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ORIGINAL ARTICLE

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Long-term cardiac, vascular, hypertension, and effusion safety of bosutinib in patients with Philadelphia chromosome–positive leukemia resistant or intolerant to prior therapy

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Abstract

Introduction: Long-term follow-up (≥4 years) demonstrated a low incidence of cardiac and vascular treatment-emergent adverse events (TEAEs) with bosutinib treatment. We evaluated cardiac, vascular, hypertension, and effusion TEAEs after ≥ 7 years of follow-up in patients with Philadelphia chromosome–positive (Ph+) leukemia.

Methods: This retrospective analysis of a phase I/II study and its ongoing extension study included data from patients with chronic phase chronic myeloid leukemia (CML) treated with bosutinib after resistance/intolerance to imatinib (CP2L) or to imatinib plus dasatinib and/or nilotinib (CP3L), and those with accelerated/blast phase CML or acute lymphoblastic leukemia after treatment with, at a minimum, imatinib (ADV).

Results: In all, 570 patients were treated with bosutinib; median treatment duration was 11.1 months (range: 0.03-133.1). The incidence of cardiac, vascular, hypertension, and effusion-related TEAEs was 10.9%, 8.8%, 9.1%, and 13.3%, respectively. Few patients had maximum grade 3-4 TEAEs (cardiac, 3.9%; vascular, 4.0%; hypertension, 3.0%; effusion, 4.6%). Grade 5 TEAEs occurred in the cardiac (0.7%) and vascular (1.8%) clusters only. In years 5-7, fewer than 5% of patients each year had newly occurring cardiac, vascular, hypertension, or effusion TEAEs. The exposure-adjusted TEAE rates (patients with TEAEs/total patient-year) pooled across CP2L, CP3L, and ADV cohorts were as follows: cardiac, 0.044; vascular, 0.035; hypertension, 0.038; and effusion, 0.056, of which, correspondingly, 0.9%, 1.2%, 0%, and 2.1% required treatment discontinuation.

Conclusions: The incidence of cardiac, hypertension, vascular, and effusion events was low in patients with Ph+ CML resistant or intolerant to prior therapy who were treated with bosutinib.

KEYWORDS

bosutinib, cardiovascular events, chronic myeloid leukemia, clinical trial, effusion events, tyrosine kinase inhibitor

Summary Statements

What is the NEW aspect of your work?

This study reviews the safety profile of bosutinib in patients with previously treated chronic myeloid leukemia with a focus on specific adverse events such as cardiac, vascular, hypertension, and effusion events.

What is the CENTRAL finding of your work?

Treatment with bosutinib resulted in an overall low incidence of cardiac, vascular, hypertension, and effusion events, and those events that did occur rarely led to treatment discontinuation.

What is (or could be) the SPECIFIC clinical relevance of your work?

Long-term (≥7 years) treatment with bosutinib was feasible. There is little risk of cardiac, hypertension, vascular, and effusion events with bosutinib treatment; however, patients considered at high risk of these events should be closely monitored.

1 | INTRODUCTION

Tyrosine kinase inhibitors (TKIs) are the primary treatment for patients with chronic myeloid leukemia (CML).[1] The use of TKIs has significantly improved survival in patients with CML, although 30%-40% of patients develop intolerance or resistance to first-line treatments requiring the use of second- and third-generation TKIs as salvage therapy.[2] Although generally well tolerated, second- and third-generation TKI therapy has been linked with cardiac and vascular adverse events (AEs).[3-5] In addition, effusion AEs have been associated with some TKIs.[6] The incidence of these events often increases with the duration of treatment, and although there are differences in the reporting, there appear to be differences in the relative incidence of AEs among the various TKIs.

Bosutinib, a second-generation oral dual Scr/Abl TKI, is indicated for the treatment of adult patients with newly diagnosed chronic phase (CP) Philadelphia chromosome–positive (Ph+) CML, and in patients with Ph + CML resistant or intolerant to prior therapy.[7] Bosutinib has been demonstrated to have a distinct safety profile, with a low incidence of some adverse side effects compared with other TKIs (eg, myocardial ischemia, and hemorrhage), but higher incidence of other adverse effects (eg, diarrhea).[6] The frequency of vascular AEs in patients receiving bosutinib also appears to be lower than in those receiving other second- and third-generation TKIs, ie, nilotinib and ponatinib.[3] The differences in vascular AEs may be explained by negative effects on vascular molecular pathways and endothelial cell functionality observed in vitro with dasatinib, nilotinib, and ponatinib treatment, but not with bosutinib.[8] Difference among the TKIs in regard to their inhibitory activity against kinases other than *BCR-ABL1* may contribute to their distinct safety profiles.[9]

The cardiac and vascular safety profile of bosutinib was first investigated as part of a retrospective analysis of two large clinical trials: a phase I/II study in previously treated patients with Ph+ leukemia, and a phase III clinical trial (BELA) in patients with newly diagnosed CP CML.[10] In both previously treated and newly diagnosed patients, the incidence of cardiac and vascular treatment-emergent AEs (TEAEs) with bosutinib (500 mg daily) was low, even after ≥ 4 years of follow-up. In the BELA trial, there was no significant difference between bosutinib and imatinib with regard to cardiac and vascular toxicity.[11] Pericardial effusion was the only individual cardiac TEAE that occurred with a higher frequency with bosutinib than with imatinib.[10] In the phase III BFORE trial in patients with newly diagnosed CP CML treated at a lower starting dose of bosutinib (400 mg daily), the rate of cardiac and vascular events was similarly low in patients receiving bosutinib vs imatinib after ≥ 1 years of follow-up.[12]

Given that the life expectancy of patients receiving TKIs approaches that of the general population and the need for prolonged therapy for most patients receiving TKIs, understanding the risks of cardiac, vascular, and effusion side effects associated with continued treatment is key to ensuring proper patient management.[13] In this retrospective analysis of the phase I/II study and its ongoing extension study, long-term (≥7 years of follow-up) cardiac, vascular, hypertension, and effusion safety data were evaluated in patients with CP CML or advanced Ph+ leukemias resistant/intolerant to imatinib. An updated analysis from BELA was not provided, as patients in the imatinib arm were discontinued from the study after their 4-year follow-up visit.

2 | MATERIALS AND METHODS

2.1 | Study design

This retrospective analysis included data from an open-label, phase I/II study (ClinicalTrials.gov: NCT00261846) and its ongoing extension study (ClinicalTrials.gov: NCT01903733). Details of the phase I/II study design and patient population have been previously published.[14-16] Eligible patients were aged ≥ 18 years with Ph+ CP CML treated with bosutinib following resistance/intolerance to imatinib (ie, second-line cohort [CP2L]) or to imatinib plus dasatinib and/or nilotinib (third-line cohort [CP3L]), or with accelerated/blast phase CML or acute lymphoblastic leukemia after prior TKI therapy (advanced [ADV] cohort). Patients were excluded if they had a prior history of clinically significant or uncontrolled cardiac disease, including a history of or active congestive heart failure; uncontrolled angina or hypertension within 3 months; myocardial infarction within 12 months; clinically significant ventricular arrhythmia; diagnosed or suspect congenital or acquired prolonged QT syndrome; unexplained syncope and a history of prolonged QTc. Additional exclusion criteria included a prolonged QTc interval (>0.45 sec), the concomitant use of

TABLE 1 Standardized MedDRA terms included in the TEAE clusters (Cardiac, vascular, hypertension, and effusion)

	TEAE Cluster			
MedDRA term	Cardiac	Vascular	Hypertension	Effusion
HLGTs	• Cardiac arrhythmias • Heart failures	*Cardiovascular* • Coronary artery disorders *Peripheral vascular* • Arteriosclerosis, stenosis, vascular insufficiency, and necrosis • Embolism and thrombosis	• Vascular hypertensive disorders	
HLTs		*Cardiovascular* • Arterial therapeutic procedures (excluding aortic) • Vascular imaging procedures NEC • Vascular therapeutic procedures NEC *Cerebrovascular* • CNS hemorrhages and cerebrovascular accidents • CNS vascular disorders NEC • Transient cerebrovascular events *Peripheral vascular* • Non–site-specific vascular disorders NEC • Peripheral vascular disorders NEC (excluding PTs flushing and hot flush)		
PTs	• Cardiac death • Ejection fraction decreased • Sudden cardiac death • Sudden death	*Cardiovascular* • Transcatheter arterial chemoembolization *Cerebrovascular* • Subarachnoid hemorrhage *Peripheral vascular* • Intestinal ischemia	• BP abnormal • BP ambulatory abnormal • BP ambulatory increased • BP diastolic abnormal • BP diastolic increased • BP increased • BP systolic abnormal • BP systolic increased	• Pericardial effusion • Pleural effusion
SMQs	• Torsades de pointes/QT prolongation (narrow)			

Abbreviations: BP, blood pressure; CNS, central nervous system; HLGT, high-level group term; HLT, high-level term; NEC, not elsewhere classified; MedDRA, Medical Dictionary for Regulatory Activities, Version 20.0; PT, preferred term; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.

medications known to prolong QTc interval, or uncorrected hypomagnesemia or hypokalemia.

Patients received bosutinib at a starting dose of 500 mg once daily. Bosutinib doses were withheld or reduced in 100-mg decrements based on the severity of treatment-related toxicities. Patients were to be discontinued from the study if more than two dose reductions were required. Dose escalations to 600 mg once daily were allowed for lack of efficacy (failure to reach complete hematologic response by week 8 or complete cytogenetic response by week 12), if the patient had no grade ≥ 3 possibly-related AEs. Patients received treatment until disease progression, toxicity, or consent withdrawal. Data are from an unlocked trial database with a data cutoff of April 20, 2017. Extension study data for 14 patients in China were excluded due to regulatory requirements.

The study protocol was approved by an independent institutional review board and the study was conducted in accordance with the provisions of the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

2.2 | TEAE assessment

TEAEs were monitored throughout the study and for 30 days following the last study dose; AEs were followed until resolution (grade < 1) or return to baseline. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, was used to grade AEs. TEAEs are reported throughout the manuscript regardless of causality, except for where noted (Table 3) where relatedness of TEAEs to the study drug was determined by the investigator. This analysis reported cardiac, vascular, hypertension, and effusion TEAEs across all years, and during years 5-7 of treatment (year 8 was reported for the CP2L cohort only). Frequency and characteristics of cardiac, vascular, hypertension, and effusion TEAEs were analyzed by selecting Medical Dictionary for Regulatory Activities (MedDRA, Version 20.0) higher-level group

TABLE 2 Summary of reasons for discontinuation from treatment, by number of years on treatment in CP2L, CP3L, and ADV patients receiving bosutinib for Ph+ leukemia

	Patients on Treatment				
	>4 Years	>5 Years	>6 Years	>7 Years	Total (Up Through Data Cutoff)
CP2L[a]	**n = 123**	**n = 115**	**n = 106**	**n = 84**	**n = 284**
Discontinued, n (%)	8 (6.5)	9 (7.8)	22 (20.8)	23 (27.4)	228 (80.3)
Adverse event	1 (0.8)	2 (1.7)	2 (1.9)	1 (1.2)	71 (25.0)
Disease progression	1(0.8)	1 (0.9)	4 (3.8)	1 (1.2)	55 (19.4)
Other	1 (0.8)	2 (1.7)	8 (7.5)	14 (16.7)	28 (9.9)
Patient request	1 (0.8)	1 (0.9)	4 (3.8)	1 (1.2)	26 (9.2)
Unsatisfactory response (efficacy)	2 (1.6)	0	1 (0.9)	1 (1.2)	23 (8.1)
Death	2 (1.6)	1 (0.9)	1 (0.9)	3 (3.6)	10 (3.5)
Investigator request	0	1 (0.9)	2 (1.9)	2 (2.4)	8 (2.8)
Lost to follow-up	0	0	0	0	4 (1.4)
Symptomatic deterioration	0	0	0	0	2 (0.7)
Study discontinuation by sponsor	0	1 (0.9)	0	0	1 (0.4)
CP3L[b]	**n = 29**	**n = 24**	**n = 19**	**N/A**	**n = 119**
Discontinued, n (%)	5 (17.2)	5 (20.8)	6 (31.6)		110 (92.4)
Adverse event	3 (10.3)	1 (4.2)	2 (10.5)		36 (30.3)
Disease progression	0	0	1 (5.3)		25 (21.0)
Unsatisfactory response	0	1 (4.2)	1 (5.3)		25 (21.0)
Patient request	1 (3.4)	1 (4.2)	1 (5.3)		8 (6.7)
Death	0	0	1 (5.3)		5 (4.2)
Investigator request	0	0	0		3 (2.5)
Other	0	1 (4.2)	0		3 (2.5)
Lost to follow-up	0	0	0		2 (1.7)
Study discontinuation by sponsor	0	1 (4.2)	0		1 (0.8)
Protocol violation	0	0	0		1 (0.8)
Symptomatic deterioration	1 (3.4)	0	0		1 (0.8)
ADV[b]	**n = 17**	**n = 13**	**n = 11**	**N/A**	**n = 167**
Discontinued, n (%)	4 (23.5)	2 (15.4)	1 (9.1)		160 (95.8)
Disease progression	1 (5.9)	0	1 (9.1)		67 (40.1)
Adverse event	2 (11.8)	2 (15.4)	0		29 (17.4)
Unsatisfactory response	1 (5.9)	0	0		18 (10.8)
Symptomatic deterioration	0	0	0		17 (10.2)
Death	0	0	0		14 (8.4)
Other	0	0	0		8 (4.8)
Patient request	0	0	0		4 (2.4)
Lost to follow-up	0	0	0		1 (0.6)
Investigator request	0	0	0		1 (0.6)
Protocol violation	0	0	0		1 (0.6)

Abbreviations: 1 year, 48 weeks; ADV, advanced phase/blast phase CML or Ph+ acute lymphocytic leukemia after at least imatinib; CP2L, chronic phase Ph+ CML in 2nd line after imatinib; CP3L, chronic phase Ph+ CML in 3rd line after imatinib and dasatinib and/or nilotinib; N/A, not applicable; Ph+, Philadelphia chromosome–positive; TEAE, treatment-emergent adverse event.

[a]8-year follow-up.

[b]7-year follow-up.

TABLE 3 Summary of TEAEs in patients receiving bosutinib for Ph+ leukemia, by TEAE cluster

TEAE Cluster and Variable	CP2L[a] (n = 284)	CP3L[b] (n = 119)	ADV[b] (n = 167)	Total (N = 570)
Cardiac cluster, n (%)				
Total patients with TEAEs	31 (10.9)	15 (12.6)	16 (9.6)	62 (10.9)
Patients with TEAEs leading to death	3 (1.1)	0	1 (0.6)	4 (0.7)
Patients with serious adverse event	13 (4.6)	5 (4.2)	6 (3.6)	24 (4.2)
Patients with TEAEs leading to permanent treatment discontinuation	1 (0.4)	3 (2.5)	1 (0.6)	5 (0.9)
Patients with drug-related TEAEs[c]	7 (2.5)	9 (7.6)	2 (1.2)	18 (3.2)
Patients with medical history of any cluster event	22 (7.7)	10 (8.4)	26 (15.6)	58 (10.2)
Vascular cluster, n (%)				
Total patients with TEAEs	26 (9.2)	9 (7.6)	15 (9.0)	50 (8.8)
Cardiovascular TEAEs	15 (5.3)	5 (4.2)	5 (3.0)	25 (4.4)
Cerebrovascular TEAEs	9 (3.2)	1 (0.8)	8 (4.8)	18 (3.2)
Peripheral vascular TEAEs	7 (2.5)	4 (3.4)	2 (1.2)	13 (2.3)
Patients with TEAEs leading to death	1 (0.4)	2 (1.7)	7 (4.2)	10 (1.8)
Patients with serious adverse event	18 (6.3)	7 (5.9)	12 (7.2)	37 (6.5)
Patients with TEAEs leading to permanent treatment discontinuation	3 (1.1)	2 (1.7)	2 (1.2)	7 (1.2)
Patients with drug-related TEAEs[c]	5 (1.8)	1 (0.8)	1 (0.6)	7 (1.2)
Patients with medical history of any cluster event	30 (10.6)	15 (12.6)	30 (18.0)	75 (13.2)
Hypertension cluster, n (%)				
Total patients with TEAEs	28 (9.9)	11 (9.2)	13 (7.8)	52 (9.1)
Patients with TEAEs leading to death	0	0	0	0
Patients with serious adverse event	3 (1.1)	0	1 (0.6)	4 (0.7)
Patients with TEAEs leading to permanent treatment discontinuation	0	0	0	0
Patients with drug-related TEAEs[c]	5 (1.8)	3 (2.5)	0	8 (1.4)
Patients with medical history of any cluster event	75 (26.4)	37 (31.1)	44 (26.3)	156 (27.4)
Effusion cluster, n (%)				
Total patients with TEAEs	38 (13.4)	21 (17.6)	17 (10.2)	76 (13.3)
Patients with TEAEs leading to death	0	0	0	0
Patients with serious adverse event	16 (5.6)	8 (6.7)	8 (4.8)	32 (5.6)
Patients with TEAEs leading to permanent treatment discontinuation	3 (1.1)	6 (5.0)	3 (1.8)	12 (2.1)
Patients with drug-related TEAEs[c]	23 (8.1)	19 (16.0)	11 (6.6)	53 (9.3)
Patients with Medical History of any cluster event	8 (2.8)	24 (20.2)	23 (13.8)	55 (9.6)

Abbreviations: ADV, advanced phase/blast phase CML or Ph+ acute lymphocytic leukemia after at least imatinib; CML, chronic myeloid leukemia; CP2L, chronic phase Ph+ CML in 2nd line after imatinib; CP3L, chronic phase Ph+ CML in 3rd line after imatinib and dasatinib and/or nilotinib; MedDRA, Medical Dictionary for Regulatory Activities; Ph+, Philadelphia chromosome–positive; SOC, system organ class; TEAE, treatment-emergent adverse event.

Total number of patients listed at a higher level are not necessarily the sum of numbers listed below as individual patients may report two or more different events within that category.

[a]8-year follow-up.

[b]7-year follow-up.

[c]Relatedness to study treatment was determined by the investigator.

terms, higher-level terms, preferred terms, and standardized MedDRA queries to generate TEAE clusters (Table 1).

2.3 | Statistical analysis

TEAEs (any event increasing in severity from baseline or any new event starting during bosutinib therapy or within 30 days of the last dose of study drug) are reported descriptively according to therapy line, and disease phase (median and range for continuous parameters and number and percentage for categorical parameters). Newly occurring AEs were defined as MedDRA preferred terms not reported for the same patient previously for those on treatment during a given year. Exposure-adjusted incidence rates were calculated as the number of patients with events divided by the sum of time to first event for those with events and treatment duration for those without events. Discontinuations due to TEAEs were also assessed by treatment year.

Multivariable logistic regression analyses using backward elimination (criteria 0.20) were performed to identify baseline prognostic factors for cardiac, vascular, hypertension, and effusion events. The 95% confidence intervals for odds ratios excluding 1 were considered predictive of the outcome; however, no adjustments were made for multiple comparisons. Parameters included age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), history of hypertension, history of hyperlipidemia, history of diabetes, history of cardiac/vascular/effusion events, imatinib resistant/intolerant, prior dasatinib, and prior nilotinib.

3 | RESULTS

3.1 | Patients and treatment

A total of 570 patients (n = 284 CP2L, 119 CP3L, 167 ADV) were enrolled in the parent study and treated with bosutinib. The median duration of treatment for all patients who received bosutinib was 11.1 months (CP2L, 25.6 months; CP3L, 8.6 months; ADV, 4.0 months), ranging from 0.03 to 133.1 months. The minimum time from the first dose of bosutinib to the data cutoff date was 94.2 months in the CP2L group, 85.2 months in the CP3L group, and 84.1 months in the ADV group; this analysis therefore reports data after 7 years of follow-up for CP3L and ADV patients and after 8 years for CP2L patients. Overall, the most common reasons for discontinuations from treatment were AEs (CP2L, 25.0%; CP3L, 30.3%; ADV, 17.4%) and lack of efficacy/disease progression (CP2L, 27.5%; CP3L, 42.0%; ADV, 50.9%) (Table 2). The percentage of patients still receiving bosutinib treatment at data cutoff was 12.6% (CP2L, 19.7%; CP3L, 7.6%; ADV, 4.2%).

3.2 | TEAEs

Any grade TEAEs occurred in 10.9%, 8.8%, 9.1%, and 13.3% of patients in the cardiac, vascular, hypertension, and effusion clusters, respectively. The rates of TEAEs, serious AEs, and permanent treatment discontinuation in the cardiac, vascular, hypertension, and effusion clusters were generally similar across the CP2L, CP3L, and ADV subgroups (Table 3). In the cardiac, vascular, hypertension, and effusion clusters, respectively, TEAEs led to permanent treatment discontinuation in 0.9%, 1.2%, 0%, and 2.1% of patients. TEAEs were generally of mild to moderate severity; maximum grade 1-2 TEAEs were reported in 6.3%, 3.0%, 6.1%, and 8.8% of patients in the corresponding clusters. The overall incidence of maximum grade 3-4 TEAEs was highest in the effusion (4.6%) and vascular (4.0%) clusters, followed by the cardiac (3.9%) and hypertension (3.0%) clusters (Table 4). Grade 5 TEAEs occurred in 4 (0.7%) patients in the cardiac cluster; these were cardiac failure congestive (n = 2), cardiac failure (n = 1), and cardiac failure acute (n = 1). Ten (1.8%) patients in the vascular cluster had grade 5 TEAEs of subarachnoid hemorrhage (n = 2), myocardial infarction (n = 2), intraventricular hemorrhage (n = 1), acute myocardial infarction (n = 1), coronary artery disease (n = 1), cerebral hemorrhage (n = 1), cerebral infarction (n = 1), and cerebrovascular accident (n = 1). Of these grade 5 TEAEs, only one (myocardial infarction) was considered related to study drug by the investigator. No grade 5 TEAEs were reported in the hypertension and effusion clusters. Overall, the most frequent TEAEs were atrial fibrillation (3.0%) in the cardiac cluster, angina pectoris (1.6%) in the vascular cluster, hypertension (8.2%) in the hypertension cluster, and pleural effusion (11.9%) in the effusion cluster. The median time to first TEAE was 92 days (range: 1-2885 days) in the cardiac cluster, 400 days (range: 8-3208) in the vascular cluster, 610 days (range 1-3404) in the hypertension cluster, and 626 days (range: 3-2829) in the effusion cluster (Table 4).

In the cardiac, vascular, hypertension, and effusion clusters, newly occurring TEAEs were reported in < 5% of patients each year during years 5-8 (Table 5). The greatest number of newly occurring TEAEs was in the effusion cluster, wherein 21 patients had effusion AEs; the most frequent was pleural effusion: 15 patients had pleural effusion and 8 had pericardial effusion events (two patients had both pleural and pericardial effusions events). There were 14 newly occurring cardiac AEs in years 5-8; the most frequent was congestive cardiac failure (n = 5). Twelve new vascular AEs occurred in years 5-8 (n = 5 cardiovascular, 4 cerebrovascular, and 3 peripheral vascular). There were four newly occurring AEs in the hypertension cluster in years 5-8, all of which were hypertension. Exposure-adjusted incidence rates were 0.044, 0.035, 0.038, and 0.056 for the cardiac, vascular, hypertension, and effusion AE clusters, respectively (Table 6.) Across all clusters, exposure-adjusted incidence rates were lower in the CP2L cohort compared with the CP3L or ADV cohort.

3.3 | Management of TEAEs

Cardiac, vascular, hypertension, and effusion TEAEs in patients treated with bosutinib were mostly managed with treatment interruptions, dose reductions, and concomitant medications (Table 7). Among patients with an event, the rates of temporary treatment

TABLE 4 Maximum toxicity (Grades 3-5) TEAEs, most frequent TEAEs,[a] and time to first event, by TEAE cluster

TEAE Cluster and Variable	CP2L[b] (n = 284)	CP3L[c] (n = 119)	ADV[c] (n = 167)	Total (N = 570)
Cardiac cluster				
Maximum toxicity, n (%)				
Grade 3	8 (2.8)	5 (4.2)	3 (1.8)	16 (2.8)
Grade 4	4 (1.4)	1 (0.8)	1 (0.6)	6 (1.1)
Grade 5	3 (1.1)	0	1 (0.6)	4 (0.7)
Most frequent TEAEs,[a] n (%)				
Atrial fibrillation	8 (2.8)	7 (5.9)	2 (1.2)	17 (3.0)
Cardiac failure congestive	8 (2.8)	4 (3.4)	3 (1.8)	15 (2.6)
Tachycardia	3 (1.1)	1 (0.8)	6 (3.6)	10 (1.8)
Cardiac failure	5 (1.8)	3 (2.5)	1 (0.6)	9 (1.6)
Bradycardia	6 (2.1)	0	1 (0.6)	7 (1.2)
Time to first event, median (range), days	136 (1-2783)	519 (1-2885)	19 (7-811)	92 (1-2885)
Vascular cluster				
Maximum toxicity, n (%)				
Grade 3	10 (3.5)	3 (2.5)	2 (1.2)	15 (2.6)
Grade 4	4 (1.4)	2 (1.7)	2 (1.2)	8 (1.4)
Grade 5	1 (0.4)	2 (1.7)	7 (4.2)	10 (1.8)
Most frequent TEAEs,[a] n (%)				
Angina pectoris	8 (2.8)	1 (0.8)	0	9 (1.6)
Coronary artery disease	4 (1.4)	2 (1.7)	2 (1.2)	8 (1.4)
Time to first event, median (range), days	809 (47-3208)	327 (8-2454)	55 (8-2712)	400 (8-3208)
Hypertension cluster				
Maximum toxicity, n (%)				
Grade 3	9 (3.2)	3 (2.5)	5 (3.0)	17 (3.0)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Most frequent TEAEs,[a] n (%)				
Hypertension	25 (8.8)	10 (8.4)	12 (7.2)	47 (8.2)
Time to first event, median (range), days	788 (1-3404)	616 (1-2854)	305 (7-2845)	610 (1-3404)
Effusion cluster				
Maximum toxicity, n (%)				
Grade 3	8 (2.8)	6 (5.0)	6 (3.6)	20 (3.5)
Grade 4	4 (1.4)	1 (0.8)	1 (0.6)	6 (1.1)
Grade 5	0	0	0	0
Most frequent TEAEs,[a] n (%)				
Pleural effusion	33 (11.6)	20 (16.8)	15 (9.0)	68 (11.9)
Pericardial effusion	9 (3.2)	7 (5.9)	6 (3.6)	22 (3.9)
Time to first event, median (range), days	1285 (16-2829)	495 (45-2048)	39 (3-1309)	626 (3-2829)

Abbreviations: ADV, advanced phase/blast phase CML or Ph+ acute lymphocytic leukemia after at least imatinib; CML, chronic myeloid leukemia; CP2L, chronic phase Ph+ CML in 2nd line after imatinib; CP3L, chronic phase Ph+ CML in 3rd line after imatinib and dasatinib and/or nilotinib; MedDRA, Medical Dictionary for Regulatory Activities; Ph+, Philadelphia chromosome–positive; TEAE, treatment-emergent adverse event.

[a]Reported for TEAEs occurring in > 1% of all patients (N = 570). By MedDRA preferred terms.

[b]8-year follow-up.

[c]7-year follow-up.

TABLE 5 Newly occurring TEAEs in years 5-8 in patients receiving bosutinib for Ph+ leukemia, by TEAE cluster

Patients with Newly Occurring TEAEs, n/N (%)	CP2L[a]	CP3L[b]	ADV[b]	Total
Cardiac cluster				
Year 5	5/123 (4.1)	0	1/17 (5.9)	6/169 (3.6)
Year 6	3/115 (2.6)	1/24 (4.2)	0	4/152 (2.6)
Year 7	2/106 (1.9)	1/19 (5.3)	0	3/136 (2.2)
Year 8	1/84 (1.2)	–	–	–
Vascular cluster				
Cardiovascular TEAEs				
Year 5	3/123 (2.4)	0	0	3/169 (1.8)
Year 6	1/115 (0.9)	0	1/13 (7.7)	2/152 (1.3)
Year 7	0	0	0	0
Year 8	0	–	–	–
Cerebrovascular TEAEs				
Year 5	1/123 (0.8)	0	0	1/169 (0.6)
Year 6	1/115 (0.9)	0	0	1/152 (0.7)
Year 7	0	0	0	0
Year 8	2/84 (2.4)	–	–	–
Peripheral vascular TEAEs				
Year 5	2/123 (1.6)	0	0	2/169 (1.2)
Year 6	0	0	0	0
Year 7	0	0	0	0
Year 8	1/84 (1.2)	–	–	–
Hypertension cluster				
Year 5	2/123 (1.6)	0	0	2/169 (1.2)
Year 6	0	0	0	0
Year 7	2/106 (1.9)	0	0	2/136 (1.5)
Year 8	0	–	–	–
Effusion cluster				
Year 5	4/123 (3.3)	1/29 (3.4)	1/17 (5.9)	6 /169 (3.6)
Year 6	5/115 (4.3)	1/24 (4.2)	0	6/152 (3.9)
Year 7	3/106 (2.8)	2/19 (10.5)	0	5/136 (3.7)
Year 8	4/84 (4.8)	–	–	–

Abbreviations: ADV, advanced phase/blast phase CML or Ph+ acute lymphocytic leukemia after at least imatinib; CML, chronic myeloid leukemia; CP2L, chronic phase Ph+ CML in 2nd line after imatinib; CP3L, chronic phase Ph+ CML in 3rd line after imatinib and dasatinib and/or nilotinib; Ph+, Philadelphia chromosome–positive; TEAE, treatment-emergent adverse event.

[a]8-year follow-up.

[b]7-year follow-up.

interruption due to TEAEs were 21.0% in the cardiac cluster, 16.0% in the vascular cluster, 7.7% in the hypertension cluster, and 56.6% in the effusion cluster. Among patients who were re-administered the study drug after dose interruption, successful treatment rechallenge (ie, no permanent treatment discontinuation due to any AE in the specific cluster) was achieved in the cardiac, vascular, hypertension, and effusion clusters in 90.9%, 100%, 100%, and 82.5% of patients, respectively. The rate of dose reductions due to TEAEs was higher in the effusion cluster (28.9%) than in the cardiac (6.5%), vascular (6.0%), and hypertension (0%) clusters. The proportion of patients treated with concomitant medication was highest in the hypertension cluster (cardiac, 48.4%; vascular, 38.0%; hypertension, 76.9%; effusion, 59.2%).

3.4 | Prognostic factors

Prognostic risk factors for cardiac TEAEs in the overall population (CP2L, CP3L, and ADV cohorts) were age ≥ 65 years, ECOG PS > 0, history of hyperlipidemia, and history of cardiac events (Table 8).

TABLE 6 Exposure-adjusted incidence rates for TEAEs, by TEAE cluster

Exposure-Adjusted Incident Rate, by TEAE cluster[c]	CP2L[a] (n = 284)		CP3L[b] (n = 119)		ADV[b] (n = 167)		Total (N = 570)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Cardiac cluster TEAEs	0.031	0.014	0.061	0.023	0.088	0.025	0.044	0.017
Vascular cluster TEAEs	0.026	0.014	0.038	0.029	0.079	0.057	0.035	0.022
Cardiovascular	0.015	0.008	0.020	0.020	0.026	0.026	0.017	0.012
Cerebrovascular	0.009	0.008	0.004	0	0.041	0.030	0.012	0.009
Peripheral vascular	0.007	0.001	0.016	0.008	0.010	0	0.009	0.002
Hypertension cluster TEAEs	0.030	0.009	0.048	0.012	0.072	0.026	0.038	0.011
Effusion cluster TEAEs	0.039	0.012	0.099	0.028	0.099	0.036	0.056	0.018

Abbreviations: ADV, advanced phase/blast phase CML or Ph+ acute lymphocytic leukemia after at least imatinib; CML, chronic myeloid leukemia; CP2l, chronic phase Ph+ CML in 2nd line after imatinib; CP3L, chronic phase Ph+ CML in 3rd line after imatinib and dasatinib and/or nilotinib; Ph+, Philadelphia chromosome–positive; TEAE, treatment-emergent adverse event.

[a]8-year follow-up.

[b]7-year follow-up.

[c]Exposure-adjusted incidence rate calculated as the number of patients with TEAEs / total patient-year, where total patient-year = sum of total time to first TEAE for all patients with TEAEs and treatment duration for patients without TEAEs.

When evaluated by cohort, cardiac prognostic factors were ECOG PS > 0, history of diabetes, and history of cardiac events for patients in the CP2L subgroup and ECOG PS > 0 and history of cardiac events in the CP3L subgroup. There were no risk factors predictive of cardiac TEAEs for the ADV cohort (Table S1). The only prognostic risk factor for vascular TEAEs overall was history of vascular events (Table 8). History of vascular events was also a prognostic factor for vascular TEAEs in the CP2L and CP3L cohorts but not the ADV cohort (Table S2). There were no prognostic risk factors for the hypertension TEAEs in the overall population (Table 8). Male was a prognostic factor for hypertension TEAEs in the CP2L cohort and female in the ADV cohort but not the CP3L cohort (Table S3). Prognostic risk factors for the effusion TEAEs overall were age ≥ 65 years, history of effusion events, and history of hypertension (Table 8). When evaluated by CP subgroup, prognostic factors were age ≥ 65 years and history of cardiac events for CP2L, age ≥ 65 years and history of effusion events for CP3L, and history of effusion events for ADV (Table S4).

4 | DISCUSSION

The results of this retrospective analysis after ≥ 7 years of follow-up indicate that cardiac, vascular, hypertension, and effusion events occurred in less than 15% of bosutinib-treated patients with Ph + leukemia. This analysis showed that during years 5 through 8, newly occurring AEs in the cardiac, vascular, hypertension, or effusion clusters occurred in fewer than 5% of patients each year. Additionally, the exposure-adjusted incidence rates across all treatment lines and disease stages were low. These results are similar to the earlier analysis of years 1 through 4, with most of the patients who experienced vascular and cardiac events doing so in the first year of bosutinib treatment.[10] The incidence of newly occurring vascular and cardiac events did not increase during the initial 4-year follow-up period and showed a decrease in the first-line setting.[10]

TEAEs associated with bosutinib treatment were generally mild to moderate severity (grade 1/2) and only infrequently (≤3% of patients) led to treatment discontinuation. TEAEs were managed predominantly through temporary treatment interruption and concomitant medication. Treatment rechallenge was successful in the majority (>80%) of patients with temporary treatment interruption. Discontinuations from treatment in years 5, 6, and 7 were infrequent.

Among the cardiac, vascular, hypertension, and effusion clusters, the effusion cluster had the greatest number of newly occurring TEAEs in years 5-8; the most frequently occurring TEAE in the cluster was pleural effusion. A medical history of effusion TEAEs was reported by 10% of patients in the overall population and by 34% for patients with effusion events. This study determined age ≥ 65 years, history of effusion events, and a history of hypertension were prognostic risk factors of effusion events. Prior dasatinib or nilotinib treatment were determined not to be a prognostic risk factor of effusion TEAEs in patients receiving bosutinib; including in the CP3L cohort, where 77% of patients in the overall cohort and 95% of patients with effusion events had received dasatinib pretreatment (data not shown). On the contrary, a history of effusion events was predictive for developing effusion events under bosutinib treatment, both in the overall population and in the CP3L cohort, suggesting that it is the development of effusions and not pretreatment with dasatinib that is a risk factor. Overall, effusion TEAEs were predominantly Grade 1/2 and occurred within the first 2 years of treatment. Effusion TEAEs were successfully managed in the majority of patients, with only 2% of patients permanently discontinuing treatment due to effusion events. A small retrospective study in patients who developed pleural effusions under previous dasatinib treatment demonstrated that 30% (n = 6/20) developed pleural effusions while receiving bosutinib; however, only 15% (3/20) permanently

TABLE 7 Management of cardiac, vascular, hypertension, and effusion TEAEs

TEAE Cluster and Variable, n (%)	CP2L[a] (n = 284)	CP3L[b] (n = 119)	ADV[b] (n = 167)	Total (N = 570)
Cardiac cluster				
Total with TEAEs	n = 31	n = 15	n = 16	n = 62
Treatment change				
Temporary treatment interruption	9 (29.0)	2 (13.3)	2 (12.5)	13 (21.0)
Treatment rechallenge	8 (88.9)	2 (100.0)	1 (50.0)	11 (84.6)
Successful treatment rechallenge	8 (100.0)	2 (100.0)	0	10 (90.9)
Dose reduction	3 (9.7)	1 (6.7)	0	4 (6.5)
Persisted	16 (51.6)	4 (26.7)	3 (18.8)	23 (37.1)
Treated with concomitant medication	16 (51.6)	8 (53.3)	6 (37.5)	30 (48.4)
Vascular cluster				
Total with TEAEs	n = 26	n = 9	n = 15	n = 50
Treatment change				
Temporary treatment interruption	6 (23.1)	0	2 (13.3)	8 (16.0)
Treatment rechallenge	6 (100.0)	0	2 (100.0)	8 (100.0)
Successful treatment rechallenge	6 (100.0)	0	2 (100.0)	8 (100.0)
Dose reduction	2 (7.7)	1 (11.1)	0	3 (6.0)
Persisted	15 (57.7)	3 (33.3)	4 (26.7)	22 (44.0)
Treated with concomitant medication	12 (46.2)	4 (44.4)	3 (20.0)	19 (38.0)
Hypertension cluster				
Total with TEAEs	n = 28	n = 11	n = 13	n = 52
Treatment change				
Temporary treatment interruption	4 (14.3)	0	0	4 (7.7)
Treatment rechallenge	4 (100.0)	0	0	4 (100.0)
Successful treatment rechallenge	4 (100.0)	0	0	4 (100.0)
Dose reduction	0	0	0	0
Persisted	17 (60.7)	7 (63.6)	9 (69.2)	33 (63.5)
Treated with concomitant medication	20 (71.4)	8 (72.7)	12 (92.3)	40 (76.9)
Effusion cluster				
Total with TEAEs	n = 38	n = 21	n = 17	n = 76
Treatment change				
Temporary treatment interruption	21 (55.3)	14 (66.7)	8 (47.1)	43 (56.6)
Treatment rechallenge	20 (95.2)	12 (85.7)	8 (100.0)	40 (93.0)
Successful treatment rechallenge	19 (95.0)	8 (66.7)	6 (75.0)	33 (82.5)
Dose reduction	11 (28.9)	6 (28.6)	5 (29.4)	22 (28.9)
Persisted	19 (50.0)	9 (42.9)	8 (47.1)	36 (47.4)
Treated with concomitant medication	20 (52.6)	14 (66.7)	11 (64.7)	45 (59.2)

Abbreviations: ADV, advanced phase/blast phase CML or Ph+ acute lymphocytic leukemia after at least imatinib; CML, chronic myeloid leukemia; CP2L, chronic phase Ph+ CML in 2nd line after imatinib; CP3L, chronic phase Ph+ CML in 3rd line after imatinib and dasatinib and/or nilotinib; Ph+, Philadelphia chromosome–positive; TEAE, treatment-emergent adverse event.

[a]8-year follow-up.

[b]7-year follow-up.

discontinued bosutinib for this reason.[17] Dasatinib treatment in patients with CML has previously been associated with fluid-retention AEs, including pleural and pericardial effusion.[18,19] With a minimum follow-up of 5 and 7 years, dasatinib-related pleural effusions were reported in 28% of patients receiving front-line therapy and 33% of patients previously treated with imatinib, respectively; there was a steady but continuous risk of developing pleural effusion over time.[20-22] The mechanism of action with dasatinib has been associated with increase of lymphocytes, specifically natural killer cells.[22] The mechanism of action for bosutinib is unclear; however, major

TABLE 8 Logistic regression analysis of risk factors for cardiac, vascular, hypertension, and effusion TEAEs (all patients)

Parameter	Cardiac OR[a] (95% CI)	Vascular OR[a] (95% CI)	Hypertension OR[a] (95% CI)	Effusion OR[a] (95% CI)
Age (<65, ≥65 y)	2.33 (1.26-4.29)	1.71 (0.87-3.34)	–	2.79 (1.55-5.03)
Sex (female, male)	1.48 (0.83-2.64)	-	–	1.66 (0.96-2.87)
ECOG PS (0, >0)	2.77 (1.54-4.96)	1.879 (0.995-3.548)	–	-
History of hypertension (yes, no)	–	–	–	0.54 (0.30-0.96)
History of hyperlipidemia/ increased cholesterol (yes, no)	0.41 (0.19-0.86)	–	–	–
History of diabetes (yes, no)	–	–	–	–
History of cardiac disorders (yes, no)	0.32 (0.16-0.65)	N/A	N/A	0.51 (0.25-1.00)
History of vascular disorder (yes, no)	N/A	0.34 (0.17-0.68)	N/A	1.72 (0.81-3.68)
History of effusion disorder (yes, no)	N/A	N/A	N/A	0.16 (0.08-0.31)
Imatinib (resistant, intolerant)	–	1.62 (0.85-3.07)	–	–
Prior dasatinib (yes, no)	–	2.06 (0.95-4.47)	–	–
Prior nilotinib (yes, no)	–	–	–	–

Abbreviations: ADV, advanced phase/blast phase CML or Ph+ acute lymphocytic leukemia after at least imatinib; CI, confidence interval; CML, chronic myeloid leukemia; CP2L, chronic phase Ph+ CML in 2nd line after imatinib; CP3L, chronic phase Ph+ CML in 3rd line after imatinib and dasatinib and/or nilotinib; ECOG PS, Eastern Cooperative Oncology performance status; N/A, not applicable; OR, odds ratio; Ph+, Philadelphia chromosome–positive; TEAE, treatment-emergent adverse event.

Dashes indicate factors that did not meet the criteria for inclusion in the final model.

[a]The first level is the reference level for interpretation of ORs for categorical characteristics.

immunological changes during treatment do not seem to be the predominant factor.[23] Although nilotinib treatment has been associated with fluid-retention AEs, such as peripheral edema, the incidence of pleural effusion is relatively low (~1-2%).[24]

This study determined age ≥ 65 years, ECOG PS > 0, a history of hyperlipidemia, and a history of cardiac disorders were prognostic risk factors of cardiac AEs and history of vascular disorders to be prognostic of vascular AEs with bosutinib treatment. These results are in keeping with previously identified risk factors for cardiovascular disease in patients with CML.[25] Although the risk of vascular events with bosutinib is relatively low (<10% of patients), the assessment of cardiovascular risk factors is recommended in all TKI-treated patients with CML. Recent studies using real-world data demonstrated that the use of the Systematic Coronary Risk Evaluation (SCORE) assessment before starting TKI treatment could identify patients at high risk of cardiovascular AEs.[26-28] Guidelines for the management of AEs, including cardiovascular AEs, incurred with bosutinib treatment have recently been published.[29]

The current analysis is the longest follow-up safety report of its kind for any second-generation TKI, as little has been reported with other TKIs following imatinib failure, therefore making a comparison with other TKIs difficult. Additionally, a comparison is further complicated by differences in search/reporting criteria and the methodology between clinical trials, particularly in the inclusion/exclusion criteria that affect the baseline characteristics of patients in each study. In a 5-year follow-up in the DASISION study of dasatinib in patients (N = 258) with newly diagnosed CP CML, arterial ischemic events were reported in 5% (n = 12) of patients, with the majority of events occurring in the first year of treatment. Ten patients had cardiovascular events, and two patients had transient ischemic attacks.[20] The dose optimization study (CA180-034) of dasatinib in patients with CP CML resistant or intolerant to prior therapy reported cardiovascular ischemic events in 4% (myocardial infarction, 2%; angina pectoris, 1%; coronary artery disease, 1%) of patients in the 100 mg once daily arm at year 7.[20] In the ENESTnd study of nilotinib in patients with newly diagnosed CP CML, cardiovascular events (ischemic heart disease, ischemic cerebrovascular events, and/or peripheral artery disease) were reported in 7.5%-13.4% of patients at year 5.[24] The cumulative frequency of patients with cardiovascular events increased linearly with time on treatment. Ponatinib, in particular, has been associated with serious cardiac and vascular events, with the US prescribing information warning of potential risk of heart failure, venous thromboembolism, and arterial occlusion.[30] In the 5-year follow-up of the PACE trial of ponatinib in patients with CP CML resistant or intolerant to prior therapy, the cumulative incidence of arterial occlusive events was 31%, with an exposure-adjusted incidence of new arterial occlusive events of 4.9 per 100 patient-years.[31] A meta-analysis determined that there was an increased risk of vascular occlusive events with dasatinib, nilotinib, or ponatinib, but not bosutinib, when compared with imatinib treatment.[32]

The results from the present analysis should be considered in light of its limitations. This analysis was a retrospective study of data from a phase I/II clinical trial designed to assess the safety

and efficacy of bosutinib and therefore was not designed specifically to evaluate cardiac, vascular, hypertension, and effusion TEAEs. Nevertheless, this analysis suggests that the incidence of these TEAEs is low in patients with CML administered long-term bosutinib treatment in the second or later setting. The TEAEs that did occur rarely led to bosutinib discontinuation and could be managed through concomitant medications, dose interruptions, and dose reductions. Despite the infrequency of cardiac, vascular, hypertension, and effusion events with bosutinib treatment, patients receiving TKIs should be screened for potential risk factors of TEAEs, and those considered at high risk should be closely monitored.

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CONFLICT OF INTEREST

JEC received research support to his institution from BMS, Novartis, Pfizer, Sun Pharma, and Takeda and served as a consultant for BMS, Novartis, Pfizer, Takeda, and Fusion. HMK has received honorarium for AbbVie, Actinium, Agios, Amgen, Immunogen, Orsinex, Pfizer, and Takeda, and research funding from AbbVie, Agios, Amgen, Aria, Astrex, BMS, Cyclacel, Daiichi-Sankyo, Immunogen, Jazz Pharma, Novartis, and Pfizer. MJ Mauro was a consultant for Bristol-Myers Squibb. F.A and S.N were employees of Pfizer at the time of the study. E.L is an employee of Pfizer and owns stock in Pfizer. C.G-P provides consultancy to Bristol-Myer Squibb and received honoraria and research support from Pfizer. THB served as a consultant for Novartis, Pfizer, Janssen, Merck, Takeda, and received research funding from Novartis and Pfizer.

DATA AVAILABILITY STATEMENT

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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