resistant and intolerant to prior treatment.