CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217729Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	sNDA and NDA
Application Number(s)	NDA 203341/S-025; NDA 217729
Priority or Standard	Priority
Submit Date(s)	March 30, 2023
Received Date(s)	March 30, 2023
PDUFA Goal Date	September 30, 2023
Division/Office	Division of Hematologic Malignancies I, Office of Oncologic Diseases
Review Completion Date	September 22, 2023
Established Name	Bosutinib
Trade Name	BOSULIF
Pharmacologic Class	Tyrosine Kinase Inhibitor
Applicant	PF Prism, C.V.
Formulation(s)	Tablets: 100 mg, 400 mg, 500 mg Capsules: 50 mg, 100 mg
Dosing Regimen	• Pediatric patients with newly-diagnosed chronic phase Ph+ CML: 300 mg/m^2 orally once daily with food. • Pediatric patients with chronic phase Ph+ CML with resistance or intolerance to prior therapy: 400 mg/m^2 orally once daily with food.
Applicant Proposed Indication(s)/Population(s)	Adult and pediatric patients greater than or equal to 1 year of age with: • Newly diagnosed chronic phase Ph+ chronic myelogenous leukemia (CML) • Chronic phase, (b) (4) Ph+ CML with resistance or intolerance to prior therapy
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult and pediatric patients 1 year of age and older with chronic phase Ph+ chronic myelogenous leukemia (CML), newly-diagnosed or resistant or intolerant to prior therapy

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Brad McKenzie, PharmD
Pharmacology/Toxicology Reviewer(s)	Shwu-Luan Lee, PhD
Pharmacology/Toxicology Team Leader(s)	Brenda Gehrke, PhD
Office of Clinical Pharmacology Reviewer(s)	Ritu Chadda, PhD; Robyn Konicki, PharmD
Office of Clinical Pharmacology Team Leader(s)	Ruby Leong, PharmD; Jiang Liu, PhD
Clinical Reviewer	Kamar Godder, MD, MPH
Clinical Team Leader	Lori Ehrlich, MD, PhD
Associate Director for Safety (ADS) - Acting	Shan Pradhan, MD
Statistical Reviewer	Haiyan Chen, PhD; Xin Wang, PhD
Statistical Supervisor	Jonathon Vallejo, PhD
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP
Cross-Disciplinary Team Leader	Lori Ehrlich, MD, PhD
Division Director (OCP/DCPI)	Brian Booth, PhD
Division Director (OOD/DHM1)	R. Angelo de Claro, MD

Additional Reviewers of Application

OPQ	Mustafa Guzel, PhD / Rohit Kolhatkar, PhD / Ramesh Raghavachari, PhD
OPQ	Sherita McLamore, PhD / Shalini Anand, PhD / Rajiv Agarwal, PhD / Kabir Shahjahan, PhD / Min Kang, PhD, Anitha Govada, PhD / Yifan Wang, PhD / Zhaoyang Meng, PhD
RBPM	Chelsea Bostic, PharmD, MBA
RBPM	Dahlia Walters, MS, PMP, FAC-P/PM
SRPM	Stacie Woods, PharmD
OPDP	Valerie Guerrier, PharmD / Jina Kwak, PharmD
OSI	Anthony Orencia, MD
OSE/DEPI	Kate Gelperin, MD / Steven Bird
OSE/DMEPA	Tayler Nalesnik, PharmD / Hina Mehta, PharmD
OSE/DPV	David Kaland, PharmD / Graca Dores, MD / Afrouz Nayernama, PharmD
OSE/DRM	Naomi Boston, PharmD

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OSE/RPM	Candido Alicea, PhD
Other (DMPP/PLT)	Ruth Mayrosh, PharmD / Barbara Fuller, RN, MSN, CWOCN

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AP	accelerated phase
AST	aspartate aminotransferase
AUC	area under concentration-time curve
AUC_{inf}	area under concentration-time curve to infinity
AUC_{last}	area under concentration-time curve to last measured
AUC_{ss}	area under concentration-time curve at steady state
AUC_{t}	area under the concentration-time curve over dosing interval tau
BA/BE	bioavailability/bioequivalence
BBSA	baseline body surface area
BCR-ABL1	breakpoint cluster region protein/Abelson murine leukemia viral oncogene
BID	twice a day
BLA	biologics license application
BLQ	below limit of quantitation
BMD	bone mineral density
BMI	body mass index
BSA	body surface area
C_{avg}	average concentration
CCyR	complete cytogenetic response
CFR	Code of Federal Regulations
CHR	complete hematological response
CIOMS	Council for International Organizations of Medical Sciences
c-KIT	proto-oncogene encoding receptor tyrosine kinase KIT (also known as CD117)
CL	clearance
CL/F	apparent clearance of drug
C_{max}	maximum observed concentration
CMC	chemistry, manufacturing, and controls
CML	chronic myelogenous leukemia

Abbreviation	Definition
COA	clinical outcome assessment
COG	Children's Oncology Group
COVID-19	coronavirus disease 2019
CP	chronic phase
CP2L	chronic phase 2nd line
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	predose concentration
CTX	Type I collagen
CYP3A	Cytochrome P450 3A
DBP	diastolic blood pressure
DCT	data collection tools
DEXA	Dual-energy X-ray absorptiometry
DLT	dose limiting toxicity
ECG	electrocardiogram
EFS	event free survival
EMA	European Medicines Agency
E-R	exposure response
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
GOF	goodness of fit
HSCT	hematopoietic stem cell transplant
ICH	International Conference on Harmonization
IEC	independent ethics committee
IGF	insulin growth factor
IIV	inter-individual variability
IRB	institutional review board
ISO	International Organization for Standardization
ITT	intent to treat
k_a	first-order absorption rate constant
KM	Kaplan-Meier
LH	luteinizing hormone
LLOQ	lower limit of quantitation
LPFV	last patient first visit

Abbreviation	Definition
LS	lumbar spine
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMR	mixed model regression
MR[number]	molecular response ≥[number]-log reduction from standardized baseline
MRD	minimal residual disease
NCA	non-compartmental analysis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
ND	newly diagnosed
NDA	new drug application
NME	new molecular entity
OS	overall survival
OSI	Office of Scientific Investigation
PCyR	partial cytogenetic response
PD	pharmacodynamics
PDGF-R	platelet-derived growth factor
PedsQL	Pediatric quality of life
Ph+	Philadelphia chromosome positive
PI	prescribing information
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPK	population pharmacokinetics
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
PWR	pediatric written request
QD	once daily
QT	QT interval
QTcB	QTc corrected using Bazett formula
QTcF	QTc corrected using Fridericia formula
REMS	risk evaluation and mitigation strategy

Abbreviation	Definition
R/I	resistant or intolerant
RP2D	recommended phase 2 dose
RP2DND	recommended phase 2 dose newly diagnosed
RP2DR/I	recommended phase 2 dose resistant or intolerant
RSE	Relative standard error
SAE	serious adverse event
SAP	statistical analysis plan
sNDA	supplementary NDA
SOC	System Organ Class
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
$t_{1/2}$	time to half C_{max}
T_{lag}	lag time (time prior to the time corresponding to the first quantifiable concentration)
T_{max}	time to first occurrence of C_{max}
TSH	thyroid-stimulating hormone
UK	United Kingdom
USPI	United States Prescribing Information
VPC	Visual predictive check
Vz/F	apparent volume of distribution for extravascular dosing
V/F	apparent volume of distribution
WR	written response

1 Executive Summary

1.1. Product Introduction

Established Name:	Bosutinib
Trade Name:	Bosulif
Dosage Forms:	Tablets (100 mg, 400 mg, and 500 mg), Capsules (50 mg, 100 mg)
Chemical Class:	Small molecule
Therapeutic Class:	Tyrosine kinase inhibitor
Mechanism of Action:	Inhibitor of BCR-ABL kinase

Bosutinib is currently approved for the treatment of adults patients with:

- Newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML).
- Chronic phase, accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance (R/I) to prior therapy.

The Applicant now submits a supplementary New Drug Application (sNDA) to support an indication for the treatment of pediatric patients 1 year and older with newly diagnosed chronic phase CML and chronic phase, (b) (4) CML with resistance or intolerance to prior therapy. The trial to support the pediatric indication was conducted under a pediatric written request, and the submission includes a request for evaluation of fulfillment of the written request. Concurrently, a new NDA was submitted to support the approval of the pediatric formulation, capsules which can be opened and administered in applesauce or yogurt.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of bosutinib for the treatment of pediatric patients age 1 year and older with chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML), newly-diagnosed or resistant or intolerant to prior therapy. The recommendation is based on the MCyR and MMR with durability of responses in Study BCHILD.

The efficacy of bosutinib has been established in an ongoing, open-label, single arm studies in pediatric patients with Ph+ CML in chronic phase, both newly diagnosed and refractory or intolerant to prior therapy. The efficacy endpoints evaluated were major cytogenetic response (MCyR, defined as complete cytogenetic response with absence of Ph+ metaphases or partial cytogenetic response of 1% to 35% Ph+ metaphases) and major molecular response (MMR; defined as ≤0.1% BCR-ABL ratio on international scale [IS]) rate, and duration of responses.

Of the 28 patients with CP Ph+ CML resistant or intolerant to prior TKI, 23 patients (82%) achieved MCyR and 14 patients (50%) achieved MMR. The median duration of response was not reached with a median duration of follow up of 23.2 months. Two patients who achieved MMR lost response at 13.6 months and 24.7 months on treatment. Of the 21 patients with newly diagnosed CP Ph+ CML, 16 patients (76%) achieved MCyR and 6 patients (29%) achieved MMR. Median duration of response was not reached with a median duration of follow up of 14.2 months. The magnitude of the achieved rates of MMR and the durability of the responses support the establishment of efficacy of nilotinib treatment in pediatric patients with Ph+ CML-CP.

(b) (4)

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

CML in childhood is rare, accounting for fewer than 3% of all pediatric leukemias, with an approximate annual incidence of 1 per million children. Over 90% of children with the clinical features of CML carry the characteristic t(9;22) translocation resulting in the BCR-ABL1 fusion oncogene. Approximately 95% of pediatric patients present with CML in chronic phase. Adults with CML have the same molecular driver mutation and share a similar natural history with the majority of adult patients with CML also present in chronic phase. Three BCR-ABL tyrosine kinase inhibitors (TKIs) are currently approved for use in children with CP CML: the first generation TKI imatinib and the second-generation TKIs, nilotinib and dasatinib. Despite available therapies, some patients become resistant or intolerant to these drugs. Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative option for pediatric patients with CML, which raises the question of the role of transplantation in the era of chronic treatment with TKI therapy. Additionally, pediatric patients have a long life expectancy and the risks with long-term TKI therapy need to be considered. Therefore, the collective evidence supports the need for alternative treatment options and clinical studies in pediatric patients with CML.

The benefit-risk assessment supports regular approval of bosutinib for the treatment pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase resistant or intolerant to prior tyrosine-kinase inhibitor therapy and newly diagnosed Ph+ CML in chronic phase (CP).

The efficacy of bosutinib has been established in an ongoing, open-label, single arm study (Study BCHILD) in pediatric patients with Ph+ CML in chronic phase, both newly diagnosed and refractory or intolerant to prior therapy. The study was conducted in 2 parts: phase 1 dose escalation which evaluated doses of 300 mg/m^2, 350 mg/m^2, and 400 mg/m^2 in patients with R/I CP CML; and phase 2 which evaluated a dose of 300 mg/m2. The primary endpoints of both parts of the study were safety and PK. Efficacy endpoints were secondary endpoints and presented descriptively, and efficacy in the pediatric population was established based on the major cytogenetic response (MCyR, defined as complete cytogenetic response with absence of Ph+ metaphases or partial cytogenetic response of 1% to 35% Ph+ metaphases) and major molecular response (MMR; defined as ≤0.1% BCR-ABL ratio on international scale [IS]) rate, and duration of responses.

In the R/I cohort of 28 patients, MCyR was achieved or maintained at any time by 100%, 90.9%, and 63.6% of patients in the 300, 350, and 400 mg/m^2 cohorts, respectively, with an overall MCyR rate of 82.1%. MMR was achieved at any time by 66.7%, 45.5%, and 45.5% of patients in the 300, 350, and 400 mg/m^2 cohorts, respectively, with an overall MMR rate of 50.0% in this population. Two of 14 patients who achieved MMR had a loss of MMR after 13.6 and 24.7 months on treatment. In the ND cohort of 21 patients, MCyR was achieved at any time by 76.2% of patients, and MMR was achieved by 28.6% of patients. No patients lost response with a median duration of follow-up of 14.2 months.

The safety profile of bosutinib was evaluated in 49 pediatric patients treated on Study BCHILD. Most AEs were manageable with dose reductions and dose interruptions or supportive measures. Common adverse reactions observed in ≥20% of pediatric patients were diarrhea (82%), abdominal pain (73%), vomiting (55%), nausea (49%), rash (49%), fatigue (37%), hepatic dysfunction (37%), headache (35%), pyrexia (31%), decreased appetite (27%), and constipation (20%). The most common laboratory abnormalities that worsened from baseline in ≥40% of pediatric patients were creatinine increased (92%), alanine aminotransferase increased (59%), white blood cell count decreased (53%), aspartate aminotransferase increased (51%), platelet count decreased (49%), and glucose increased (41%). No new safety signals were identified in pediatric participants compared to the known safety profile in adults, and although not all adverse reactions were observed in children, the same warnings and precautions for adult patients should also be considered for pediatric patients.

The PK evaluation did not demonstrate equivalent PK between adults and children with lower C_{trough} observed in pediatric patients; (b) (4) However, the submitted pediatric data supports a dose of 300 mg/m^2 in pediatric patients with ND CP CML, and 400 mg/m^2 in patients with R/I CP CML.

The conclusion for substantial evidence of effectiveness is provided by the durable major molecular response rate of 50% and 29% in pediatric patients with resistant or intolerant Ph+ CML-CP and newly diagnosed Ph+ CML-CP, respectively. The safety profile is similar to the known profile in adult patients and was demonstrated to be tolerable and manageable in pediatric patients. Overall, the risk-benefit assessment of bosutinib is favorable for the treatment pediatric patients with Ph+ CML in chronic phase.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric participants with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) account for 3% of newly diagnosed pediatric leukemias, with an annual incidence of 1 case per million in children younger than 15 years of age and 2.2 cases per million in adolescents between 15 and 19 years of age.	Chronic myeloid leukemia in pediatric participants is a rare, but serious and life-threatening disease.
Current Treatment Options	• A first generation TKI of imatinib or second generation TKI of dasatinib or nilotinib is the recommended first-line therapy and are FDA approved for pediatric participants with Ph+ CML in chronic phase (CP). These therapies are intended to be given as life-long therapy. • Up to 40% of participants discontinue imatinib, dasatinib or nilotinib due to intolerance, declining response, or progressive disease. Moreover, nilotinib requires twice daily dosing on an empty stomach, which is less practical for children. • Allogeneic hematopoietic stem cell transplantation is the only curative treatment option available for pediatric participants with Ph+ CML in chronic phase but may be associated with long term sequel.	The optimal treatment strategy for pediatric participants with Ph+ CML in chronic phase remains uncertain. Expanding treatment options are needed for pediatric participants with Ph+ CML.
Benefit	• Study ITCC-054 (BCHILD) is an ongoing, open-label, single-arm study of bosutinib in pediatric participants with resistant or intolerant Ph+ CML in chronic phase and newly diagnosed Ph+ CML in chronic phase. • In Phase 1, 28 patients with R/I CP CML were treated with doses of 300 mg/m^2, 350 mg/m^2, and 400 mg/m^2 and achieved MCyR in 82.1% (95% CI: 63.1, 93.9) and MMR in 50.0% (95% CI: 30.6, 69.4). MR4.5 was achieved in 17.9% (95% CI: 6.1, 36.9). Two patients who achieved MMR lost response after 13.6 months and 24.7 months on	Bosutinib is effective in treating pediatric participants with Ph+ CML in chronic phase. The magnitude and duration of major molecular response are clinically meaningful.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment. • In Phase 2, 21 patients with ND CP CML were treated with 300 mg/m^2 of bosutinib and achieved MCyR in 76.2% (95% CI: 52.8, 91.8) and MMR in 28.6% (95% CI: 11.3, 52.3). At the time of data cutoff, no patients had lost response with a median duration of follow-up of 14.2 months (range: 1.1, 26.3 months).	
Risk and Risk Management	• Common adverse reactions observed in ≥20% of pediatric patients were diarrhea (82%), abdominal pain (73%), vomiting (55%), nausea (49%), rash (49%), fatigue (37%), hepatic dysfunction (37%), headache (35%), pyrexia (31%), decreased appetite (27%), and constipation (20%). • The most common adverse reactions in greater than 10% of participants include diarrhea, abdominal pain, vomiting, nausea, rash, fatigue, hepatic dysfunction, headache, pyrexia, decreased appetite, and constipation. • The most common laboratory abnormalities that worsened from baseline in ≥40% of pediatric patients were creatinine increased, alanine aminotransferase increased, white blood cell count decreased, aspartate aminotransferase increased, platelet count decreased, and glucose increased. • The most common Grade 3-4 adverse reactions include hepatic dysfunction and diarrhea; and Grade 3-4 laboratory abnormalities include platelet count deceased, ALT increased, and neutrophil count decreased. • The frequency of Grade 3-4 toxicity in pediatric patients was similar to that in adults.	Overall, the safety profile in pediatric participants is consistent with the safety profile in adult participants. The safety profile of bosutinib in pediatric participants is tolerable and manageable. Long-term safety information is needed in the pediatric population since bosutinib is intended for prolonged use and there is potential cumulative toxicity and effects on growth and development. The risk associated with bosutinib in pediatric participants can be adequately addressed with labeling. Labeling includes warnings and precautions, along with instruction for monitoring and dose modification, or discontinuation for toxicity. Additional information on growth and development will be accumulated with a longer follow-up.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The proposed labeling includes warnings and precautions for gastrointestinal toxicity, myelosuppression, hepatic toxicity, cardiovascular toxicity, fluid retention, renal toxicity, and embryo-fetal toxicity.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include: PedsQL questionnaire to assess gastro-intestinal toxicity and palatability questionnaire.				Section where discussed, if applicable 8.1.2 Efficacy Results – Secondary or exploratory COA (PRO) endpoints
	☐	Clinical outcome assessment (COA) data, such as			
			x	Patient reported outcome (PRO)	8.1.2 Efficacy Results – Secondary or exploratory COA (PRO) endpoints
			☐	Observer reported outcome (ObsRO)	
			☐	Clinician reported outcome (ClinRO)	
			☐	Performance outcome (PerfO)	
	☐	Qualitative studies (eg, individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc)			
	☐	Patient-focused drug development or other stakeholder meeting summary reports			[eg, Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data			
	☐	Natural history studies			
	☐	Patient preference studies (eg, submitted studies or scientific publications)			
	☐	Other: (Please specify)			
☐	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Lori Ehrlich, MD, PhD
Cross-Disciplinary Team Leader

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:
CML is a clonal myeloid neoplasm that originates from the translocation t(9;22)(q34;q11), the consequence of which is the generation of the Ph chromosome. The molecular product of the t(9;22) translocation is the BCR-ABL1 oncogene, which encodes the constitutively activated bcr-abl 1 kinase that activates several downstream signaling pathways that mediate myeloproliferation, resistance to apoptosis and genetic instability[1].

CML in childhood is relatively rare, accounting for fewer than 3% of all pediatric leukemias, with an approximate annual incidence of 1 per million children[2]. As in adults with CML, over 90% of children with the clinical features of CML carry the characteristic t(9;22) translocation resulting in the BCR-ABL1 fusion oncogene[1]. The natural history of CML in children is not significantly different from that of adults with CML, although published studies are small[1]. In the era before TKI therapy, HSCT was the standard of care for children with CML, with 3- to 5-year EFS rates ranging from 61 to 63% in children receiving matched sibling donor transplants, and from 27 to 55% for children receiving transplants from matched unrelated donors[3]. The advent of therapies targeting the bcr-abl fusion protein, such as imatinib and other TKIs, have dramatically improved outcomes in adults and children with CML, and have become the new standard of care[4].

The FDA's Assessment:
FDA agrees with the Applicant's analysis of condition. CML in children is a rare and serious disease and its molecular features and natural history are similar to that of adults. BCR-ABL TKIs have improved the outcomes and can be considered standard of care for pediatric patients with chronic phase CML.

2.2. Analysis of Current Treatment Options

The Applicant's Position:
Current treatment options for pediatric patients with ND or R/I CML are presented in Table 1. Current international guidelines recommend a similar strategy to that in adults for the choice of the TKI in the initiation or continuation of treatment of CML in children. Choice of TKI is determined by multiple factors including tolerability, CML mutation status, and formulation[5, 6]. Imatinib has improved the prognosis for many patients with CML worldwide. However, inability to achieve a cytogenetic remission, loss of a CCyR, and intolerance are significant problems with imatinib. As a result, second-generation TKIs have been developed[7]. Despite the success of imatinib and the approved second-generation TKIs nilotinib and dasatinib that are available to

children, some patients are intolerant to these drugs or have disease that progresses despite therapy. In children, a TKI is considered to be the preferred first-line therapy for CML. With the approval of dasatinib some pediatric oncologists may favor this drug due to its good tolerability profile, the rapid deep response, and the availability of an oral solution. The other 2nd generation TKI, nilotinib, has the slight disadvantage that it may need to be taken twice daily and requires fasting, which is unpractical for children. Nevertheless, when certain resistance mutations are present the choice of TKI needs to be based on the sensitivity profile of that particular mutation[8, 9].

For children whose disease fails or progresses or who are intolerant of imatinib, there are presently 4 treatment options: 1) increase the dose of imatinib (if not intolerant); 2) change to another TKI; 3) allogeneic HSCT; or 4) treatment with other established drugs for CML, such as interferon-α or hydroxyurea[4]. In practice, most patients now switch to second line therapy if the response criteria as defined by European Leukemia Net are not met[10]. HSCT, while the only potentially curative approach, is now considered a third-line therapy following imatinib failure/other TKI-failure in children. Identification of an optimally HLA-matched stem cell donor is not possible for many patients. Although safer than in adult patients, the acute and chronic morbidity and mortality associated with HSCT and its most recognized complication, graft versus host disease, remains formidable. In addition, for those patients with advanced phase CML who plan to undergo HSCT, there is evidence to suggest that in patients who fail imatinib, achieving a second chronic phase with another TKI prior to undergoing HSCT may confer a better outcome[4].

Imatinib may be the preferred first-line therapy in children with CML due to the largest experience in this setting of patients since its approval in 2003. In March 2018 nilotinib was approved by FDA and EMA for paediatric patients. Safety and efficacy data with other TKIs in the pediatric CML population are limited. Dasatinib is the best studied second generation TKI, approved for pediatric indication in November 2017[9, 11, 12, 13]. Side effects of imatinib in children occur with the same or lower frequency and tend to be less severe than in adults[14, 15]. Frequent side effects include myelosuppression, nausea, fluid retention, muscle cramps, bone pain, skin rash, diarrhea, lethargy, and weight gain. Dasatinib seems to be better tolerated in children than in adults[16, 17]. Of note, there is preclinical and clinical evidence that long-term exposure to imatinib results in growth impairment and dysregulation of bone metabolism. Prepubertal children seem to be at greatest risk, with impaired bone remodeling resulting in growth retardation or arrest and a significant reduction in height[7, 18]. The mechanism of impaired growth may be related to “off-target” TKI inhibition, such as inhibition of c-KIT and PDGF-R, and/or the development of an acquired growth hormone deficiency[3, 10, 19]. Recently data on growth in pediatric patients treated with dasatinib showed that, although BMI and bone densitometry in ND and R/I patients seemed to be only minimally impacted by dasatinib, growth velocity was clearly altered especially in prepubertal ND patients[2]. The optimal approach to management of this side effect has not yet been established. No data on this

toxicity are currently available for other TKIs. Preclinical data indicated that this toxicity may not be observed or less prominent with bosutinib[20].

Ease of administration is an important challenge in children, and strongly influences compliance to therapy. Bosutinib is administered once a day and with food. Apart from data on growth there are emerging data on long-term safety with some second generation TKIs including liver function abnormalities, pulmonary toxicity or vascular events which may drive selection of a TKI with the best long-term safety profile for children. In this regard, bosutinib showed a better profile in terms of musculoskeletal symptoms (less cramps and myalgia reported) and vascular toxicity, more similar to imatinib than to nilotinib in adult CML. On the contrary, more gastro-intestinal side-effects are reported in adults during the initial phase of therapy with bosutinib[21, 22, 23]. Therefore, there is a continued unmet medical need for pediatric CML patients, with an urgent need for new treatment options that[24] improve efficacy and/or have improved short- and long-term safety profile combined with ease to administer the drug for patients who are resistant or intolerant to currently available TKIs and for newly diagnosed patients.

Table 1. Applicant - Summary of Treatment Options Relevant to the Proposed Indication

Product(s) Name Approval Year Relevant Indication Dosing/Administration	Efficacy Information	Safety Information (Most Common Adverse Reactions)
GLEEVEC® (Imatinib) 2002 Children with newly diagnosed Ph+ CML in chronic phase 340 mg/m^2/day, once daily or split into 2 portions	Newly-diagnosed CML: - CHR at 8 weeks: 78% - CCyR at any time: 65%, median time to CCyR 6.74 months - PCyR at any time: 16% CML after stem cell transplant or resistant to interferon-alpha: - MCyR: 4 of 13 participants - CCyR: 7 of 13 participants - Minimal CyR: 2 of 13 participants	Most common ADRs in pediatric patients include hematologic toxicity, nausea, vomiting, rash, fatigue.
TASIGNA® (Nilotinib) 2010 Pediatric patients ≥1 year of age with newly diagnosed CP Ph+ CML or CP and AP Ph+ CML with resistance or intolerance to prior TKI therapy 230 mg/m^2 twice daily, fasted for at least 2 hours	Newly-diagnosed CML: - Cumulative MMR: 64.0% by 12 cycles; 68.0% by 24 cycles; 76.0% by 66 cycles - Cumulative MR4.5: 44% by 66 Cycles Median time (range) in months to MMR: 5.6 (2.7, 16.6) Prior Imatinib or Dasatinib: - Cumulative MMR: 47.7% by 12 cycles; 57.6% by 24 cycles; 60.6% by 66 cycles - Cumulative MR4.5: 12.1% by 66 Cycles Median time (range) in months to MMR: 60.5 (0.7, 63.5)	Most common ADRs in pediatric patients include hematologic toxicity, hyperbilirubinemia, ALT and AST increased, rash, pyrexia, nausea, vomiting, diarrhea.

Table 1. Applicant - Summary of Treatment Options Relevant to the Proposed Indication

Product(s) Name Approval Year Relevant Indication Dosing/Administration	Efficacy Information	Safety Information (Most Common Adverse Reactions)
SPRYCEL® (Dasatinib) 2010 Pediatric patients 1 year of age and older with Ph+ CML in chronic phase. 40-100 mg/day, once daily with or without food	<u>Newly diagnosed CML:</u> - CCyR (95% CI): 43.1% (29.3, 57.8) at 3 months; 66.7% (52.1, 79.2) at 6 months; 96.1% (86.5, 99.5) at 12 and 24 months - MCyR (95% CI): 60.8% (46.1, 74.2) at 3 months; 90.2% (78.6, 96.7) at 6 months; 98.0% (89.6, 100) at 12 and 24 months - MMR (95% CI): 7.8% (2.2, 18.9) at 3 months; 31.4% (19.1, 45.9) at 6 months; 56.9% (42.2, 70.7) at 12 months, 74.5% (60.4, 85.7) at 24 months Median time (95% CI) in months to MCyR, CCyR, MMR, respectively: 3.0 (2.8, 4.3), 5.5 (3.0, 5.7), 8.3 (5.0, 11.8) <u>Prior Imatinib:</u> - CCyR (95% CI): 45.7% (30.9, 61.0) at 3 months; 71.7% (56.5, 84.0) at 6 months; 78.3% (63.6, 89.1) at 12 months - MCyR (95% CI): 60.9% (45.4, 74.9) at 3 months; 82.6% (68.6, 92.2) at 6 months; 89.1% (76.4, 96.4) at 12 months - MMR (95% CI): 15.2% (6.3, 28.9) at 3 months; 26.1% (14.3, 41.1) at 6 months; 39.1% (25.1, 54.6) at 12 months Median time (95% CI) in months to MCyR, CCyR, MMR, respectively: 2.9 (2.8, 3.5), 3.3 (2.8, 4.7), 8.3 (5.0, 11.8)	Most common ADRs in pediatric patients include hematologic toxicity, hyperbilirubinemia, headache, nausea, diarrhea, rash, vomiting.
Gleevec USPI; Tasigna USPI; Sprycel USPI		

The FDA's Assessment:
The FDA agrees with the summary of current treatment options. HSCT is commonly considered a third-line option after failure of two prior TKIs. Moreover, in participants with progressive disease, achieving a second chronic phase with another TKI prior to undergoing HSCT may confer a better outcome. However, the identification of an optimal stem cell donor is not currently considered a limitation to HSCT, and the mortality rate had decreased significantly, but long-term morbidity remains the major challenge with HSCT.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Bosulif was first approved on 04 September 2012 in the US for the treatment of adult patients with CP, AP, or BP Ph+ CML with resistance or intolerance to prior TKI therapy; subsequently bosutinib was granted conditional approval in the EU on 27 March 2013. On 19 December 2017, Bosulif received accelerated approval for the treatment of adult patients with newly diagnosed CP Ph+ CML and as part of PMR 3317-1, was converted to regular approval based on the submission of 5-year data from Study B1871053 on 14 May 2021. The same indication was approved in the EU in April 2018. Bosutinib has received marketing authorization in over 50 countries and is currently marketed in 43 countries.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the marketing history.

3.2. Summary of Presubmission/Submission Regulatory Activity

Key interactions held with the FDA regarding the bosutinib PWR and the related studies are summarized in Table 2.

Table 2. Applicant - Key US Regulatory Activities

Date (s)	Meeting Type	Description
30 July 2015	N/A	Initial PWR issued with reference to age-appropriate formulation
14 October 2015	N/A	PWR Amendment 1 removed the reference to needing efficacy studies – addition noted that adequately powered efficacy studies in children are not necessary since efficacy of bosutinib in CML can be extrapolated from the adult experience. In addition, the small population of pediatric participants with CML who develop resistance to or who are intolerant of other TKI therapy would make efficacy studies infeasible.
08 August 2019	Type A, guidance	In response to FDA's 05 June 2019 feedback on the Pfizer proposed amendment to WR dated, 22 February 2019, at this meeting, obtained feedback on SAP; FDA recommended to conduct Bayesian analysis for the ND patients. Per FDA suggestion, Pfizer agreed to submit revised protocol/SAP.
30 October 2019	N/A	PWR Amendment 2 issued. Phase 2 portion of the BCHILD study was expanded to include ND Ph+ CP CML participants with agreed starting dose of 300 mg/m^2 selected based on Phase 1 dose escalation in R/I participants) and the Phase 2 primary endpoint included population PK parameters evaluation for bosutinib based on combined PK data from Phase 1 and 2. As part of Amendment 2, based on formulation development, oral capsules of size 2 (b) (4) and tablets were nominated as age-appropriate formulation. Timeline for submission of study reports changed from 21 January 2021 to 20 December 2022.
02 June 2020	Type C, guidance	FDA recommended to evaluate the lower dose (100 mg) film-coated tablets in Study B1871061 that demonstrated bioequivalence between the age-appropriate capsule and the approved film-coated tablet under fed conditions. In addition, FDA recommended to characterize the relative bioavailability under fasted conditions. FDA also recommended an in vivo relative bioavailability study to test the soft foods intended for inclusion in the label.
20 January 2022	Type C, pre-sNDA	FDA agreed to Pfizer's proposal to reduce the pediatric patient number from 60 to 45 in the PWR. Amendment 3 of the PWR issued on 01 July 2022.
09 May 2022	Type C, CMC	FDA agreed to Pfizer's proposal to include limited Quality information in the sNDA in Module 2 to allow for the sNDA review, independent of the new NDA 217729 review. For NDA 217729 FDA agreed to 1) cross reference to the approved application for drug substance 2) proposed validation strategy, and 3) proposed shelf-life.

Table 2. Applicant - Key US Regulatory Activities

Date (s)	Meeting Type	Description
11 October 2022	Type B, pre-sNDA and NDA	Review Division amenable to proposed revised submission strategy of 1 sNDA with both ND/RI indications if the extension is granted and an alternate submission strategy with complete data from 45 ND and R/I pediatric participants with DLT table for the 10th R/I participant by 20 Dec 2022, if FDA declines to extend the submission due date, subject to due date extension and application review. FDA agreed to Pfizer's approach to propose only the 50 and 100 mg capsules in the draft labeling.
26 October 2022	N/A	FDA issued PWR amendment 4 and extended the PWR report submission due date from 20 December 2022 to 11 September 2024.

The FDA's Assessment:

FDA agrees with the Applicant's summary of regulatory interactions. The pediatric study was the subject of a pediatric written request (PWR). This sNDA to include pediatric data in labeling and the NDA for the capsule formulation were submitted in response to the PWR. See Section 10 for additional information on the PWR.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Onsite clinical inspections were not requested for this Application. Each clinical site enrolled few patients and there did not appear to be any sites that overly influenced the efficacy or safety evaluations. In lieu of site inspections, OSI conducted an inspection of the Applicant (Pfizer, PF PRISM CV) with a focus on the Applicant's monitoring and oversight of the Utrecht, Netherlands site. Site monitoring reports for this site were found to be adequate. OSI also conducted a limited remote regulatory assessment (RRA) of Erasmus MC which was the study sponsor and protocol author. The study was co-sponsored by the Children's Oncology Group for the US sites and the protocol co-author. Pfizer confirmed that there was no data monitoring committee for the study.

Based on the Pfizer inspection and the limited clinical investigator RRA results from Erasmus MC, the study appears to have been conducted adequately and the data are considered reliable. The data from Study ITCC-054/AAML1921 submitted to the Agency for assessment appear acceptable in support of the proposed indication.

4.2. Product Quality

From the Executive Summary of the OPQ review:
OPQ recommends APPROVAL of NDA 217729 for the commercialization of bosutinib 50 mg and 100 mg capsules. Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

4.3. Clinical Microbiology

No microbiology assessment was requested.

4.4. Devices and Companion Diagnostic Issues

The cytogenetic and molecular diagnostic tools for assessment of the Philadelphia chromosome translocation and BCR::ABL fusion gene are commercially available.

5. Nonclinical Pharmacology/Toxicology

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA concurs with the Applicant's statement that no new pharmacology/toxicology data for bosutinib were submitted to the current supplement for NDA 203341 or to NDA 217729. A separate Pharmacology/Toxicology review for the safety assessment of the bosutinib capsule drug product has been documented under NDA 217729.

6. Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Bosutinib is an oral Src-Abl tyrosine kinase inhibitor (TKI) approved for the treatment of adult patients with newly diagnosed (ND) Philadelphia chromosome positive (Ph+) CML as well as chronic phase (CP), accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance (R/I) to prior therapy. The Applicant is seeking approval of bosutinib for the treatment of pediatric patients 1 year of age and older with ND Ph+ CP CML or with R/I Ph+ CML in CP (b) (4) The proposed dosage is 300 mg/m^2 once daily (QD) with food in ND pediatric patients, and 400 mg/m^2 QD with food in R/I pediatric patients for the age-appropriate capsule formulation (supportive data for the age-appropriate capsule formulation was submitted under Original NDA 217729). The proposed dosing in the pediatric population is based on body surface area (BSA) and the Applicant has proposed the use of dose banding (using available strengths of capsules or tablets) to simplify instructions for administration to pediatric patients.

Study BCHILD was a Phase 1/2, single-arm trial conducted to evaluate the pharmacokinetics (PK), safety, tolerability, and efficacy of bosutinib in pediatric patients 1 year of age and older with ND or R/I CP Ph+ CML. In 21 pediatric patients with ND CP Ph+ CML, a complete cytogenetic response (CCyR) of 71% and a major molecular response (MMR) of 29% were observed with a minimum follow-up of 11 months. In 28 pediatric patients who received prior TKI therapy, a CCyR of 79% and MMR of 50% were observed with a minimum follow-up of 14 months. Refer to Section 8.1 for detailed efficacy assessment. The overall safety profile of bosutinib in pediatric patients was consistent with that established in adult patients with ND CML or R/I CML.

The key review questions focused on the appropriateness of the proposed dosing regimen of 300 mg/m^2 for ND and 400 mg/m^2 for R/I pediatric patients with Ph+ CML, the proposed BSA dose banding, and the bioavailability/bioequivalence (BA/BE) studies to support the age-appropriate capsule formulation and administration of opened capsules with applesauce or yogurt.

(b) (4)

The bosutinib population PK (PPK) model was determined to be inadequate for the purpose of characterizing PK in pediatric patients with CML. Therefore, PK assessment conclusions are

based on exposure in patients in Study BCHILD from noncompartmental analysis (NCA). (b) (4)

The approval and benefit/risk assessment are therefore primarily based on the clinical efficacy and safety data from Study BCHILD.

Across pediatric patients aged 1 year and older, PK assessment supports the proposed BSA-based dose banding with the proposed dosage of 300 mg/m^2 QD with food for ND Ph+ CP CML and 400 mg/m^2 QD with food for R/I Ph+ CP CML in pediatric patients aged 1 year and older. No significant differences in dose-normalized exposure were observed across BSA or age in Study BCHILD. The proposed dose increase by 50 mg increments up to a maximum of 100 mg above starting dose (BSA <1.1 m^2) or 100 mg increments up to a maximum of 600 mg QD (BSA ≥1.1 m^2) in pediatric patients with insufficient response after 3 months is also acceptable.

Additional clinical pharmacology studies were conducted in healthy adults to support the bridging of the age-appropriate capsule formulation to the approved immediate-release film-coated tablet and to support characterization of the food and vehicle effect on bosutinib PK for the new age-appropriate capsule formulation.

Overall (b) (4) clinical data provide sufficient evidence of efficacy in pediatric patients. The Applicant's proposed dosing regimen of 300 mg/m^2 for ND and 400 mg/m^2 for R/I pediatric patients with CP Ph+ CML and the proposed BSA dose banding are acceptable. The capsule formulation is bioequivalent to the tablet and the capsule should be administered with food. In patients unable to swallow capsules, the capsule can be opened, and the contents can be sprinkled in applesauce or yogurt for administration.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in the submitted efficacy supplement and it is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below.

<table>
<tr><th>Review Issues</th><th>Recommendations and Comments</th></tr>
<tr><td>Evidence of effectiveness</td><td>Study BCHILD: A Phase 1/2, single-arm trial was conducted to evaluate the PK, safety, tolerability, and efficacy of bosutinib in pediatric patients 1 year of age and older with ND or R/I CP Ph+ CML.</td></tr>
<tr><td>General Dosing instructions</td><td>The recommended dosage of bosutinib is 300 mg/m^2 for ND and 400 mg/m^2 for R/I pediatric patients with Ph+ CML with the proposed BSA dose banding:

Table 3. Dosing of BOSULIF for Pediatric Patients with Newly Diagnosed CP Ph+ CML or with CP Ph+ CML with Resistance or Intolerance to Prior Therapy
<table>
<tr><th>BSA[1]</th><th>Newly Diagnosed Recommended Dose (Once Daily)</th><th>Resistant or Intolerant Recommended Dose (Once Daily)</th></tr>
<tr><td>< 0.55 m^2</td><td>150 mg</td><td>200 mg</td></tr>
<tr><td>0.55 to < 0.63 m^2</td><td>200 mg</td><td>250 mg</td></tr>
<tr><td>0.63 to < 0.75 m^2</td><td>200 mg</td><td>300 mg</td></tr>
<tr><td>0.75 to < 0.9 m^2</td><td>250 mg</td><td>350 mg</td></tr>
<tr><td>0.9 to < 1.1 m^2</td><td>300 mg</td><td>400 mg</td></tr>
<tr><td>≥ 1.1 m^2</td><td>400 mg*</td><td>500 mg*</td></tr>
</table>
* maximum starting dose (corresponding to maximum starting dose in adult indication)
[1] BSA=Body Surface Area

Source: Applicant's proposed USPI</td></tr>
</table>

<table>
<tr><th>Review Issues</th><th>Recommendations and Comments</th></tr>
<tr><td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td><td>The recommended dosage with renal and hepatic impairment in pediatric patients is based on the effects of renal and hepatic impairment on exposure in adults. The recommended dosage modifications for pediatric patients with renal or hepatic impairment are presented in Table 4.
Table 4. Dosage Adjustments for Renal and Hepatic Impairment in Pediatric Patients
<table>
<tr><th></th><th colspan="3">Newly Diagnosed CP Ph+ CML Recommended Starting Dose (Once Daily) By Organ Function</th></tr>
<tr><th>Pediatric Patients by Separated BSA[1] Band</th><th>Renal Impairment: Creatinine clearance 30 to 50 mL/min</th><th>Renal Impairment: Creatinine clearance less than 30 mL/min</th><th>Hepatic Impairment: Mild (Child-Pugh A), Moderate (Child-Pugh B) or Severe (Child-Pugh C)</th></tr>
<tr><td>Pediatric < 0.55 m^2</td><td>100 mg</td><td>100 mg</td><td>100 mg</td></tr>
<tr><td>Pediatric 0.55 to < 0.63 m^2</td><td>150 mg</td><td>100 mg</td><td>100 mg</td></tr>
<tr><td>Pediatric 0.63 to < 0.75 m^2</td><td>150 mg</td><td>100 mg</td><td>100 mg</td></tr>
<tr><td>Pediatric 0.75 to < 0.9 m^2</td><td>200 mg</td><td>150 mg</td><td>100 mg</td></tr>
<tr><td>Pediatric 0.9 to < 1.1 m^2</td><td>200 mg</td><td>200 mg</td><td>150 mg</td></tr>
<tr><td>Pediatric ≥ 1.1 m^2</td><td>300 mg</td><td>200 mg</td><td>200 mg</td></tr>
<tr><th></th><th colspan="3">CP Ph+ CML with Resistance or Intolerance to Prior Therapy Recommended Starting Dose (Once Daily) By Organ Function</th></tr>
<tr><th>Pediatric Patients by Separated BSA[1] Band</th><th>Renal Impairment: Creatinine clearance 30 to 50 mL/min</th><th>Renal Impairment: Creatinine clearance less than 30 mL/min</th><th>Hepatic Impairment: Mild (Child-Pugh A), Moderate (Child-Pugh B) or Severe (Child-Pugh C)</th></tr>
<tr><td>Pediatric < 0.55 m^2</td><td>150 mg</td><td>100 mg</td><td>100 mg</td></tr>
<tr><td>Pediatric 0.55 to < 0.63 m^2</td><td>200 mg</td><td>150 mg</td><td>100 mg</td></tr>
<tr><td>Pediatric 0.63 to < 0.75 m^2</td><td>200 mg</td><td>200 mg</td><td>150 mg</td></tr>
<tr><td>Pediatric 0.75 to < 0.9 m^2</td><td>250 mg</td><td>200 mg</td><td>150 mg</td></tr>
<tr><td>Pediatric 0.9 to < 1.1 m^2</td><td>300 mg</td><td>250 mg</td><td>200 mg</td></tr>
<tr><td>Pediatric ≥ 1.1 m^2</td><td>400 mg</td><td>300 mg</td><td>200 mg</td></tr>
</table>
[1] BSA=Body Surface Area
[see Use in Specific Populations (8.6, 8.7) and Clinical Pharmacology (12.3)].
Source: Applicant's Proposed USPI</td></tr>
</table>

There is no postmarketing requirement (PMR) or postmarketing commitment (PMC) from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:
Bosutinib plasma PK has been evaluated in clinical studies involving adult patients and analysis of clinical studies in adult patients with ND or R/I Ph+ CML have been previously submitted to regulatory agencies.

The pediatric PK data provided in this sNDA are from the BCHILD study (see Section 8.1.1 for details of the study design with respect to pediatric participants with ND or R/I Ph+ CML). The PK results and analyses provided in this application include:

- The noncompartmental PK results from BCHILD participants
- PPK analysis based on data in pediatric participants from BCHILD
- E-R analyses for safety endpoints based on data in pediatric participants from BCHILD
- E-R analyses for efficacy endpoints based on data in pediatric participants from BCHILD

Clinical pharmacology results of BCHILD and analyses of results (b) (4) are summarized in Section 6.2.2 and further described in Section 19.4).

In addition to the pediatric clinical study data from BCHILD, clinical pharmacology studies in support of the pediatric-enabling capsule drug product include:

- Study B1871061: A Phase 1, Open-label, Randomized, 2-Period, 2-Sequence, Crossover Study to Evaluate the Bioequivalence of Bosutinib Pediatric Capsule and the Commercial Tablet Formulations in Healthy Participants under Fed Condition
- Study B1871062: A Phase 1, Randomized, Open-label, 3-Period, 4-Sequence, Crossover Single-dose Study to Compare the Bioavailability of Orally Administered Bosutinib Capsules and to Estimate the Effect of Food on Bosutinib Capsule
- Study B1871063: A Phase 1, Open-label, Randomized, 3-Period, 6-Sequence, Crossover Study to Evaluate the Bioavailability of Bosutinib Administered as a Capsule Contents Mixed with Applesauce or Yogurt Relative to Intact Capsules in Healthy Participants Under Fed Condition

These studies are presented in the NDA for the capsule drug product.

The Applicant's Position:
(b) (4) The capsule drug product was characterized and supported by the clinical pharmacology package to enable dosing in the pediatric population.

The FDA's Assessment:
FDA agrees that the PK NCA along with clinical efficacy and safety data support the proposed dosing regimen in pediatric patients with ND Ph+ CML and R/I Ph+ CML. FDA does not agree (b) (4) . The bosutinib PPK model was determined to be inadequate for the purpose of characterizing PK in pediatric patients with CML (refer to Section 6.2.2.1), and so PK assessment is based on NCA.

According to results from Study BCHILD:

- The C_{max} and AUC of the bosutinib tablet were approximately dose proportional following single- and multiple-dose administration in pediatric patients for the observed dose range of 300 to 400 mg/m^2.
- FDA agrees with the proposed BSA-based dose banding (Table 3) as each starting dose band is predicted to provide comparable exposure across the age range of 1 to <18 years in patients with Ph+ CML.

In pediatric patients with an insufficient response after 3 months and BSA <1.1 m^2, the proposed labeling permits dose increases by 50 mg increments up to maximum of 100 mg above starting dose. In pediatric patients with an insufficient response after 3 months and BSA ≥1.1 m^2, the proposed labeling permits dose increases by increments of 100 mg up to a maximum of 600 mg QD, which is the same recommendation for adult patients with Ph+ CML. The maximum dose in pediatric and adult patients is 600 mg QD.

FDA agrees that the clinical pharmacology studies support approval of the age-appropriate capsule formulation, recommended administration with food, and administration of opened capsule contents with applesauce or yogurt. Refer to Section 6.3.2.4.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data supporting the adult dose recommendations of 400 and 500 mg QD for the ND and R/I indications, respectively, have been previously provided. The following outlines the dose selection and general dosing recommendations in pediatric patients.

In order to identify a dose in pediatric patients, a Phase 1 dose escalation was conducted in pediatric R/I participants within the BCHILD study. The starting dose of 300 mg/m^2 was selected as 100% of the approved adult dose (500 mg) in patients with R/I CML adjusted for BSA and was expected to provide equivalent exposure levels in the pediatric patients. Consistent with adult recommendations, all pediatric participants were instructed to administer study medication following a meal.

RP2D identification was based on 2 criteria pre-specified in the protocol and SAP:

- The first, is based on PK exposure matching (Within ±20% of adult geomean AUC)
- Safety at dose level (which requires 6 DLT evaluable patients if no DLTs are observed and 10 DLT evaluable patients if 1 DLT observed)

In Phase 2, participants were to be dosed according to the RP2D as established in Phase 1 according to the participants population (ND or R/I).

Phase 1 and 2 data from the BCHILD study were combined for PPK and E-R analyses for safety and efficacy.

Data

RP2D

The 300 mg/m^2 dose was well tolerated in the first cohort of R/I CML pediatric participants enrolled in the Phase 1 (no DLTs were observed) and based on the preliminary PK data from the first 5 pediatric participants treated at 300 mg/m^2 in this study, the geometric mean AUCss was 2178 ng•hr/mL which was within ±20% of the geometric mean AUCss in adult CML patients treated at 400-mg daily (target range 1896 - 2844 ng•hr/mL)), thus supporting use of the 300 mg/m^2 dose for pediatric patients with ND CML and was selected to move forward into Phase 2 in the pediatric ND population. This dose was later confirmed in Phase 1 and 2 participants administered the 300 mg/m^2 dose level with a geometric mean AUC_t of 1980, within the targeted exposure-matching range for ND participants. Dose escalation in the R/I pediatric population was subsequently continued to 350 and 400 mg/m^2 where the 400 mg/m^2 dose in pediatric participants produced an AUC of 2661 ng•h/mL which was within the target AUC range of 2520 to 3780 ng•hr/mL from the 500 mg R/I adult dose. This dose was shown to be well tolerated (1 DLT out of 10 evaluable participants) and was declared the recommended Phase 2 dose for the pediatric R/I participants.

PPK

(b) (4)

(b) (4)

Table 5. Applicant - Proposed Bosutinib Dosing Instructions for Pediatric Patients

BSA (m^2)	(b) (4)	ND Recommended Dose	(b) (4)	R/I Recommended Dose
<0.55	(b) (4)	150 mg	(b) (4)	200 mg
0.55 – <0.63	(b) (4)	200 mg	(b) (4)	250 mg
0.63 - <0.75	(b) (4)	200 mg	(b) (4)	300 mg
0.75 - <0.9	(b) (4)	250 mg	(b) (4)	350 mg
0.9 - <1.1	(b) (4)	300 mg	(b) (4)	400 mg
≥1.1	(b) (4)	400 mg[a]	(b) (4)	500 mg[a]

[a] maximum starting dose (corresponding to maximum starting dose in adult indication)

(b) (4)

No consistent trends for exposure with AEs or efficacy endpoints of interest in pediatric participants were identified. Based on the binomial logistic regression analysis, no E-R relationship was identified for individual adverse effects occurring in ≥20% frequency (Diarrhoea Grade ≥2, Nausea Grade ≥2), TEAEs Grade ≥3, or AEs leading to discontinuation, modification, interruption, and no clinically relevant covariates were identified. Descriptive analyses for efficacy are expanded in Section 6.3.2.1.

The dose modification instructions for pediatric patients in proposed labeling are as follows:

- Dose modification instructions in case of toxicity for patients with BSA <1.1 m^2 would specify reductions in 50-mg increments with allowance for a total of 2 dose reductions.
- Dose modification instructions in the case of insufficient response for patients with BSA <1.1 m^2 would allow for dose increases in 50-mg increments to a maximum of 2 escalations (100-mg increase).
- Dose modification instructions for toxicity and insufficient response for pediatric patients with BSA ≥1.1 m^2 would follow instructions consistent with adult indications.

These recommendations reflect the pediatric clinical study experience for dose reductions and escalations during study conduct.

<u>The Applicant's Position:</u>
The BCHILD data is supportive of the recommended starting dose levels of 300 mg/m^2 orally QD with food in ND pediatric patients and 400 mg/m^2 orally QD with food in R/I pediatric patients based on acceptable tolerability in the respective patient populations (b) (4)

(b) (4) Recommendations for dose modifications for toxicity or insufficient response are provided in labeling to allow consistency with adult recommendations as well as pediatric clinical study experience.

The FDA's Assessment:
The current PK, efficacy, and safety data from Study BCHILD support the proposed BSA-based dosage of 300 mg/m^2 QD with food for pediatric patients aged 1 year and older with ND Ph+ CP CML and 400 mg/m^2 QD with food for pediatric patients aged 1 year and older with R/I Ph+ CP CML (Table 3). The proposed dose banding in Table 3 and the proposed dose increases in patients with insufficient response are also supported by the assessment of clinical pharmacology. However, FDA does not agree (b) (4) The approval and benefit/risk decision are thus primarily based on the clinical efficacy and safety data from BCHILD.

FDA assessed bosutinib PK in pediatric patients in two separate analyses: NCA and PPK analysis. The NCA evaluated PK data from 34 pediatric patients in Study BCHILD with adequate PK sampling. The PPK analysis evaluated PK data from 41 pediatric patients in Study BCHILD with at least one post-dose PK sample. Although the NCA was limited by the smaller sample size in each pediatric age group, the NCA is the more accurate analysis of exposure across pediatric patient characteristics compared to the pediatric PPK analysis. The PPK analysis had significant issues and poorly characterized covariate effects, the details of which are discussed in Section 19.4.1.

Summary of NCA-Derived Bosutinib PK and Exposure in Pediatric Patients

The NCA included 34 patients aged 4 to <18 years with ND or R/I CP Ph+ CML who had adequate dose and PK concentration records in Study BCHILD. NCA-derived PK are summarized by dose cohort in Table 6. NCA-derived apparent clearance (CL/F), apparent volume of distribution (V/F), and time of maximum concentration after last dose (Tmax) are summarized by age subgroup in Table 7.

Table 6. Summary of NCA-Derived Bosutinib Exposure in Study BCHILD Patients by Dose Level

		BCHILD patients aged 4 to <17 years (N=27)			BCHILD patients aged 4 to <18 years (N=34)		
Exposure	**Statistic**	**300 mg/m^2 n=15**	**350 mg/m^2 n=6**	**400 mg/m^2 n=6**	**300 mg/m^2 n=20**	**350 mg/m^2 n=6**	**400 mg/m^2 n=8**
$AUC_{tau,ss}$ (ng·hr/mL)	Geo Mean (CV%)	2027.5 (47.4%)	2516.2 (38.2%)	2513.7 (34.6%)	1979.9 (43.8%)	2516.2 (38.2%)	2660.7 (31.9%)
	Min - Max	688.8 - 4240	1845.7 - 4624.5	1474.7 - 3922.2	688.8 - 4240	1845.7 - 4624.5	1474.7 - 3922.2

		BCHILD patients aged 4 to <17 years (N=27)			BCHILD patients aged 4 to <18 years (N=34)		
Exposure	**Statistic**	**300 mg/m^2 n=15**	**350 mg/m^2 n=6**	**400 mg/m^2 n=6**	**300 mg/m^2 n=20**	**350 mg/m^2 n=6**	**400 mg/m^2 n=8**
$C_{max,ss}$ (ng/mL)	Geo Mean (CV%)	159.2 (41.7%)	221.2 (51.6%)	198.1 (36.7%)	148 (42%)	221.2 (51.6%)	198.1 (34.9%)
	Min - Max	80.6 - 336	153 - 528	111 - 297	75 - 336	153 - 528	111 - 297
$C_{trough,ss}$ (ng/mL)	Geo Mean (CV%)	49.1 (52.9%)	46.3 (50.5%)	41.7 (105%)	48.2 (51.9%)	46.3 (50.5%)	48.9 (93.5%)
	Min - Max	20.6 - 103	28 - 91	11.7 - 137	19.9 - 103	28 - 91	11.7 - 137
Tmax (hours)	Median	3.08	3.295	3.01	3.105	3.295	3.01
	Min - Max	1 - 8	1 - 6	2.9 - 5.7	1 - 8	1 - 6	2.9 - 8

Pediatric steady state exposure was calculated on Day 14 based on NCA in Study BCHILD patients with newly diagnosed or refractory/intolerant chronic phase Philadelphia chromosome-positive CML.
$AUC_{tau,ss}$ = area under the concentration-versus-time curve over one dosage interval at steady state;
$C_{max,ss}$ = maximum concentration at steady state; CML = chronic myelogenous leukemia; $C_{trough,ss}$ = trough concentration at steady state; CV = coefficient of variation; GeoMean = geometric mean;
NCA = noncompartmental analysis; Tmax = time of maximum concentration after last dose.
Source: Reviewer's analysis and Table 2 in the Applicant's Summary of Clinical Pharmacology

Table 7. Summary of NCA-Derived Bosutinib PK Parameters in Study BCHILD By Age Subgroup

Parameter	Statistic	4 to <6 years	6 to <12 years	12 to <18 years	Overall
CL/F (L/h)	N	4	12	18	34
	GeoMean (CV%)	119.6 (78%)	136.9 (21%)	235.3 (33.2%)	179.5 (46.8%)
	Min - Max	54.1 - 290.4	100.2 - 178.9	122.3 - 449.6	54.1 - 449.6
BSA-normalized CL/F (L/h per m^2)	N	4	12	18	34
	GeoMean (CV%)	158.4 (78.9%)	130.9 (35%)	143.2 (31.8%)	140.4 (38.1%)
	Min - Max	75.1 - 403.3	64.7 - 198.8	85 - 252.6	64.7 - 403.3
V/F (L)	N	4	12	18	34
	GeoMean (CV%)	1423.7 (74.6%)	1874.4 (27.9%)	4996.1 (46.8%)	3049.4 (76.1%)
	Min - Max	626.8 - 3071.6	1290.1 - 3361.4	2147.4 - 10423.5	626.8 - 10423.5
BSA-normalized V/F (L per m^2)	N	4	12	18	34
	GeoMean (CV%)	1886 (72.9%)	1792.7 (35.9%)	2503.3 (30.7%)	2038.2 (42.2%)
	Min - Max	870.5 - 4266.1	1049.8 - 3734.9	1491.3 - 3998.5	870.5 - 4266.1
Tmax (hours)	N	4	12	18	34
	Median	3	3.4	3	3.1
	Min - Max	1 - 6	3 - 6.2	1 - 8	1 - 8

BSA = body surface area; CL/F = apparent clearance; CV = coefficient of variation; GeoMean = geometric mean; NCA = noncompartmental analysis; PK = pharmacokinetic; Tmax = time of maximum concentration after last dose; V/F = apparent volume of distribution.
Source: Reviewer's analysis

Bosutinib has dose-proportional exposure over the dosage range of 300 to 400 mg/m^2 and so

individual NCA-derived exposures could be dose-normalized. The dose-normalized exposure was calculated according to the following equation:

$$Exposure\ dose\text{-}normalized\ to\ proposed\ dosage\ = Observed\ Exposure \cdot \left(\frac{proposed\ dose\ (mg)}{actual\ dose\ (mg)}\right)$$

where exposure is AUC, C_{max}, or C_{trough}; actual dose (mg) is the actual dose amount in mg from dose records in the Applicant's Study BCHILD adexsum.xpt dataset, and the proposed dose (mg) is the proposed dose in mg according to BSA dose band as described in Table 3.

Table 8 summarizes dose-normalized steady state exposure following the proposed dosage in Study BCHILD pediatric patients aged less than 17 years (n=27) and in all Study BCHILD patients (n=34). Table 9 summarizes dose-normalized steady state exposure in Study BCHILD patients by age subgroup.

Table 8. Summary of NCA-Derived Bosutinib Dose-Normalized Steady State Exposure in Study BCHILD

		BCHILD patients aged 4 to <17 years (N=27)		BCHILD patients aged 4 to <18 years (N=34)	
Exposure	**Statistic**	**300 mg/m² daily** Banded dose, max 400 mg daily	**400 mg/m² daily** Banded dose, max 500 mg daily	**300 mg/m² daily** Banded dose, max 400 mg daily	**400 mg/m² daily** Banded dose, max 500 mg daily
$AUC_{tau,ss}$ (ng·hr/mL)	GeoMean (CV%)	1969.8 (42.9%)	2527.9 (42.9%)	1906.9 (41.3%)	2433.9 (41.5%)
	Median	1959.7	2482.9	1854.9	2453.6
	Min - Max	688.8 - 3963.8	918.3 - 5285.1	688.8 - 3963.8	918.3 - 5285.1
$C_{max,ss}$ (ng/mL)	GeoMean (CV%)	158.7 (44.9%)	203.7 (45.6%)	146.6 (46.1%)	187.1 (47.1%)
	Median	159	209.3	136.3	172.8
	Min - Max	74 - 452.6	92.5 - 603.4	60 - 452.6	75 - 603.4
$C_{trough,ss}$ (ng/mL)	GeoMean (CV%)	41.3 (64.7%)	52.9 (64.7%)	41.4 (61.6%)	52.8 (61.6%)
	Median	42.9	56.5	43	55.3
	Min - Max	7.8 - 102.7	9.8 - 137	7.8 - 102.7	9.8 - 137

Pediatric steady state exposure was calculated on Day 14 based on NCA.
$AUC_{tau,ss}$ = area under the concentration-versus-time curve over one dosage interval at steady state;
$C_{max,ss}$ = maximum concentration at steady state; $C_{trough,ss}$ = trough concentration at steady state; CV = coefficient of variation; GeoMean = geometric mean; NCA = noncompartmental analysis.
Source: Reviewer's analysis

Table 9. Summary of NCA-Derived Bosutinib Dose-Normalized Steady State Exposure

Proposed Indication	Proposed Pediatric Dosage	Parameter	Statistic	4 to <6 years	6 to <12 years	12 to <18 years	Overall
Newly-Diagnosed CP Ph+ CML	**300 mg/m² daily** Banded dose, max 400 mg daily	$AUC_{tau,ss}$ (ng·hr/mL)	N	4	12	18	18
			GeoMean (CV%)	1842.7 (84%)	2339.7 (31.6%)	1676.5 (32.8%)	1906.9 (41.3%)
			Median	2067.2	2475.8	1699	1854.9
			Min - Max	688.8 - 3963.8	1537.3 - 3925.9	889.7 - 3358.8	688.8 - 3963.8
		$C_{max,ss}$ (ng/mL)	N	4	12	18	34
			GeoMean (CV%)	177.7 (81%)	189 (33.3%)	118.5 (35%)	146.6 (46.1%)
			Median	165.5	200.4	118.7	136.3
			Min - Max	80.6 - 452.6	103 - 311.1	60 - 268.5	60 - 452.6
		$C_{trough,ss}$ (ng/mL)	N	4	12	18	34
			GeoMean (CV%)	50.1 (44.1%)	46.8 (64.7%)	36.5 (62.5%)	41.4 (61.6%)
			Median	52.8	47.8	42	43
			Min - Max	29.9 - 78	18.7 - 102.7	7.8 - 78.9	7.8 - 102.7
Refractory or Intolerant CP Ph+ CML	**400 mg/m² daily** Banded dose, max 500 mg daily	$AUC_{tau,ss}$ (ng·hr/mL)	N	4	12	18	34
			GeoMean (CV%)	2456.9 (84%)	3036.8 (29.4%)	2095.6 (32.8%)	2433.9 (41.5%)
			Median	2756.2	3094.7	2123.7	2453.6
			Min - Max	918.3 - 5285.1	2049.7 - 4907.4	1112.1 - 4198.5	918.3 - 5285.1
		$C_{max,ss}$ (ng/mL)	N	4	12	18	34
			GeoMean (CV%)	237 (81%)	245.3 (31.6%)	148.2 (35%)	187.1 (47.1%)
			Median	220.7	259.1	148.4	172.8
			Min - Max	107.5 - 603.4	137.3 - 388.9	75 - 335.6	75 - 603.4
		$C_{trough,ss}$ (ng/mL)	N	4	12	18	34
			GeoMean (CV%)	66.8 (44.1%)	60.8 (62.4%)	45.6 (62.5%)	52.8 (61.6%)
			Median	70.5	63.7	52.5	55.3
			Min - Max	39.9 - 104	24.9 - 137	9.8 - 98.6	9.8 - 137

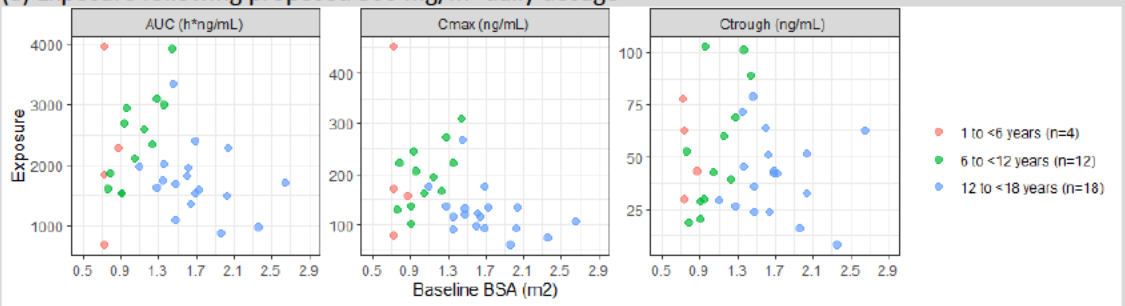
Pediatric steady state exposure was calculated on Day 14 based on NCA.
$AUC_{tau,ss}$ = area under the concentration-versus-time curve over one dosage interval at steady state; $C_{max,ss}$ = maximum concentration at steady state; CML = chronic myelogenous leukemia; CP = chronic phase; $C_{trough,ss}$ = trough concentration at steady state; CV = coefficient of variation; GeoMean = geometric mean; NCA = noncompartmental analysis; Ph+ = Philadelphia chromosome-positive.
Source: Reviewer's analysis

Following the proposed BSA-based dosage in Study BCHILD patients, there was a large overlap in NCA-derived exposures across the range of BSA (0.7 to 2.6 m^2; Figure 1), age (4 to <18 years; Figure 2), or body weight (17.1 to 141.6 kg). No clear trends in exposure were observed across BSA, age, or body weight. Although the minimum age was 4 years old in the group of patients with adequate PK records for NCA, no significant differences in exposure are expected in patients aged 1 to <4 years compared to older pediatric patients following the proposed BSA-based dosage. The PK of bosutinib in patients younger than 1 year of age was not studied, and it is unknown if patients younger than 1 year of age would have differences in bosutinib PK compared to older patients.

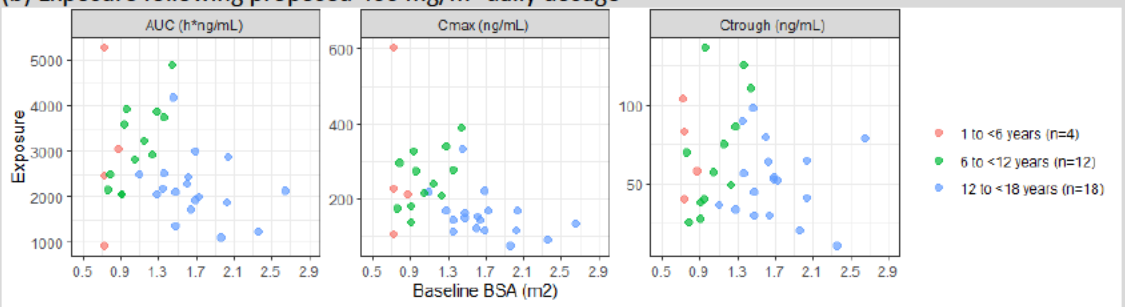
Overall, the NCA results support the BSA-based dosage (i.e., mg/m^2) in the general pediatric patient population aged 1 year and older.

Figure 1. NCA-Derived Exposure in Study BCHILD Patients Following Proposed Pediatric Dosage versus Baseline BSA

(a) Exposure following proposed 300 mg/m^2 daily dosage



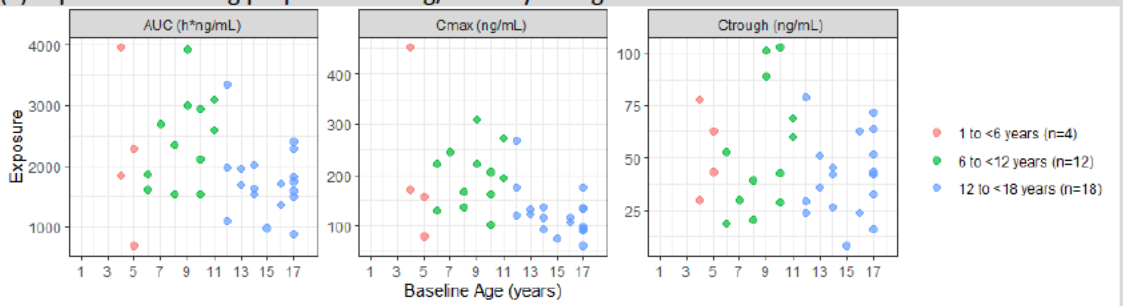
(b) Exposure following proposed 400 mg/m^2 daily dosage



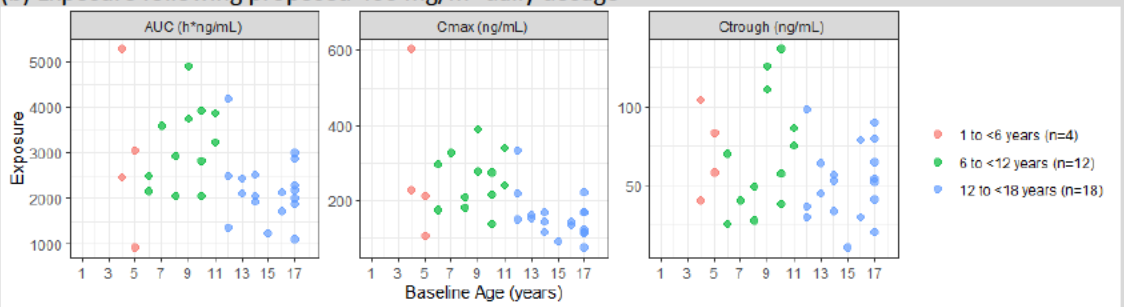
Pediatric dose-normalized exposure following the proposed 300 mg/m^2 daily and 400 mg/m^2 daily dosage regimens was calculated on Day 14 (i.e., steady state) based on NCA.
AUC = area under the concentration-versus time curve over one dosage interval; BSA = body surface area; Cmax = maximum concentration; Ctrough = trough concentration; NCA = noncompartmental analysis.
Source: Reviewer's analysis

Figure 2. NCA-Derived Exposure in Study BCHILD Patients Following Proposed Pediatric Dosage versus Baseline Age

(a) Exposure following proposed 300 mg/m² daily dosage



(b) Exposure following proposed 400 mg/m² daily dosage



Pediatric dose-normalized exposure following the proposed 300 mg/m² daily and 400 mg/m² daily dosage regimens was calculated on Day 14 (i.e., steady state) based on NCA.
AUC = area under the concentration-versus time curve over one dosage interval; Cmax = maximum concentration; Ctrough = trough concentration; NCA = noncompartmental analysis.
Source: Reviewer's analysis

The proposed dose banding in Table 3 differs from the dosage administered in Study BCHILD in two ways. First, Study BCHILD used dose bands which increased in increments of 25 mg while the proposed dose bands increase in increments of 50 mg. Second, the maximum starting dose in Study BCHILD was slightly higher than the maximum starting dose in the proposed dosage regimens. In Study BCHILD, the maximum starting dose was 500 mg for the 300 mg/m² dosage and 600 mg for the 400 mg/m² dosage. The proposed maximum starting dose is 400 mg for the 300 mg/m² dosage and 500 mg for the 400 mg/m² dosage.

To assess potential PK differences between the Study BCHILD and proposed dose banding, the Reviewer calculated the dose-normalized exposure in BCHILD patients (n=34) following the BCHILD dose banding and the proposed dose banding. The change from 25 mg increments to 50 mg increments did not result in any significant PK differences, and so the 50 mg increments in the proposed dose banding are acceptable. The proposed maximum starting doses are acceptable given the proposed dose increases in patients with insufficient response, which are described in Section 6.2.1.

Summary of PPK Analysis in Pediatric Patients

The Applicant's PPK analysis was conducted using data from 41 patients aged 1 to <18 years in Study BCHILD. The objectives of the bosutinib pediatric PPK analysis were to characterize PK, to characterize covariate effects, and to predict bosutinib exposure in pediatric patients with Ph+ CML.

The PPK analysis should be interpreted with caution due to significant issues with the Applicant's pediatric PPK model. (b) (4)

(b) (4)

Ultimately, the PPK analysis is inadequate for the purposes of bosutinib PK characterization and exposure prediction across BSA and age in pediatric patients with Ph+ CML. The results of the NCA are more likely to accurately reflect PK in Study BCHILD pediatric patients than the pediatric PPK analysis, and therefore the NCA-derived exposures should be used for the pediatric PK assessment.

(b) (4)

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(b) (4)

Conclusions

FDA does not agree that the PPK analysis is adequate for the purpose of characterizing PK and exposure across the range of BSA or age in pediatric BCHILD patients. Although the NCA has a smaller sample size, the NCA is still the more accurate analysis in patients aged 1 to <18 years compared to the pediatric PPK analysis.

(b) (4)

The assessment of bosutinib efficacy in pediatric patients aged 1 year and older with ND or R/I CP Ph+ CML is based primarily on the clinical efficacy data in Section 8.1.

FDA agrees with the proposed BSA-based dosage (i.e., mg/m^2) in pediatric patients aged 1 year and older. The proposed BSA-based dosage is supported by the NCA results, which did not identify any clear trends in exposure across BSA, age, or body weight following the proposed 300 mg/m^2 or 400 mg/m^2 dosage regimens in Study BCHILD patients.

The proposed dose banding in Table 3 and the proposed dose increases in patients with insufficient response are also supported by the assessment of clinical pharmacology.

6.2.2.2. Therapeutic Individualization

Data:

None of the tested covariates other than BSA were considered significant from the pediatric PPK model. There were no significant covariates identified in exposure-response modeling for safety. (b) (4), the BCHILD study was not powered for efficacy and multivariate analyses for efficacy exposure-response in the pediatric ND and R/I populations were not feasible.

The Applicant's Position:

There is no recommended therapeutic individualization for pediatric patients as the general dose recommendations for ND and R/I pediatric patients include adjustments for differences in CL based on body size in this population. Consistent with previous labeling instructions, no dose adjustment is needed based on intrinsic factors including age, sex, race, and mild renal impairment; however, a reduced dose may be needed for hepatic impairment (all severity) and moderate or severe renal impairment based on data collected from adults.

The FDA's Assessment:

FDA does not agree that the PPK analysis adequately characterizes the PK and exposure across the range of BSA or age in the BCHILD pediatric patients. Refer to the PPK analysis summary in the Section 6.2.2.1 of the FDA Assessment and the detailed analysis in Section 19.4.1. However, based on the NCA described in the FDA Assessment of Section 6.2.2.1, no clear differences in exposure were identified across BSA, age, or body weight following the proposed dosage in Study BCHILD pediatric patients. The proposed BSA-based dosage (i.e., mg/m^2) is acceptable in pediatric patients aged 1 year and older from a clinical pharmacology perspective.

(b) (4) Based on exposure differences in adult patients with renal impairment or hepatic impairment, the FDA recommended dosage adjustments in pediatric patients with renal impairment or hepatic impairment.

Compared to adult patients with creatinine clearance (CLcr) >50 mL/min, the recommended starting dosage is 20 to 25% lower in adult patients with CLcr between ≥30 to 50 mL/min and 40 to 50% lower in adult patients with CLcr less than 30 mL/min. The Applicant proposed 20 to 33% reduced BSA-based starting dosage for pediatric patients with CLcr ≥30 to 50 mL/min and 33 to 50% reduced BSA-based starting dosage with CLcr less than 30 mL/min compared to the recommended dosage in pediatric patients with normal renal function (Table 4). Of note, these CLcr are slightly different than the current standard renal impairment categories of 30 to 59 mL/min for moderate renal impairment and 15 to 29 mL/min for severe renal impairment.

The recommended starting dosage is 50 to 60% lower in adult patients with mild, moderate, or severe hepatic impairment compared to adult patients with normal hepatic function. The Applicant proposed 33 to 60% reduced BSA-based starting dosage for pediatric patients with mild, moderate, or severe hepatic impairment compared to the recommended dosage in pediatric patients with normal hepatic function (Table 4).

The clinical pharmacology assessment supports the proposed pediatric dosage adjustments with respect to renal and hepatic impairment in pediatric patients with ND or R/I CML listed in Table 4.

6.2.2.3. Outstanding Issues

The FDA's Assessment:
FDA did not identify any outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
As described in Section 6.2.1, the primary pediatric PK data provided in this sNDA are for participants from the BCHILD study. Overall, the exposures of bosutinib in pediatric patients aged ≥1 years at the recommended dose levels were found to be similar to that of adult patients for the respective indication. At steady state, bosutinib exposure increased approximately proportionally to dose over the clinical dose range of 300- to 400-mg/m^2 QD with food.

(b) (4)

(b) (4)

In addition to supporting pediatric data, 3 biopharmaceutics studies were conducted to characterize the pediatric-enabling capsule drug product which concluded the following:

- The bosutinib capsule drug product is bioequivalent to the commercial tablet under fed conditions, pediatric patients can receive either capsules or tablets as appropriate based on the dose.
- Bosutinib capsule strengths may be combined as appropriate to achieve the desired dose.
- Bosutinib capsules should be taken once daily with food. Plasma exposures of bosutinib capsules are reduced when administered under fasted conditions.

The Applicant's Position:
The totality of clinical pharmacology findings support the recommended dose of 300 mg/m^2 QD with food for the pediatric ND indication and 400 mg/m^2 QD with food for the pediatric R/I indication.

The FDA's Assessment:
The proposed BSA-based dosage (i.e., mg/m^2) is supported by the NCA results, which did not identify any clear trends in exposure across BSA, age, or body weight following the proposed dosage in Study BCHILD pediatric patients aged 1 year and older. Refer to the FDA Assessment in Section 6.2.2.1 for details.

The FDA does not agree with the Applicant's conclusion (b) (4)

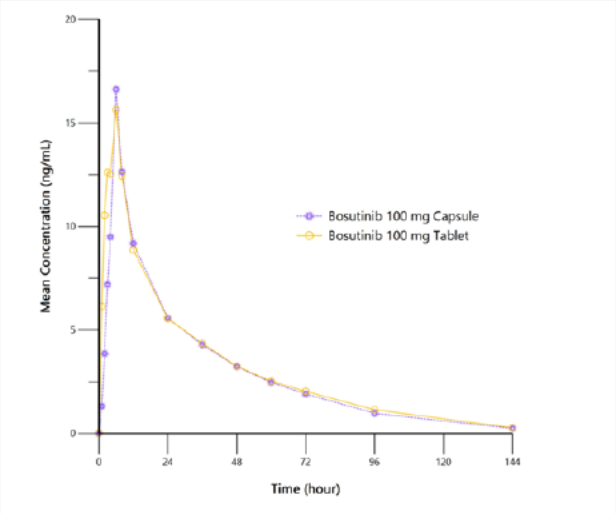
Refer to the FDA Assessment in Section 6.2.2.1 for details.

The PK assessment is based on the NCA, which more accurately characterized the PK in pediatric patients aged 1 to <18 years. FDA does not agree that the PPK analysis is adequate for the purpose of characterizing PK and exposure across the range of BSA or age in pediatric BCHILD patients. Refer to the PPK analysis summary in the Section 6.2.2.1 FDA Assessment and to the detailed analysis of the Applicant's pediatric PPK model in Section 19.4.1.

There were 3 additional clinical pharmacology studies conducted to include evaluation of relative bioavailability of capsules to tablets (B1871061), of the food effect (B1871062), and the vehicle effect for drug administration (B1871063). Refer to the FDA Assessment in Section 6.3.2.4 for details on administration of the age-appropriate capsule formulation with food and vehicles.

Based on results from the relative bioavailability study (B1871061) of the 100 mg capsule and 100 mg tablet under fed conditions in 64 healthy adult subjects, FDA agrees that the PK exposure for age-appropriate capsule formulation was comparable to that of the approved tablet formulation (geometric mean ratio % [90% CI] for AUC_{inf}: 93 [89, 97] and C_{max}: 96 [90, 102]) (Figure 3, Table 12). Study B1871062 evaluated the relative bioavailability of 4 × 25 mg capsules and 100 mg tablet under fed conditions in 31 healthy adult subjects, which showed PK comparability (Figure 4, Table 13).

Figure 3. FDA- Mean Bosutinib Plasma Concentration versus Time Plot with Capsule vs Tablet Formulations



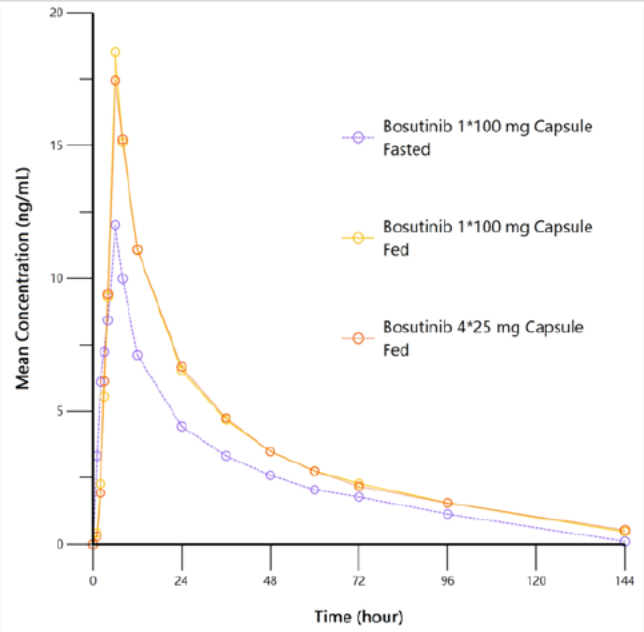
Source: Reviewer's Analysis

Table 12. Summary of Statistical Analysis of Bosutinib PK Parameters with 100 mg Capsule vs. 100 mg Tablet Formulations from Study B187061

PK Endpoints	GMR% (90% CI) n=64 (capsule): n=63 (tablet)
AUC_{inf}	92.83 (89.06, 96.77)
AUC_{last}	94.12 (90.33, 98.06)
C_{max}	95.61 (90.07, 101.48)

Source: Applicant's Final study report/Protocol B1871061/Table8

Figure 4. Mean Bosutinib Plasma Concentration versus Time Plot with High-Fat Meal vs. Fasted Conditions and 4 x 25 mg Capsules vs. 100 mg Tablet



Source: Reviewer's analysis

Table 13. Summary of Statistical Analysis of Bosutinib PK Parameters with 4 × 25 mg Capsules vs. 100 mg Tablet Formulations from Study B187062

PK Endpoints	GMR% (90% CI) n=31 (4*25 mg capsule Fed); n= 30 (1*100 mg capsule Fed)
AUC_{inf}	99.17 (93.72, 104.93)
AUC_{last}	98.21 (93.83, 102.80)
C_{max}	93.77 (90.08, 97.61)

Source: Applicant's Final study report/Protocol B1871062/Table13

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Based on the understanding of the disease pathology, mechanism of action, and evidence across the drug class, (b) (4) the BCHILD study was not powered for efficacy.

The exposure-efficacy relationship for bosutinib was previously characterized from adult E-R modeling in support of the adult R/I and ND indications, where it was concluded that most

efficacy metrics appeared to have reached or be near a plateau at plasma concentrations within the targeted dose level for these indications.

An exploratory E-R analysis was conducted to assess association of exposure and efficacy metrics using descriptive analyses for ND Ph+ CML and R/I Ph+ CML in pediatric patients. Based on visual assessment of exposure box plots by response, none of the bosutinib exposure metrics appeared to be a significant predictor for the efficacy measures for the ND indication. There were mixed and inconsistent trends of higher exposure with achieving CCyR and MMR for the R/I population, however data is limited to enable further characterization. In the R/I population, observed response rates across evaluated dose groups (300– 400 mg/m^2 with food) were comparable.

The Applicant's Position:

(b) (4)

The FDA's Assessment:

No, the clinical pharmacology assessment is not sufficient (b) (4) . Refer to the FDA Assessment of bosutinib PK and the Applicant's exposure-matching analysis in Section 6.2.2.1.

Additionally, the Applicant's E-R efficacy analysis utilized exposure derived from the pediatric PPK model which is inadequate for prediction of exposure in pediatric patients (refer to Section 6.2.2.2). Therefore, the accuracy of the E-R analysis is uncertain, as discussed in Section 19.4.2. No conclusions regarding exposure and efficacy can be drawn from the E-R efficacy analysis.

The FDA assessment of bosutinib efficacy for the proposed pediatric indications is primarily based on clinical efficacy data in Section 8.1.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

The proposed dosing regimens for ND and R/I pediatric patients are supported by data from BCHILD summarized in Section 6.2.2.1. The BSA-based regimen accounts for differences in CL/F with body size in this patient population. The CL/F and V/F estimates from the pediatric PPK model outlined in Section 6.3.1 correspond to a half-life of >15 hours and support once-daily administration.

Bosutinib was administered in the fed state in the BCHILD study. A pediatric-enabling capsule drug product was developed to support the pediatric dose recommendations and is bioequivalent to the commercial tablet drug product in the fed state. The capsule strengths support the final pediatric dose recommendations and may be taken intact or, alternatively, for patients unable to swallow the intact dosage form, the capsules may be opened, and the contents mixed with applesauce or yogurt as a vehicle to facilitate administration.

The Applicant's Position:
The proposed dosing regimens are appropriate for the ND and R/I pediatric patient populations.

The FDA's Assessment:
The FDA agrees that the proposed BSA-based dosages are appropriate in the general pediatric patient population with Ph+ CML.

The PPK analysis is inadequate evidence due to significant issues identified with the pediatric PPK model, as discussed in Section 6.2.2.1. However, the NCA in Study BCHILD pediatric patients did not identify any significant differences in exposure across BSA, age, or body weight following the proposed dosage in Study BCHILD pediatric patients aged 1 year and older. The proposed BSA-based dosage regimens are adequately supported by the NCA results. Refer to the FDA Assessment in Section 6.2.2.1 for details.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:
Relevant PPK covariates for bosutinib were described in the initial NDAs for adult indications. There were no substantial differences based on visual inspection of potential covariates in the pediatric PPK model development and, other than BSA, no covariates of significance on bosutinib exposure in pediatric patients were identified. Similarly, there were no baseline factors associated with safety or efficacy from the pediatric exposure-response analyses.

The Applicant's Position:
Dose adjustment for subpopulations based on intrinsic patient factors should follow the current approved label for bosutinib.

The FDA's Assessment:
Following the proposed BSA-based dosage, no significant difference in NCA-derived exposure was observed across age and BSA in Study BCHILD pediatric patients (refer to Section 6.2.2.1). No alternative dosage is recommended for pediatric patients with Ph+ CML according to age or BSA.

Based on impact of renal and hepatic impairment on bosutinib exposure in adult patients,

lower starting doses are recommended for pediatric patients with CLcr <50 mL/min and pediatric patients with mild, moderate, or severe hepatic impairment. Refer to Section 6.1 for the FDA assessment of the need for alternative dosage and recommended dosage adjustments in pediatric patients with renal impairment or hepatic impairment. Refer to Table 4 in Section 6.1 for recommended starting dosages in pediatric patients with renal impairment or hepatic impairment.

The NCA-derived exposure did not differ significantly according to sex, race (African American or Black [n=4] or White [n=18]), ethnicity (Hispanic or Latino [n=7] or not Hispanic or Latino [n=19]), or CML subgroup (newly diagnosed CP Ph+ CML [n=15] or resistant/intolerant CP Ph+ CML [n=19]). Potential PK associations with racial subgroups other than African American or Black and White could not be evaluated due to inadequate numbers of patients. No clinically significant PK differences are expected according to sex, race, ethnicity, or ND versus R/I CML status.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:
Data around drug-drug interactions and food-drug interactions have been previously submitted for the tablet drug product. No changes to drug-drug interactions are anticipated for the capsule drug product.

The effect of meal administration on bosutinib exposure was explored for the capsule drug product in study B1871062. Under fed (high-fat, high-calorie meal) condition for bosutinib capsule administration, plasma exposures of bosutinib were approximately 36%, 47%, and 63% higher for AUC_{inf}, AUC_{last}, and C_{max}, respectively, compared to the fasted condition. There was no impact of vehicle on bosutinib capsule exposure when capsules were opened and contents mixed with applesauce or yogurt compared to when capsules were administered intact.

The Applicant's Position:

Bosutinib tablets and capsules should be taken orally once daily with food, consistent with BCHILD clinical study conduct instructions. For patients who are unable to swallow an intact capsule, bosutinib capsules can be opened and contents mixed with applesauce or yogurt for administration. Recommendations concerning drug interactions for pediatric patients and using the capsule drug product should follow those previously provided for the adult population and tablet drug product.

The FDA's Assessment:
Based on results from the food effect study (B1871062) conducted with a bosutinib 100 mg capsule with a high-fat meal (50% fat, 0.8-1 kCAL) compared to the fasted state in 32 healthy subjects, FDA agrees that capsules should be administered with food because exposures of bosutinib were approximately 36%, 47%, and 63% higher for AUC_{inf}, AUC_{last}, and C_{max},

respectively, with a high-fat meal compared to the fasted condition (Figure 4, Table 14).

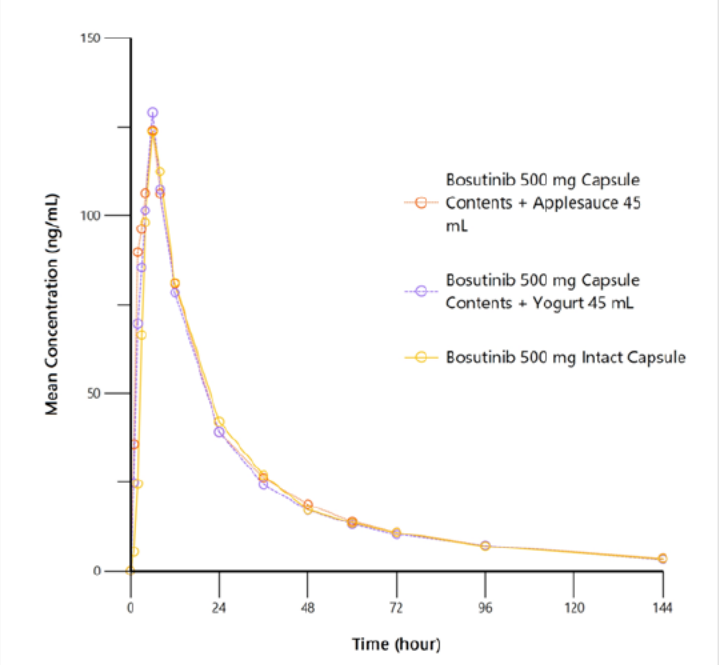
Table 14. Summary of Statistical Analysis of Bosutinib PK Parameters with High-Fat Meal vs. Fasted Conditions from Study B187062

PK Endpoints	GMR% (90% CI) n=30 (Fed): n=12 (Fasted)
AUC_{inf}	135.90 (109.28, 169.01)
AUC_{last}	146.70 (117.88, 182.58)
C_{max}	162.54 (130.25, 202.84)

Source: Applicant's Final study report/Protocol B1871062/Table14

A vehicle effect study (B1871063) was conducted with bosutinib 5 × 100 mg capsules opened and mixed with 45 mL applesauce or yogurt compared to intact capsules under fed conditions in 18 healthy subjects. For patients who have difficulty swallowing, FDA agrees that the capsules can be opened and administered with applesauce or yogurt because bosutinib PK exposure was comparable when capsule contents were administered with applesauce (Table 15) or yogurt (Table 16) versus the intact capsules (Figure 5).

Figure 5. Mean Bosutinib Plasma Concentration versus Time Plot with Opened Capsule Contents Mixed with Applesauce or Yogurt vs. Intact Capsules from Study B187063



Source: Reviewer's analysis

Table 15. Summary of Statistical Analysis of Bosutinib PK parameters with Capsule Contents with Applesauce vs. Intact Capsules from Study B187063

PK Endpoints	GMR% (90%CI) n=16 (Applesauce): n=18 (Intact)
AUCinf	106.27 (97.76, 115.53)
AUC_{last}	106.23 (97.54, 115.68)
C_{max}	96.82 (86.37, 108.53)

Source: Applicant's Final study report/Protocol B1871063/Table14

Table 16. Summary of Statistical Analysis of Bosutinib PK parameters with Capsule Contents with Yogurt vs. Intact Capsules from Study B187063

PK Endpoints	GMR% (90% CI) n=17 (Yogurt): n=18 (Intact)
AUC_{inf}	101.93 (93.97, 110.56)
AUC_{last}	102.08 (93.95, 110.91)
C_{max}	95.39 (85.34, 106.61)

Source: Applicant's Final study report/Protocol B1871063/Table14

The FDA agrees that drug-drug interactions for bosutinib have been previously characterized. Refer to the original NDA 203341 for drug-drug interactions.

X X

Ritu Chadda, PhD
Primary Reviewer

Ruby Leong, PharmD
Team Leader

X X

Robyn Konicki, PharmD
Pharmacometrics Primary Reviewer

Jiang Liu, PhD
Team Leader

7. Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 17. Applicant - Listing of Clinical Trials Relevant to this Supplemental NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
ITCC-054 (BCHILD, B187-WI202099)	NCT04258943	A Phase 1/2, multicenter, international, single-arm, open-label study of bosutinib in pediatric participants with ND CP or R/I Ph+ CML. Phase 1 only enrolled pediatric participants with Ph+ CP, AP, or BP CML who were R/I to previous TKIs. Phase 2 enrolled pediatric participants with ND Ph+ CP CML, and pediatric participants with Ph+ CP, AP, or BP CML who were R/I to previous TKIs.	Phase 1: Dose-finding groups: Bosutinib (Route: Oral; Dose Regimen: 300 mg/m^2 QD, 350 mg/m^2 QD, 400 mg/m^2 QD) Phase 2: Bosutinib (Route: Oral; Dose Regimen: 300 mg/m^2 QD)	See Table 18 and Table 19	Bosutinib tablets or capsules orally QD with a meal. Capsule contents could be added suitable foodstuff (applesauce or yogurt) for administration. Phase 1: dose depends on the dose cohort (300, 350, and 400 mg/m^2 cohort) that R/I Ph+ CML is assigned; In Phase 2, ND Ph+ CML participants were dosed according to the RP2D$_{ND}$ as established in Phase 1. The dose was	50 participants were enrolled (49 received at least 1 dose of bosutinib [6 in Phase 1 300 mg/m^2 cohort, 11 in Phase 1 350 mg/m^2 cohort, 11 in Phase 1 400 mg/m^2 cohort, and 21 in Phase 2 300 mg/m^2 cohort; 1 participant with R/I CML was screened but not assigned to a study cohort and did not initiate study treatment]). 4 participants completed the study (1 in the Phase 1 300 mg/m^2 cohort and 3 in the	Phase 1 only enrolled pediatric participants with Ph+ CP, AP, or BP CML who were R/I to previous TKIs. Phase 2 enrolled pediatric participants with ND Ph+ CP CML.	29 sites in 8 countries (France, Germany, Italy, Spain, Switzerland, the Netherlands, UK, and USA)

					adjusted for BSA.	Phase 1 350 mg/m^2 cohort).		
B1871061[a]	NCT04549480	A Phase 1, open-label, randomized, 2-period, 2-sequence, crossover study to evaluate the bioequivalence of bosutinib pediatric capsule and the commercial tablet formulations in healthy participants under fed condition	Bosutinib (Route: Oral; Dose Regimen: Randomized to 1 of 2 sequences of 2 treatments: Treatment A (Test):100-mg capsule QD [fed], and treatment B (Reference):100-mg tablet QD [fed])	Plasma AUC_{inf} and C_{max} for bosutinib; AUC_{last}, T_{max}, CL/F, Vz/F, and $t_{½}$ for bosutinib; safety laboratory tests, vital signs, ECGs, and AE monitoring.	Single dose with ≥14-day washout between doses. Participants remained in the study for up to ~3 months, including the screening and follow-up periods.	Enrolled: 66 (33 per sequence) Treated: Bosutinib 100-mg capsule: 64 Bosutinib 100-mg tablet: 63	Healthy adult	1, The Netherlands
B1871062[a]	NCT05032690	A Phase 1, randomized, open-label, 3-period, 4-sequence, crossover, single-dose study to compare the bioavailability of orally administered bosutinib capsules and to estimate the effect of food on bosutinib capsule	Bosutinib (Route: Oral; Dose Regimen: Randomized to 1 of 4 sequences of 3 treatments: (A) 1*100-mg capsule QD [fed], (B) 4*25-mg capsule QD [fed], (C) 1*100-mg capsule [fasted])	Plasma AUC_{inf} and C_{max} for bosutinib (AUC_{last} would be used as the primary estimate if AUC_{inf} could not be reliably estimated); plasma AUC_{last}, T_{max}, CL/F, Vz/F, and $t_{½}$ for bosutinib; safety laboratory tests and AE monitoring.	Single dose with ≥14-day washout between doses. Participants remained in the study for ≤13 weeks, including the screening and follow-up periods.	Enrolled: 32 (7 per sequence) Treated: Bosutinib 1*100-mg capsule (fed): 30 Bosutinib 4*25-mg (fed): 31 Bosutinib 1*100-mg capsule (fasted): 12 Completed: 25	Healthy adult	1, Belgium

B1871063[a]	NCT04916769	A Phase 1, open-label, randomized, single dose, 3-period, 6-sequence, crossover study to evaluate the bioavailability administered as capsule contents mixed with applesauce or yogurt relative to intact capsules in healthy participants under fed condition	Bosutinib: (Route: Oral; Dose Regimen: 500-mg QD as (A) intact capsule, (B) capsule contents mixed with applesauce, or (C) capsule contents mixed with yogurt)	Plasma AUC_{inf} and C_{max} for bosutinib (AUC_{last} would be used as the primary estimate if AUC_{inf} could not be reliably estimated); plasma AUC_{last}, T_{max}, CL/F, Vz/F, and $t_{½}$ for bosutinib; safety laboratory tests and AE monitoring; Responses to the Bosutinib Taste Assessment Questionnaire that document overall liking, mouth feel, bitterness, and tongue/mouth burn of sensory attributes.	Single dose with ≥14-day washout between doses. Participants remained in the study for up to ~13 weeks, including the screening and follow-up periods.	Enrolled: 18 (3 per sequence [6 sequences total]) Treated: Bosutinib 500-mg intact capsule: 18 Bosutinib 500-mg capsule contents mixed with applesauce: 16 Bosutinib 500-mg capsule contents mixed with yogurt: 17 Completed: 16	Healthy adult	1, Belgium
[a]These studies support the formulation NDA and are detailed in that submission.								

The Applicant's Position:
The clinical study relevant to this submission is presented below.

The FDA's Assessment:
The application includes a single Phase I/II efficacy clinical trial (ITCC-054, BCHILD, AAML1921), a bioequivalence study of the new capsule to commercial tablet (B1871061), a bioavailabilty and food effect study (B1871062), and a study where capsule content was mixed with applesauce or yogurt (B1871063).

Analyses by the FDA's clinical reviewer were performed using JMP 16.0 (SAS Institute, Inc., Cary, NC) and MAED version 3.7. Analyses by the FDA's statistical reviewer were performed using SAS release 9.04.01M7P08062020 (SAS Institute Inc., Cary, NC).

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study ITCC-054/AAML1921 (B187-WI202099)

- A Phase 1/2 Study of Bosutinib in Pediatric Patients With Newly Diagnosed Chronic Phase or Resistant/Intolerant Ph+ Chronic Myeloid Leukemia

Study Design
Basic study design and study location

This was a Phase 1/2, multicenter, international, single-arm, open-label study conducted in the US and Europe designed to identify a recommended dose of bosutinib administered orally QD in pediatric participants with ND Ph+ CML in CP and pediatric participants with Ph+ CML who have received at least 1 prior TKI therapy (R/I Ph+ CML), to estimate the safety and tolerability and efficacy, and to evaluate the PK of bosutinib in this participant population.

Diagnostic criteria

- Cytogenetic and molecular diagnosis of Ph+ CML[2] at either time of initial CML diagnosis or at time of study screening
- Resistance (suboptimal response or failure, as defined by 2013 European Leukemia Net guidelines[2]) or intolerance (with or without suboptimal response or failure) to at least one prior TKI)

Study treatments and choice of control group
All BCHILD participants were assigned to active treatment according to the assigned dose level. Phase 1 consisted of R/I participants, whereas Phase 2 included both ND and R/I participants at the selected dose identified from the Phase 1 dose escalation. At the time of data cut for this filing, only ND participants were enrolled and dosed in Phase 2.

Bosutinib capsules or tablets were administered orally with a meal (approximately at the same time of day, preferably in the morning). In Phase 1, the dose of bosutinib depended on which dose level the participant was assigned (ie, 300, 350, or 400 mg/m^2). In Phase 2, the participant was to be dosed according to the RP2D as established in Phase 1 according to the participant population (ND or R/I; ie, 300 mg/m^2). The dose was to be adjusted for the participant's BSA measured during screening. The BSA calculation was to be repeated at the beginning of every 3rd cycle (cycle 4, 7, etc), and the dose was adapted in case of a change in BSA of at least ≥10% compared to the last assessment and according to the rounded dosages provided in the protocol.

Dose selection

Phase 1 dose escalation was conducted in pediatric R/I participants. The starting dose of 300 mg/m^2 was selected as 100% of the approved adult dose (500 mg) in patients with R/I CML adjusted for BSA and was expected to provide equivalent exposure levels in the pediatric patients. The per protocol analysis set (evaluable for RP2D) for Phase 1 included all enrolled participants who received at least 1 dose of study medication, had no major protocol deviations during first 28 days of dosing, and had sufficient information to estimate the AUC for bosutinib. Participants with major protocol deviations in the first 28 days were not evaluable for the DLT assessment and could be replaced as needed to permit RP2D estimation. Reasons for participant replacement may have included administration of less than 75% of planned doses or administration of more than 100% of the planned doses of bosutinib over the first 28 days, and insufficient information to estimate the AUC for bosutinib.

RP2D identification for the ND and R/I pediatric populations was based on 2 criteria pre-specified in the protocol and SAP:

- PK exposure matching (within ±20% of adult geomean AUC for the adult dose of 400 and 500 mg QD for the ND and R/I patient populations, respectively)
- Safety at dose level (which requires 6 DLT evaluable participants if no DLTs are observed and 10 DLT evaluable participants if 1 DLT observed)

In Phase 2, participants were dosed according to the RP2D as established in Phase 1 according to the participant population (ND or R/I).

Dose modification, dose discontinuation

In the event of significant toxicity, dosing may have been delayed and/or reduced. In the event of multiple toxicities, dose modifications were based on the worst toxicity observed.

Participants experiencing the following AEs were to have continuous daily treatment interrupted:

- Grade ≥2 potentially treatment-related non-hematologic toxicity not responding to optimal management including anti-diarrheals or
- Grade ≥3 potentially treatment-related hematologic toxicity.

Retreatment at the same dose following treatment interruption for treatment related toxicity did not occur until all of the following parameters were met:

- Hematologic toxicities had returned to baseline or Grade ≤2 severity within 2 weeks of treatment hold.
- Non hematologic toxicities had returned to baseline or Grade ≤1 severity within 4 weeks of treatment hold.

Following dosing interruption due to toxicity, the bosutinib dose may be reduced when treatment is resumed. Dosing interruption and dose reduction is advised for the management of hematologic and non-hematologic adverse drug reactions. Dose reduction of bosutinib by 1 and, if needed, 2 dose levels from assigned dose level at start of treatment was allowed depending on the type and severity of toxicity encountered. Participants requiring more than 2 dose reductions were to be discontinued from the treatment and entered into the follow up phase, unless otherwise agreed between the Investigator and the Sponsor. For participants requiring a dose reduction due to toxicity, but then free of the specific toxicity (Grade ≤1) for at least 3 Cycles and are otherwise tolerating bosutinib well, the Investigator may choose to re-escalate the dose by 1 dose level each Cycle until the participant is back to the starting or previous dose (whichever is higher).

In Phase 2, intra-participant dose escalation for RP2D participants ($RP2D_{ND}$ and $RP2D_{R/I}$) were permitted if there was an unsatisfactory disease response (suboptimal response or failure), beginning with the first efficacy assessment at Cycle 3, or if there were signs of disease progression to bosutinib, and if the participant was adequately tolerating therapy at the RP2D.

Participants treated at the RP2D could have been escalated to the next highest dose level; If applicable, consultation with the Sponsor was necessary if all of the following conditions were satisfied: 1. Maximum study drug related toxicity during prior cycles of therapy was Grade ≤2; 2. The decision to increase the dose was approved by the Sponsor, following discussion with the Investigator. For these participants, trough PK sampling and ECGs were to be obtained 2-4 weeks after initiation of the new dose (once bosutinib had achieved steady-state levels).

Administrative structure

The study was managed by Erasmus MC (Sponsor) and COG (Co-sponsor) and conducted by investigators contracted by and under the direction of the Sponsors. The investigators were responsible for adhering to the study procedures described in the protocol, for keeping records

of study drug, and for accurately completing and signing the CRFs/DCTs supplied by the Sponsor.

A steering committee was established before start of the enrollment of participants. The steering committee was responsible for monitoring the scientific integrity of the clinical study, the scientific validity of the study protocol, assessment of study quality, and conduct as well as for the scientific quality of the final study report. The steering committee selected the RP2Ds for continuation of the Phase 2 part of the study.

Procedures and schedule

Each treatment cycle lasted for 28 days. In Cycle 1 visits were conducted on Day 1, 8, 14, 15, and 22. Additional visits were conducted at the beginning of each cycle for Cycles 2-7 and at the beginning of every 3rd cycle for Cycles 8 and greater. Safety assessments were performed at each visit (on Day 15 ECG was the only safety assessment conducted) and disease response assessments were performed at the beginning of Cycle 4, 7, and every 3rd cycle for Cycles 8 and greater.

Concurrent medications, dietary restrictions, and rescue medications

Prohibited medications: anti-leukemia treatments other than regimen defined in protocol (including donor lymphocyte infusions), any investigational agents, prophylactic use of hematopoietic growth factors (therapeutic use was allowed in case of life-threatening infections), moderate or strong CYP3A inducers and inhibitors, and proton pump inhibitors. Permitted treatments: hydroxyurea and anagrelide (at investigator discretion for severe hyperleukocytosis) during the first 2 weeks of bosutinib treatment, treatment of diarrhea and other GI symptoms (eg, antidiarrheals, antiemetics, and/or fluid replacement), palliative and supportive care for disease-related symptoms or toxicity due to study treatment, growth factors were permitted in Cycle 2 and beyond, supplementation for potassium or magnesium.

Treatment compliance

Treatment compliance was assessed at every scheduled clinic visit via treatment compliance diary.

Participant completion, discontinuation, and withdrawal

If a participant discontinued or was withdrawn from the study the site was to attempt to document the participant's outcome, if possible, and the participant was requested to return for a final visit and, if possible, participants were followed for ongoing AEs.

The FDA's Assessment:

FDA agrees with Applicant's description of the study design. Although phase 2 was planned to include both participants with ND disease and those with R/I disease, only participants with ND disease were recruited in phase 2. Therefore, phase 1 includes participants with R/I disease only and Phase 2 includes participants with ND disease only.

Eligibility Criteria

The Applicant's Description
Pediatric participants with ND Ph+ CP CML or R/I Ph+ CML were enrolled in this study.

Main Phase 1 Inclusion Criteria (R/I participants only)

- Cytogenetic and molecular diagnosis of Ph+ CML at either time of initial CML diagnosis or at time of study screening.
- Resistance (suboptimal response or failure, as defined by 2013 European Leukemia Net guidelines) or intolerance (with or without suboptimal response or failure) to at least 1 prior TKI.
- Age ≥1 and <18 years at day of signing the informed consent.
- Lansky performance status ≥50% for participants ≤16 years of age, or Karnofsky scale ≥50% for participants >16 years of age.

Main Phase 1 Exclusion Criteria (R/I participants only):

- Diagnosis of primary Ph+ acute lymphoblastic leukemia.
- In participants with AP/BP CML: leptomeningeal leukemia, defined as positive cytology on lumbar puncture (including both CNS2 and CNS3 status), or clinical symptoms or signs present. This assessment was not required for inclusion of CP CML participants.
- Extramedullary disease only.
- Documented prior history of T315I or V299L BCR-ABL1 mutations (Note: BCR-ABL1 mutation testing was performed at screening for a baseline assessment, but results were not used to determine eligibility. This exclusion criterion was based on whether there was a known history of these mutations at the time of study entry. If these mutations became evident during the study, the participant went off study).
- Allogeneic stem cell transplantation within 3 months prior to bosutinib treatment.

Main Phase 2 Inclusion Criteria

Participants with Newly Diagnosed CML

- ND CP Ph+ CML of ≤6 months (from initial diagnosis) without any previous TKI treatment (with the exception of hydroxyurea and/or anagrelide) for CML.
- Age ≥1 and <18 years at day of attaining the informed consent.
- Lansky performance status ≥50% for participants ≤16 years of age, or Karnofsky scale ≥50% for participants >16 years of age.

Main Phase 2 Exclusion Criteria

Participants with Newly Diagnosed CML

Participants presenting with any of the following were not included in the study:

- Diagnosis of primary Ph+ acute lymphoblastic leukemia.
- Extramedullary disease only.
- Documented prior history of T315I or V299L BCR-ABL1 mutations (Note: BCR-ABL1

mutation testing was performed at screening for a baseline assessment, but results were not used to determine eligibility. This exclusion criterion was based on whether there was a known history of these mutations at the time of study entry. If these mutations became evident during the study, the participants went off study.)

- Any prior treatment with a TKI or other antitumor or anti-leukemia treatment (with the exception of hydroxyurea and/or anagrelide)

The FDA's Assessment:
FDA agrees with the Applicant's description of the inclusion criteria.

Study Endpoints

The Applicant's Description:
Objectives and endpoints are provided below in Table 18 and Table 19. The endpoints and/or measures used in this study (eg, efficacy, PK, safety, PROs, and other endpoints, as applicable) were standard, considered to be reliable, and relevant to the objectives set forth in the protocol.

Table 18. Applicant – Objectives and Endpoints of Phase 1

Type	Objective	Endpoints
Primary		
Safety	• To determine the RP2D of bosutinib for R/I ($RP2D_{R/I}$) and ND CP ($RP2D_{ND}$) pediatric participants with Ph+ CML, based on the PK, safety, and tolerability profile of bosutinib observed at various dose levels in pediatric participants with Ph+ CML who are resistant or intolerant to prior TKI therapy	• Incidence and severity of DLTs assessed during the first 28 days of treatment
PK		• PK parameters of bosutinib: C_{max}, T_{max}, AUC_t, C_{trough}, CL/F • Dose normalized PK parameters: C_{max}, AUC_t, C_{trough}; BSA adjusted CL/F[a]
Secondary		
Safety	• To evaluate the overall safety profile during the first cycle of therapy (28 days) • To evaluate the safety and tolerability profile during prolonged exposure to bosutinib	• AEs, as characterized by type, frequency, severity (as graded using CTCAE version, v4.03), timing, seriousness, and relation to study therapy • Laboratory abnormalities as characterized by type, frequency, severity and timing • ECG and performance status abnormalities
Efficacy	• To preliminarily evaluate the anti-leukemic activity in pediatric participants with Ph+ CML following resistance or intolerance to one or more TKIs	• Overall cumulative disease response: CHR, McyR (CCyR+PcyR), CcyR, MMR, deep molecular response
Exploratory		

Type	Objective	Endpoints
Safety	• To evaluate the effects of bosutinib on growth and bone metabolism	• Parameters of bone growth: including linear growth, bone age, BMD of LS, physical signs of pubertal maturation (Tanner stage and testicular volume of boys), hormones associated with growth and pubertal development (IGF-1, free T4[b], TSH[b], LH, FSH, and estradiol for girls; testosterone for boys), and a marker of bone formation and bone resorption (bone alkaline phosphatase and CTX)
PRO	• To assess the changes in GI symptoms as reported by participants and/or caregivers	• Participant and/or caregiver-reported assessments of GI symptoms as measured by selected domains from the PedsQL GI Symptom Scale
	• To assess the palatability of the bosutinib formulation (taste, texture, ease of swallowing) in participants aged 4-18 years of age	• Participant and/or caregiver-reported assessment of the taste and ability to swallow the medicine as measured by the Palatability Questionnaire for Bosutinib in participants aged 4-18 years of age
Efficacy	• To describe the clinical efficacy of bosutinib in pediatric participants with Ph+ CML following resistance or intolerance to one or more TKIs[a]	• Time to and duration of the respective responses by line of therapy • EFS (including time to transformation to AP and BP CML) by line of therapy • OS in pediatric participants with Ph+ CML by line of therapy

a. Study objective/endpoint that was added after the final SAP but before database lock.
b. Hormone associated with growth and pubertal development that is being collected in the US only as requested by FDA.

Table 19. Applicant – Objectives and Endpoints of Phase 2

Type	Objective	Endpoints
Primary		
PK	• To assess the PK of bosutinib at the $RP2D_{ND}$ and $RP2D_{R/I}$ in pediatric participants with ND or R/I Ph + CML	• C_{max}, T_{max}, AUC_t, C_{trough}, CL/F • Dose normalized PK parameters: C_{max}, AUC_t, C_{trough}; BSA adjusted CL/F[a]
	• To assess the population PK of bosutinib	• Population PK parameters of bosutinib including clearance and volume of distribution based on combined PK data from Phase 1 and Phase 2[b]
Safety	• To assess the pooled safety and tolerability profile (based on Aes) of bosutinib in pediatric participants with ND and R/I Ph+ CML	• AEs, as characterized by type, frequency, severity (as graded using CTCAE version, v4.03), timing, seriousness, and relation to study therapy (pooled across ND and R/I Ph+ CML participants and by line of therapy).
Secondary		
Efficacy	• To describe the clinical efficacy of bosutinib in pediatric participants with ND Ph+ CML in CP	• Overall cumulative disease response: CHR, McyR (CCyR+PcyR), CcyR, MMR, deep molecular response

Type	Objective	Endpoints
	• To describe the clinical efficacy of bosutinib in pediatric participants with Ph+ CML in any phase of disease following resistance or intolerance to one or more TKIs	• Time to and duration of the respective responses by line of therapy • EFS (including time to transformation to AP and BP CML) by line of therapy • OS in pediatric participants with Ph+ CML by line of therapy
Safety	• To assess other safety parameters of bosutinib	• Laboratory abnormalities as characterized by type, frequency, severity and timing (pooled across ND and R/I Ph+ CML and by line of therapy). • ECG and performance status abnormalities
PK	• To assess the relationship between the PK of bosutinib and key safety and efficacy metrics	• Relationships between PK parameters of bosutinib and key safety and efficacy metrics[b]
Exploratory		
Safety	• To evaluate the effects of bosutinib on growth and bone metabolism	• Parameters of bone growth: including linear growth, bone age, BMD of LS, physical signs of pubertal maturation (Tanner stage and testicular volume of boys), hormones associated with growth and pubertal development (IGF-1, free T4[c], TSH[c], LH, FSH, and estradiol for girls; testosterone for boys), and a marker of bone formation and bone resorption (bone alkaline phosphatase and CTX)
PRO	• To assess the changes from baseline in GI symptoms occurring during the course of therapy as reported by the participants and/or caregivers	• Participant and/or caregiver-reported assessments of GI symptoms as measured by selected domains from the PedsQL GI Scale
	• To assess the palatability of the bosutinib formulation (taste, texture, ease of swallowing) in participants aged 4-18 years of age	• Participant and/or caregiver-reported assessment of the taste and ability to swallow the medicine as measured by the Palatability Questionnaire for Bosutinib in participants aged 4-18 years of age

a. Study objective/endpoint was added after the final SAP but before database lock.
b. Analysis results will be provided in a separate report instead of the CSR.
c. Hormone associated with growth and pubertal development that is being collected in the US only as requested by FDA.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the objectives and endpoints of the protocol.

Statistical Analysis Plan and Amendments

The Applicant's Description:
A minimum of 60 total evaluable participants including at least 15 participants <12 years were expected to be enrolled combining Phase 1 and 2 to fulfill the WR commitment. At least 35 evaluable participants were planned to be enrolled in Phase 2 to fulfill the PIP commitment

(~50 total evaluable participants with both phases combined). This study does not include any formal sample size determination but is based on feasibility due to the rarity of pediatric CML.

Samples below the LLOQ were set to zero for the PK analysis. Actual sample collection times were used for the PK analysis.

Review of safety information and AEs took place on an ongoing basis by the Sponsor. Decision to stop enrollment may have been made as the results of these reviews. A Bayesian sequential monitoring was utilized for ND participants only to stop the study and enrollment early for futility based on the cumulative MMR rate. Enrollment of R/I participants was to also stop if the futility bound for ND participants was crossed. A Beta-binomial model was to be used for sequential monitoring. The sequential monitoring was to start at 20 ND participants with at least 12 months of follow-up and was to be performed for every 5 additional participants with adequate follow-up.

Analysis sets are defined as follows:

- Safety analysis set for Phase 1 and 2: the safety analysis set includes all enrolled participants who receive at least one dose of study medication.
- Full analysis set for Phase 1 and 2: The full analysis set consists of all enrolled participants regardless of whether they received a dose of study medication.
- Per protocol analysis set (evaluable for RP2D) for Phase 1:
    - The per protocol analysis set includes all enrolled participants who receive at least one dose of study medication, have no major protocol deviations during first 28 days of dosing, and have sufficient information to estimate the AUC for bosutinib.
    - Participants with major protocol deviations in the first 28 days are not evaluable for the DLT assessment and will be replaced as needed to permit RP2D estimation.
- PK concentration analysis set: the PK concentration analysis set is defined as all enrolled participants who are treated with bosutinib and have at least one reportable bosutinib concentration.
- PK parameter analysis set: the PK parameter analysis set is defined as all enrolled participants who are treated with bosutinib and have at least 1 of the PK parameters selected as primary endpoints.
- The PedsQL set: all enrolled participants who have at least returned one GI symptoms questionnaire.

Pharmacometrics analyses for PPK and E-R were conducted using the PK concentration analysis set based on a data cut-off of 13 June 2022.

The FDA's Assessment:
The statistical analysis plan above does not mention the details of the efficacy analysis. Both the Applicant and FDA base the primary efficacy analysis on the safety analysis set. Only

descriptive analyses are performed. For binary endpoints (including CHR, MCyR, CCyR and MMR), the response rate along with 2-sided 95% CI based on the exact method by Clopper-Pearson are summarized for each cohort and overall. Time to event endpoints (including time to response, duration of response, OS and EFS) are analyzed by Kaplan-Meier (KM) method.

Protocol Amendments

The Applicant's Description:

The original protocol (version 1.0, version date: 26 November 2015) was amended and superseded by version 2.0 (version date: 14 April 2016) prior to any regulatory submissions. The study started with the protocol version 2.0. A note to file dated on 22 July 2022 was written by Erasmus MC (the Sponsor) to document protocol version 1.0 was not implemented.
All subsequent changes in the conduct of the study were implemented by the following protocol versions (most relevant changes given below):

Version 3.0 (12 July 2018)

- Modification of the definition of hematologic, and molecular response to add definitions of CHR for AP/BP CML and loss of CHR
- Addition of dosing instructions for younger children
- Revising the duration of treatment for Phase 1 participants to 2 years from LPFV, and clarifying the follow-up period for patients after treatment discontinuation
- Revising the total trial duration and clarification on end of trial definition
- Addition of a palatability questionnaire

4.0 (10 Oct 2019)

- A cohort of ND pediatric participants with CML in chronic phase was added in Phase 2 using the 300 mg/m^2 once daily dose and the title was changed to reflect this
- DL2 was changed to 400 mg/m^2 (DL2B) instead of 350 mg/m^2 (DL2A) based on PK results obtained in the DL1 cohort
- The objectives of the Phases 1 and 2 were modified according to the new design of the study; ie, safety and PK are the primary objectives in all cohorts, and response is considered a secondary objective
- Based on the simulations from an updated population PK analysis using data from adult patients with CML or solid tumors and healthy volunteers, the AUCss are updated to 3150 ng•hr/mL for the dose of 500 mg/day, and 2270 ng•hr/mL for the dose of 400 mg/day.
- Sample size has been updated to 60 participants in total

4.1 (19 Dec 2019) (Implemented in US Only)

- Additional growth and bone metabolism parameters added

The FDA's Assessment:
FDA agrees with the Applicant's summary of protocol amendments.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:
This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki Council and CIOMS International Ethical Guidelines, applicable ICH GCP Guidelines, applicable ISO 14155 guidelines, and other applicable laws and regulations, including privacy laws.

Participants or their legally authorized representative were informed that their participation was voluntary. Participants or their legally authorized representative signed a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.

The FDA's Assessment:
The FDA agrees with the statement regarding good clinical practice.

Financial Disclosure

The Applicant's Position:
The integrity of the clinical study data was not affected by the financial interest of the investigators.

The FDA's Assessment:
The Applicant provided a disclosure statement that one (0.55%) of the 181 clinical investigators had disclosable financial interests in and/or arrangements with any sponsor of the clinical studies. FDA agreed that the data is not affected by financial interests of the investigators.

Patient Disposition

Data:
In Phase 1 cohorts (300, 350, and 400 mg/m^2 cohorts), bosutinib was evaluated pediatric participants with R/I Ph+ CML. In the Phase 2 CP1L cohort, bosutinib was evaluated in pediatric participants with ND Ph+ CML.

As of the data cutoff date of 19 September 2022, 52 participants were enrolled at 29 sites in 8 countries (France, Germany, Italy, Spain, Switzerland, the Netherlands, UK, and US). Forty-nine participants received study treatment: 6 in the Phase 1 300 mg/m^2 cohort, 11 in the Phase 1 350 mg/m^2 cohort, 11 in the Phase 1 400 mg/m^2 cohort, and 21 in the Phase 2 300 mg/m^2 cohort.

Overall, 44.9% of the participants discontinued treatment: 83.3% in the Phase 1 300 mg/m^2 cohort, 63.6% in the Phase 1 350 mg/m^2 cohort, 45.5% in the Phase 1 400 mg/m^2 cohort, and 23.8% in the Phase 2 300 mg/m^2 cohort.

The most common reasons for treatment discontinuation were:

- Unacceptable toxicity or more than 2 dose reductions (20.4%): 16.7% in the Phase 1 300 mg/m^2 cohort, 36.4% in the Phase 1 350 mg/m^2 cohort, 18.2% in the Phase 1 400 mg/m^2 cohort, and 14.3% in the Phase 2 300 mg/m^2 cohort.

- Unsatisfactory response or disease progression (20.4%): 33.3% in the Phase 1 300 mg/m^2 cohort, 27.3% in the Phase 1 350 mg/m^2 cohort, 27.3% in the Phase 1 400 mg/m^2 cohort, and 9.5% in the Phase 2 300 mg/m^2 cohort.

2 (4.1%) participants discontinued study treatment due to "Other" reasons, both in the 350 mg/m^2 cohort: 1 participant decided to stop the study treatment and was transitioned to adult care with 19 cycles completed; the other participant reached end of treatment with 24 cycles completed according to the protocol version 2.0.

8.2% of the participants completed the protocol and reached end of study. The reported study discontinuation included withdrawal of consent (4.1%), death (2.0%), lost to follow-up (2.0%), and other (2.0%, 1 participant refused to sign PA ICF for follow up.

The Applicant's Position:
The causes of study treatment discontinuation were consistent with the disease under study.

The FDA's Assessment:
FDA agrees with Applicant's summary of the participants' dispositions including reasons for study discontinuation and confirms the frequencies as above.

Protocol Violations/Deviations
Data:
Important protocol deviations are summarized in Table 20.

Table 20. Applicant – Summary of Important Protocol Deviations (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Protocol Deviation Category/Subcategory	Phase 1 (300mg/m²) (N=6) n (%)	Phase 1 (350mg/m²) (N=11) n (%)	Phase 1 (400mg/m²) (N=11) n (%)	Phase 2 CP1L (300mg/m²) (N=21) n (%)	Total (N=49) n (%)
Informed Consent	0	2 (18.2)	1 (9.1)	2 (9.5)	5 (10.2)
ICF signed too late	0	0	0	1 (4.8)	1 (2.0)
No (applicable) subcategory	0	0	0	1 (4.8)	1 (2.0)
Old version ICF signed	0	1 (9.1)	0	0	1 (2.0)

Table 20. Applicant – Summary of Important Protocol Deviations (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Protocol Deviation Category/Subcategory	Phase 1 (300mg/m²) (N=6) n (%)	Phase 1 (350mg/m²) (N=11) n (%)	Phase 1 (400mg/m²) (N=11) n (%)	Phase 2 CP1L (300mg/m²) (N=21) n (%)	Total (N=49) n (%)
Signature missing	0	1 (9.1)	1 (9.1)	0	2 (4.1)
Medication	2 (33.3)	2 (18.2)	3 (27.3)	0	7 (14.3)
IMP	1 (16.7)	2 (18.2)	1 (9.1)	0	4 (8.2)
No (applicable) subcategory	0	0	1 (9.1)	0	1 (2.0)
Other drugs (non-IMP)	0	1 (9.1)	0	0	1 (2.0)
Treatment	1 (16.7)	0	1 (9.1)	0	2 (4.1)
Other	0	3 (27.3)	2 (18.2)	0	5 (10.2)
No (applicable) subcategory	0	3 (27.3)	2 (18.2)	0	5 (10.2)
Procedures	6 (100)	9 (81.8)	1 (9.1)	11 (52.4)	27 (55.1)
Assessment not performed	5 (83.3)	9 (81.8)	1 (9.1)	9 (42.9)	24 (49.0)
Assessment out of window	1 (16.7)	4 (36.4)	0	5 (23.8)	10 (20.4)
Procedures not followed	1 (16.7)	0	0	0	1 (2.0)
Safety	1 (16.7)	1 (9.1)	0	0	2 (4.1)
No (applicable) subcategory	0	1 (9.1)	0	0	1 (2.0)
SAE reported too late	1 (16.7)	0	0	0	1 (2.0)
Samples	6 (100)	4 (36.4)	0	2 (9.5)	12 (24.5)
For inclusion missing/out of window	0	1 (9.1)	0	0	1 (2.0)
No (applicable) subcategory	4 (66.7)	0	0	1 (4.8)	5 (10.2)
Other missing/out of window	0	0	0	1 (4.8)	1 (2.0)
PK missing/out of window	4 (66.7)	3 (27.3)	0	2 (9.5)	9 (18.4)
Time/date not recorded adequately	0	1 (9.1)	0	0	1 (2.0)
Source/CRF	1 (16.7)	0	0	2 (9.5)	3 (6.1)
No (applicable) subcategory	1 (16.7)	0	0	2 (9.5)	3 (6.1)
Source docs missing	1 (16.7)	0	0	0	1 (2.0)

A participant with multiple deviations is counted in the corresponding categories and subcategories.
Important protocol deviations are protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.
Note: All protocol deviations are included irrespective of whether they occurred before or after the data cutoff date.
PFIZER CONFIDENTIAL SDTM Creation: 22DEC2022 (10:44) Source Data: dv Table Generation: 19JAN2023 (13:42) (Data cutoff date : 19SEP2022) Output File: ./csr1/BCHILD CSR2023/addv s014
Table 14.1.1.2 Bosutinib is for Pfizer internal use.

Note: Per the errata, 1 subject had the important protocol deviation "Treatment continued despite a Grade 3 treatment-related hematologic toxicity (neutrophil count decreased)."

The Applicant's Position:
Five (10.2%) participants had important protocol deviations classified under "Other" category: 3 in the Phase 1 350 mg/m^2 cohort: 1 participant did not meet the ELN 2013 guideline definition for resistance/intolerance but was deemed eligible prior to treatment after Sponsor evaluation confirmed resistance/intolerance criteria were met; 1 participant had followed a wrong protocol version; and 1 participant took pantoprazole (a PPI) while on treatment with bosutinib. 2 in the Phase 1 400 mg/m^2 cohort: missing urinalysis on Cycle 4 Day 1, and loss of bottle for Cycle 1 IP.

None of the protocol deviations reported was considered to have a significant impact on the analysis sets or the risk/benefit assessment.

The FDA's Assessment:
Using the ADDV dataset, protocol deviations were higher than reported in the table above. There was a total of 22 medication errors, of which 12 occurrences in 7 patients were considered important by the decision team: 4 in each cohort of 300 mg/m^2, 350 mg/m^2 and 400 mg/m^2. No important medication errors were reported in phase 2 of the study. FDA could not locate the definition of important protocol deviations that are reported in the table. However, the description of the medication deviations did not appear to impact the outcome of the study.

Similarly, regarding procedures, 109 deviations in 27 patients were considered important: 46 in the 300 mg/m^2, 32 in the 350 mg/m^2, 3 in the 400 mg/m^2 cohorts of Phase 1, and 28 in phase 2. This included 93 events of assessments not performed, in 15 events of assessments out of window, and in 1 event of procedure not followed.

We concur with the frequencies of protocol deviation in the categories of informed consent, other, safety, and source/CRF. We believe that the above noted differences in deviation between the Applicant's and our assessments did not change the results of efficacy or safety of the product in a meaningful way.

Table of Demographic Characteristics
Data:
Demographics are summarized in Table 21.

Table 21. Applicant – Demographic Characteristics (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

	Phase 1 (300mg/m²) (N=6)	Phase 1 (350mg/m²) (N=11)	Phase 1 (400mg/m²) (N=11)	Phase 2 CP1L (300mg/m²) (N=21)	Total (N=49)
Age (Years), n (%)					
>=1 - <6	2 (33.3)	2 (18.2)	0	2 (9.5)	6 (12.2)
>=6 - <12	3 (50.0)	4 (36.4)	3 (27.3)	3 (14.3)	13 (26.5)
>=12 - <18	1 (16.7)	5 (45.5)	8 (72.7)	16 (76.2)	30 (61.2)
Median (range)	8.50 (1, 17)	11.00 (4, 17)	15.00 (6, 17)	14.00 (5, 17)	13.00 (1, 17)
Mean (SD)	8.33 (5.57)	10.45 (4.41)	13.27 (3.74)	13.43 (3.84)	12.10 (4.45)
Gender, n (%)					
Male	5 (83.3)	4 (36.4)	7 (63.6)	14 (66.7)	30 (61.2)
Female	1 (16.7)	7 (63.6)	4 (36.4)	7 (33.3)	19 (38.8)
Race, n (%)					
White	0	5 (45.5)	7 (63.6)	17 (81.0)	29 (59.2)
Black or African American	0	1 (9.1)	1 (9.1)	3 (14.3)	5 (10.2)
Asian	0	1 (9.1)	3 (27.3)	0	4 (8.2)
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	1 (4.8)	1 (2.0)
Unknown[a]	6 (100.0)	4 (36.4)	0	0	10 (20.4)
Ethnicity, n (%)					
Hispanic or Latino	0	0	2 (18.2)	7 (33.3)	9 (18.4)
Not Hispanic or Latino	0	8 (72.7)	9 (81.8)	14 (66.7)	31 (63.3)
Unknown[a]	6 (100.0)	3 (27.3)	0	0	9 (18.4)

The denominator to calculate percentages is N, the number of participants in the safety analysis set within each cohort.
Age (Years)= age at enrollment.
a. Race and ethnicity were initially not captured in the case report form (included after CRF v2.1).
PFIZER CONFIDENTIAL SDTM Creation: 22DEC2022 (10:44) Source Data: adsl Table Generation: 19JAN2023 (13:42) (Data cutoff date : 19SEP2022) Output File: ./csr1/BCHILD_CSR2023/adsl_s001
Table 14.1.2.1 Bosutinib is for Pfizer internal use.

The Applicant's Position:

The baseline demographics were consistent with those expected for the underlying condition.

The FDA's Assessment:

FDA concurs with the Applicant's summary of demographic information. FDA considers the pediatric population to include those patients from birth to younger than 17 years (i.e., through 16 years of age). As such, the number of pediatrics participants ≥12 and <17 in each cohort are

as follows: 0 participants in phase 1 300 mg/m^2, 4 participants in Phase 1 350 mg/m^2, 6 participants in Phase 1 400 mg/m^2, and 10 participants in Phase 2. Efficacy and safety analyses were performed on all patients enrolled on the study (N=49) from age 1 to <18 years.

Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)
Data:
Additional Baseline Characteristics are presented in Table 22.

Table 22. Applicant – Baseline and Disease Characteristics (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

	Phase 1 (300 mg/m²) (N = 6)	Phase 1 (350 mg/m²) (N = 11)	Phase 1 (400 mg/m²) (N = 11)	Phase 2 CP1L (300 mg/m²) (N = 21)	Total (N = 49)
Disease Stage, n (%)					
Chronic Phase (CP)	6 (100.0)	11 (100.0)	11 (100.0)	21 (100.0)	49 (100.0)
Accelerated Phase (AP)	0	0	0	0	0
Blast Phase (BP)	0	0	0	0	0
Prior HSCT	0	0	0	0	0
Prior TKI Use, n (%)					
Prior Imatinib	6 (100.0)	11 (100.0)	7 (63.6)	0	24 (49.0)
Prior Nilotinib	1 (16.7)	0	2 (18.2)	0	3 (6.1)
Prior Dasatinib	3 (50.0)	4 (36.4)	9 (81.8)	0	16 (32.7)
Other	0	0	1 (9.1)	0	1 (2.0)
Number of Prior TKI, n (%)					
0	0	0	0	21 (100.0)	21 (42.9)
1	3 (50.0)	7 (63.6)	6 (54.5)	0	16 (32.7)
2	2 (33.3)	4 (36.4)	3 (27.3)	0	9 (18.4)
3	1 (16.7)	0	2 (18.2)	0	3 (6.1)
BCR-ABL transcript type, n (%)					
P190 (e1-a2)	0	0	0	0	0
P210 (e13a2/a14a2)	6 (100.0)	11 (100.0)	11 (100.0)	21 (100.0)	49 (100.0)
Other	0	0	0	0	0
Unknown	0	0	0	0	0
Prior Imatinib Therapy, n (%)					
Yes	6 (100.0)	11 (100.0)	7 (63.6)	0	24 (49.0)
Discontinued Reasons					
Progression	6 (100.0)	7 (63.6)	6 (54.5)	0	19 (38.8)
Toxicity	0	4 (36.4)	0	0	4 (8.2)
Completed Therapy	0	0	0	0	0

Table 22. Applicant – Baseline and Disease Characteristics (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

	Phase 1 (300 mg/m²) (N = 6)	Phase 1 (350 mg/m²) (N = 11)	Phase 1 (400 mg/m²) (N = 11)	Phase 2 CP1L (300 mg/m²) (N = 21)	Total (N = 49)
Other	0	0	1 (9.1)	0	1 (2.0)
Unknown	0	0	0	0	0
Prior Nilotinib Therapy, n (%)					
Yes	1 (16.7)	0	2 (18.2)	0	3 (6.1)
Discontinued Reasons					
Progression	0	0	2 (18.2)	0	2 (4.1)
Toxicity	1 (16.7)	0	0	0	1 (2.0)
Completed Therapy	0	0	0	0	0
Other	0	0	0	0	0
Unknown	0	0	0	0	0
Prior Dasatinib Therapy, n (%)					
Yes	3 (50.0)	4 (36.4)	9 (81.8)	0	16 (32.7)
Discontinued Reasons					
Progression	1 (16.7)	4 (36.4)	8 (72.7)	0	13 (26.5)
Toxicity	2 (33.3)	0	0	0	2 (4.1)
Completed Therapy	0	0	0	0	0
Other	0	0	1 (9.1)	0	1 (2.0)
Unknown	0	0	0	0	0

Note: Progression includes discontinuation due to suboptimal response/treatment failure.
PFIZER CONFIDENTIAL SDTM Creation: 22DEC2022 (10:44) Source Data: adsl Table Generation: 19JAN2023 (13:43) (Data cutoff date : 19SEP2022) Output File: ./csr1/BCHILD_CSR2023/adsl_ns_bc
Table 14.1.2.2 Bosutinib is for Pfizer internal use.

The Applicant's Position:
Baseline and disease characteristics were consistent with those expected for the underlying condition.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the baseline disease characteristics. FDA agrees that these reflect the expected pediatric population with CML.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Data:
Treatment Compliance

Total median relative dose intensity for the study was 95.50% and median relative dose intensity for was maintained above 90% for all individual treatment groups. 49.0% of all participants had at least 1 dose delay with the median time to first dose delay occurring on Day 143. One participant in the Phase 1 300 mg/m^2 cohort had 2 dose escalations, up to a highest dose of 400 mg/m^2.

Rescue Medication Use
Not applicable

The FDA's Assessment:
FDA agrees with the median relative dose intensity, number of dose delays, and number of dose escalations. However, the median time to first dose delay assessed in the ADEXSUM dataset was 28 days (range 2 to 1215 days).

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)
No applicable, the study in this submission did not have a primary efficacy endpoint.

The FDA's Assessment:
FDA agrees that efficacy endpoints in the study were not primary endpoints. Descriptive efficacy endpoints were included as secondary endpoints in both phase 1 and phase 2.

Data Quality and Integrity
The Applicant's Position:

Study sites were monitored by Sponsor and/or CRO. Sites were visited at regular intervals and a Visit Log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to participant medical and laboratory records was permitted to verify entries on the study specific CRFs.

COVID-19 Summary of Impact

The study has been ongoing since 14 November 2016 and includes the period during which the COVID-19 pandemic was occurring globally (anchor date: 11 March 2020).

Alternative study measures followed during the COVID-19 pandemic included (if applicable):

- Participant visits: The feasibility of each participant to return for scheduled visits was evaluated and the visits were rescheduled if necessary; efforts were made to keep participants on treatment if it was in their best interest. The study drug was sent to participants who were unable to visit the hospital but did need a new supply of the study drug.

- Disease evaluation visits: Central laboratory testing was continued if possible; the cytogenetic and MRD evaluations were allowed to be done locally during an outbreak situation. Central laboratory testing were resumed as soon as conditions permitted.

- Exposure to COVID-19: Related events were reported. The study drug was on hold for participants who required treatment for COVID-19 infection. For participants with asymptomatic or suspected COVID-19 infection, their benefit/risk was evaluated by the investigator to determine any requirements for dose hold, dose modifications, or other prohibitions and considerations.

- Monitoring visits: Routine on-site monitoring visits were postponed or replaced by remote visits depending on local restrictions. Additional monitoring visits were conducted to catch up on monitoring activities that can only be performed on-site.

All protocol deviations due to COVID-19 were recorded and reviewed by the study team and were deemed to have a negligible impact on the prespecified endpoints and study results.

Overall, there was a minimal impact of the COVID-19 pandemic on the conduct and data quality of the study.

The FDA's Assessment:
The data submitted to this sNDA were of adequate quality to perform the safety review. Accommodations during the COVID-19 pandemic are acceptable.

Efficacy Results – Secondary and other relevant endpoints

Data:

(b) (4)

Table 23. Applicant – Summary of Cumulative Major Cytogenetic Response (MCyR) (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Cytogenetic Response	Phase 1 (300mg/m²) (N=6)	Phase 1 (350mg/m²) (N=11)	Phase 1 (400mg/m²) (N=10)	Phase 1 Total (R/I) (N=27)	Phase 2 CP1L (300mg/m²) (N=18)
(b) (4)					

Table 24. Applicant – Summary of Cumulative MCyR/CCyR Excluding Participants with Respective Baseline Response MCyR/CCyR for Resistant/Intolerant Participants (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Cytogenetic Response	Phase 1 (300mg/m²) (N=6)	Phase 1 (350mg/m²) (N=11)	Phase 1 (400mg/m²) (N=10)	Phase 1 Total (R/I) (N=27)
(b) (4)				

Table 24. Applicant – Summary of Cumulative MCyR/CCyR Excluding Participants with Respective Baseline Response MCyR/CCyR for Resistant/Intolerant Participants (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Cytogenetic Response	Phase 1 (300mg/m²) (N=6)	Phase 1 (350mg/m²) (N=11)	Phase 1 (400mg/m²) (N=10)	Phase 1 Total (R/I) (N=27)
(b) (4)				

(b) (4)

The Applicant's Position:
Although this study was not powered to evaluate efficacy measures, the results in the BCHILD study demonstrated rapid and deep early responses in CML, comparable to those demonstrated in adult studies. Therefore, it is anticipated that the early markers of efficacy demonstrated are expected to result in favorable survival outcomes with longer duration of therapy. Efficacy results support use of bosutinib as an effective potential therapeutic option for both R/I and ND CML pediatric patients at the doses identified in the BCHILD study.

The FDA's Assessment:
Although the results presented above in Table 23 and Table 24 are claimed to be based on safety analysis set with 28 R/I and 21 ND patients from Phase 1 and 2 cohorts, respectively, the sample sizes in the header do not match with those presented in the above sections in Table 20, Table 21 and Table 22. In particular, patient numbers in columns "Phase 1 (400 mg/m2) (N = 10)", "Phase 1 Total (R/I) (N = 27)", and "Phase 2 CP1L (300 mg/m²) (N = 18)" are smaller than the corresponding number of patients in safety analysis set, i.e., N = 11, 28, and 21, respectively. Therefore, FDA does not consider the results presented above in Table 23 and Table 24 as the primary efficacy results. Instead, Table 25 below presents the correct results of the major efficacy endpoints based on the safety analysis set. Note the rates of hematologic and cytogenetic responses are reported by all patients enrolled regardless of baseline response status in patients with R/I disease.

Table 25: Summary of Cumulative Response Rates (Safety Analysis Set)

Parameter	Phase 1				Phase 2 (ND) (N = 21)
	300 mg/m2 (N = 6)	350 mg/m2 (N = 11)	400 mg/m2 (N = 11)	Total (R/I) (N = 28)	
CHR, n % (95% CI)	6 100 (54, 100)	10 91 (59, 100)	8 73 (39, 94)	24 86 (67, 96)	18 86 (64, 97)
MCyR, n % (95% CI)	6 100 (54, 100)	10 91 (59, 100)	7 64 (31, 89)	23 82 (63, 94)	16 76 (53, 92)
CCyR, n % (95% CI)	5 83 (36, 100)	10 91 (59, 100)	7 64 (31, 89)	22 79 (59, 92)	15 71 (48, 89)
MMR, n % (95% CI)	4 67 (23, 96)	5 46 (17, 77)	5 46 (17, 77)	14 50 (31, 69)	6 29 (11, 52)

Cumulative response is defined as any on-treatment response.
Source: CSR Section 14.2

Dose/Dose Response

Data:

Based on the acceptable tolerability and lack of exposure-safety relationship across the evaluated dose range, (b) (4) the recommended doses for pediatric patients are 300 and 400 mg/m^2 once daily following a meal, for the ND and R/I indications, respectively.

The Applicant's Position:

Although the study was not powered to detect differences in efficacy, different doses were assessed in the R/I population; across dose ranges responses were similar. The ND population was evaluated at a single dose level, therefore dose-response assessments cannot be conducted.

The FDA's Assessment:

FDA agrees that the responses were similar across the dose range with a trend toward lower responses at higher doses; however, this was likely influenced by the shorter duration on therapy for patients enrolled at the higher doses. Patients with ND disease were enrolled at a single dose level. The lower response rate in these patients also likely reflects a shorter duration on therapy.

Durability of Response

Data:

Duration of response

As the study is ongoing, the median follow up varies significantly across cohorts; therefore, KM estimates for each cohort are presented for the timepoint where a sufficient number of participants have an adequate follow-up.

- KM estimates of maintaining CHR at Month 12 was 100% for all treatment arms except Phase 1 400 mg/m^2, where the KM estimate of maintaining CHR at Month 12 was 87.5%. One confirmed loss of CHR was erroneously reported for 1 participant in the 400 mg/m^2 cohort, which is corrected in the BCHILD errata. KM estimates of maintaining CHR at Month 24 was 100% for all sufficiently mature treatment arms.
- KM estimates of maintaining CcyR and McyR at Month 12 were 100% for all treatment arms, and 100% at Month 24 for all sufficiently mature treatment arms.
- KM estimate of maintaining MMR was 100% at Month 12 for all treatment arms (with the exception of the Phase 1 400 mg/m^2 cohort which had a KM estimate of 100% at 6 months). Only the 300 mg/m^2 cohort was sufficiently mature to demonstrate a KM estimate of 100% at 24 months.

Event-Free Survival

Phase 1 groups 350 and 400 mg/m^2 reported 1 participant with progression (9.1%). No participants had progression in the remaining treatment arms. Estimated EFS rates were as follows:

- Phase 1 300 mg/m^2: 100% at Month 12 and 24
- Phase 1 350 mg/m^2: 100% at Month 12 and 24
- Phase 1 400 mg/m^2: 87.5% at Month 12
- Phase 2 300 mg/m^2: 95.2% at Month 12

Note: an erroneous event is included in this analysis, but corrected in the BCHILD errata.

Overall survival was not mature at the time of data cutoff. There were no on-treatment deaths. One participant in the 300 mg/m^2 cohort died 15 months after the last dose of bosutinib.

The Applicant's Position:

Although this study was not powered to demonstrate efficacy outcomes and follow-up was limited, treatment with bosutinib showed a clinically meaningful durability across all depths of responses (hematologic, cytogenetic, and molecular) in pediatric participants. Maintenance of responses at 12 months was 100% for nearly all sufficiently mature measures, and additional follow-up is required to further inform long-term maintenance.

The FDA's Assessment:

The study is ongoing, and the follow-up was limited. The study is continuing to recruit patients in phase 2, and all patients will be followed including efficacy evaluations for 2 years after the final patient is enrolled with additional follow up for safety for up to 10 years. Later evaluation of efficacy endpoints will allow more precise description of the response rates and durability of

responses.

Persistence of Effect

Data:
Adult Participants with ND or R/I Ph+ CML

ND CML participants

In Study B1871053 (hereafter referred to as Study 1053), ND adults with CP CML were treated with bosutinib 400 mg QD or imatinib 400 mg QD, which demonstrated an improvement in early and persistent molecular response rates of participants in the bosutinib arm. The study met its primary and secondary efficacy Month 12 (48 weeks) objectives and demonstrated that the proportion of participants with MMR at Month 12 and CCyR by Month 12 in the mITT population were statistically significantly higher in the bosutinib arm (47% and 77%, respectively) compared to the imatinib arm (37% and 66%, respectively). By Month 60, participants treated with bosutinib had deep molecular responses, compared to imatinib. In the mITT population, MMR by Month 60 was achieved by 74.0% and 65.6% of participants in the bosutinib and imatinib arms, respectively. At 60 Months, the estimated OS rate in the bosutinib and imatinib groups was 95% and 94%, respectively. The median treatment duration for the bosutinib and imatinib arms was 55.1 and 55.0 months, respectively. This long-term follow-up of ND CML participants demonstrated persistence of efficacy in the patient population expected to be similar to that in pediatric patients in the BCHILD study.

R/I CML participants

Study B1871040 (hereafter referred to as Study 1040) was a long-term treatment extension study for R/I CML participants who received bosutinib in Study B1871006 (hereafter referred to as Study 1006).

Study 1006, a single-arm, open-label, multicenter study in patients with CML who were resistant or intolerant to prior therapy, was conducted to evaluate the efficacy and safety of bosutinib 500 mg once daily in patients with imatinib-resistant or -intolerant CML with separate cohorts for CP, AP, and BP disease previously treated with 1 prior TKI (imatinib) or more than 1 TKI (imatinib followed by dasatinib and/or nilotinib). In this study, bosutinib demonstrated clinically meaningful efficacy across all CML patient populations including those in CP, AP, and BP, regardless of whether the previous treatment was with imatinib alone, or with both imatinib and a second generation TKI (dasatinib or nilotinib), and responses were reported in a small population that was previously treated with all of these 3 currently approved TKI therapies for CML. In the CP2L evaluable population, MCyR was attained/maintained at 24 weeks and at any time in 40.1% and 59.5% of participants, respectively.

In the long-term follow-up Study 1040, analysis was based on a minimum of 60 Months for patients with CP CML treated with 1 prior TKI (imatinib) and a minimum of 48 Months for

patients with CP CML treated with imatinib and at least 1 additional TKI. For the 59.5% of patients with CP CML treated with 1 prior TKI (imatinib) who achieved a MCyR at any time, the median duration of MCyR was not reached. Among these patients, 65.4% and 42.9% had a MCyR lasting at least 18 and 54 months, respectively. For the 40.2% of patients with CP CML treated with imatinib and at least 1 additional TKI who achieved a MCyR at any time, the median duration of MCyR was not reached. Among these patients, 64.4% and 35.6% had a MCyR lasting at least 9 and 42 months, respectively.

The response rates seen in Study 1006, comparable with those in the BCHILD study, have demonstrated persistence at the 60-Month follow-up in Study 1040. It is therefore expected that similar persistence is seen in pediatric patients with R/I CML.

Pediatric Participants with ND or R/I Ph+ CML

A total of 49 participants with R/I or ND Ph+ CML have been treated with bosutinib for a median of 14.29 months (range: 0.30, 21.36 months) and 10.94 months (range: 0.20, 26.35 months), respectively. As the study has been ongoing for several years, the median follow-up varies significantly across individual treatment groups. Bosutinib demonstrated persistence of efficacy in R/I and ND CML participants, with most participants attaining (or maintaining, in the instance of R/I) MCyR and CCyR. Of the MCyR and CCyR responders, only 2 participants reported response loss: 1 (10.0%) participant in the Phase 1 350 mg/m^2 cohort and 1 (14.3%) participant in the Phase 1 400 mg/m^2 cohort. There were no other reports of response loss, PD, or death in any participant with MCyR or CCyR. Most participants achieving a response were able to maintain it long-term with KM estimates of 92.3% at Month 24 for the R/I population and 100% at Month 12 for ND population, for both MCyR and CCyR.

Despite limited duration of therapy in the Phase 2 cohort in particular, MMR was achieved in 50.0% and 28.6% of R/I and ND populations, respectively. Of all of the MMR responders, only 2 participants (both in R/I population) lost their response: 1 (20.0%) participant in the Phase 1 350 mg/m^2 cohort and 1 (20.0%) participant in the Phase 1 400 mg/m^2 cohort. There were no other reports of response loss, PD, or Death in any participant with MMR. Most participants achieving a response were able to maintain it long-term with KM estimates of 72.0% at Month 24 for the R/I population and 100% at Month 12 for ND population.

As follow-up in the Phase 2 ND cohort was short, the standard practice milestone of MR2 at 6 months was used and was achieved in 57.1% of evaluable participants.

The Applicant's Position:
Bosutinib treatment in pediatric participants as reported in the BCHILD study showed clinically meaningful and durable responses in both ND and R/I CML participant populations at the dose of 300 and 400 mg/m^2, respectively. The persistence of effect in pediatric participants is expected to be similar to that demonstrated in long-term follow-up of adult participants treated with bosutinib.

The FDA's Assessment:
The long term follow data presented by the Applicant in adults with CML is reported in the current version of the USPI. Response rates in children were reported at any time, not at specific timepoints as routinely done in the adult studies, making direct comparisons of response rates difficult. FDA agrees that the hematological, cytogenetic, and molecular response rates in ND and R/I pediatric patients are generally consistent with those in the adult studies accounting for the shorter duration on study for some pediatric patients enrolled later in the study.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Data:
Selected domains of a validated PRO (the PedsQL Gastrointestinal Symptom Scale) were used to assess problems with stomach pain and hurt, problems with nausea and vomiting, and problems with diarrhea. Most responses indicated that participants "never" or "almost never" experienced on-treatment gastrointestinal symptoms.

The Palatability Questionnaire for Bosutinib was developed as an exploratory questionnaire to determine whether other attributes of the formulation such as taste and texture are acceptable to pediatric patients. The palatability responses indicated that 71.7% of responses in swallowing showed no trouble swallowing, 69.3% of responses indicated that participants liked or remained neutral to the taste, and 66.9% of responses indicated that participants liked or remained neutral to the study intervention.

The Applicant's Position:
Exploratory PROs suggest bosutinib did not cause GI symptoms in patients and palatability was acceptable.

The FDA's Assessment:
A total of 44 patients or caregivers filled out palatability assessments and most had more than one assessment. In 84% of the questionnaires the patient (≥8 to <18 years old) gave the report and in 16% it was the caregiver. The majority of questionnaires (89%) were with the capsules or tablets swallowed whole with 6% dissolved and administered via oral syringe and 5% with the capsule content added to foodstuff and swallowed. Regarding the palatability, 14% of the questionnaires reported dislike the taste very much, difficulty swallowing was reported in 10%, and 15% reported disliked very much overall. The palatability evaluation can vary in patient from visit-to-visit making overall palatability difficult to assess. For example, in response to palatability, one patient responded liked a little, dislikes a little, and not sure on three different occasions. Similarly, in terms of difficult to swallow, the patient had difficult to swallow, no problem swallowing, and not sure on three different occasions. However, the majority of patients found the tablets and capsules palatable which was reflected in the overall compliance with treatment.

As to the PedsQL Gastrointestinal Symptom Scale, all 49 patients or caregivers responded. The most frequent complaint was watery diarrhea in 7%. We agree with the Applicant's assessment that GI QOL was not significantly affected in patients on the BCHILD study.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

A total of 49 pediatric patients with R/I or ND Ph+ CML have been treated with bosutinib on Study BCHILD. The median time on treatment was 12.2 months (range, 0.2 to 60.9 months) with longer treatment reported in patients with R/I disease, particularly those enrolled earlier in the study. Bosutinib demonstrated persistence of efficacy in R/I and ND CML participants, and most participants attained MCyR and CCyR. Of the 20 patients who achieved MMR, only 2 participants reported response loss of MMR after 13.6 and 24.7 months of treatment; both patients who lost response on study had R/I disease. Response rates are not affected by dose or patient's age and are comparable to those reported in adults. A trend toward lower response was observed in patients treated at higher doses, but this is likely reflecting a shorter duration on treatment for patients enrolled later in the study.

(b) (4)

(b) (4)

the pediatric study was evaluated separately in support of the pediatric indication. Study BCHILD enrolled only patients with chronic phase CML, either ND or R/I to prior therapy. There was no hypothesis testing for efficacy in either cohort of pediatric patients. Sample size was based on the number of patients needed for PK assessments across age groups and feasibility of enrollment for this rare disease in pediatric patients. The final sample size exceeded that number needed for PK. Efficacy evaluations were descriptive with information collected on the hematologic, cytogenetic, and molecular response rate, as well as durability of responses. (b) (4)

For approvals in adults with CML, MCyR, and MMR can be considered direct measures of clinical benefit with regular approval typically established with 2 years of follow up for the R/I population and 5 years of follow up for ND population, and a randomized trial is generally needed to support a new indication for first-line treatment of CML. However, the Applicant is targeting a rare pediatric population, and even with other approved TKIs in this setting, bosutinib might address an unmet medical need. The number of patients enrolled was reasonable in both the ND and R/I populations with CP CML and similar to the number of pediatric patients with CML enrolled to establish efficacy for other TKIs in this class. (b) (4)

(b) (4) the activity of bosutinib in the treatment of CML supports the observed response rates in pediatric patients where the driver mutation is the same and the disease is similar in both populations. In addition, there were few patients enrolled in the lower age cohorts, among which the youngest patient enrolled was 1 year old. Within the pediatric patients, there were no apparent differences in efficacy observed by age. BSA-adjusted dose across the pediatric age range resulted in similar exposure by age. Based on the results observed in pediatric patients with CP CML enrolled in the BCHILD study, the observed rates of MCyR and MMR with durability are considered clinically meaningful. Given the relatively short follow up for patients enrolled, the long-term benefit in pediatric patients with CP CML is unknown; however, patients who are continuing on treatment with bosutinib will be followed for at least an additional two years for efficacy, and the longer term benefit is well established in adult patients with CP CML.

(b) (4)

8.1.4. Assessment of Efficacy Across Trials

This application is supported by a single study; thus, this section is not applicable to this review.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

As of the data cutoff date of this report, bosutinib demonstrated clinical benefits in pediatric participants with R/I Ph+ CML as well as in pediatric participants with ND Ph+ CML. These early responses are in keeping with internationally accepted milestones for optimal CML therapy and are known to have a significant influence on survival outcomes[25], [26]. Although survival estimates within the study are still immature, it is recognized that achievement of deep responses, most notably CcyR (even in those patients that do not subsequently achieve MMR), as early as 3 months after initiation of therapy is a determinant of improved EFS and OS in adult CML patients. It is described that achievement of a BCR-ABL ratio ≤10% at 3 months, supported by achievement of CcyR translates significantly into improved survival benefit for ND CML patients treated with first- and second-generation TKIs. Among evaluable participants in the BCHILD study Phase 2 ND CML cohort, 81.8% had achieved this response milestone. Optimal response to therapy is widely regarded as having a BCR-ABL ratio of ≤10% at 3 months and subsequently ≤1% at 6 months.

As these findings are taken from the setting of an adult CML population, applicability to a pediatric population is widely accepted due to the identical treatment approach, and as results in the BCHILD study are comparable to those in adult studies it is anticipated that the early

markers of efficacy demonstrated are expected to result in favorable survival outcomes with longer follow-up.

The FDA's Assessment:
FDA concurs with the Applicant's conclusion that the effectiveness results are comparable to those achieved in adults with CP CML treated with bosutinib and in pediatric patients who received other TKIs.

8.2. Review of Safety

The Applicant's Position:
This safety review of bosutinib is primarily based on the results from the BCHILD Study in the treatment of pediatric participants with ND CML or R/I CML.

The safety profile observed for bosutinib in the BCHILD Study is consistent with that observed in studies in the initial NDA; no new safety concerns were observed.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

8.2.1. Safety Review Approach

The Applicant's Position:
The safety population for the BCHILD study is defined as all participants who received at least one dose of study medication. The clinical review of safety is based on the following: AEs, SAEs, vital signs and physical examination, ECG (12-lead), echocardiogram, laboratory assessments including pregnancy tests, verification of concomitant treatments, and assessments of growth and bone metabolism. The safety review approach implemented was appropriate for the patient population studied, and consistent with that evaluated in the previous submission.

The FDA's Assessment:
FDA agrees with the Applicant's approach to the review of safety data. As noted, FDA review is based on the pediatric population enrolled in the BCHILD study. It is premature to comment on bosutinib effect on growth and bone metabolism, since follow up time is too short, and data on growth and development is not being considered in this safety review. The study is planned to follow participants for up to 10 years. A PMR regarding growth and development will be issued with the approval in pediatric patients. See Section 13 on postmarketing requirements and commitment for additional details.

8.2.2. Review of the Safety Database

Overall Exposure

Data:
Treatment exposure is presented in Table 26.

Table 26. Applicant – Duration of Treatment (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

	Phase 1 (300mg/m²) (N=6)	Phase 1 (350mg/m²) (N=11)	Phase 1 (400mg/m²) (N=11)	Phase 1 Total (R/I) (N=28)	Phase 2 CP1L (300mg/m²) (N=21)	Total (N=49)
Duration of treatment (Months)[a]						
N	6	11	11	28	21	49
Mean (SD)	27.72 (19.53)	16.95 (13.38)	11.28 (7.47)	17.03 (14.02)	11.38 (7.44)	14.61 (11.90)
Median (range)	20.09 (9.26, 60.85)	9.86 (0.95, 38.57)	11.89 (0.30, 21.36)	14.29 (0.30, 60.85)	10.94 (0.20, 26.35)	12.19 (0.20, 60.85)
Category (Months)						
<=1	0	1 (9.1)	2 (18.2)	3 (10.7)	1 (4.8)	4 (8.2)
>1 - <=2	0	0	0	0	2 (9.5)	2 (4.1)
>2 - <=4	0	0	1 (9.1)	1 (3.6)	1 (4.8)	2 (4.1)
>4 - <=8	0	4 (36.4)	1 (9.1)	5 (17.9)	3 (14.3)	8 (16.3)
>8 - <=12	1 (16.7)	1 (9.1)	2 (18.2)	4 (14.3)	4 (19.0)	8 (16.3)
>12 - <=24	3 (50.0)	0	5 (45.5)	8 (28.6)	9 (42.9)	17 (34.7)
>24	2 (33.3)	5 (45.5)	0	7 (25.0)	1 (4.8)	8 (16.3)

a. The Total Number of Days From First To and Including Last Day of each study treatment.
NOTE: The duration is defined as (last dosing date – first dosing day + 1)/30.4375, where last dosing date is last non-zero dose date.
PFIZER CONFIDENTIAL SDTM Creation: 22DEC2022 (10:44) Source Data: adexsum Table Generation: 19JAN2023 (14:32)
(Data cutoff date : 19SEP2022) Output File: ./csr1/BCHILD CSR2023/adex ns s001
Table 14.4.1.1 Bosutinib is for Pfizer internal use.

The Applicant's Position:

The number of pediatric patients exposed to bosutinib, and the median duration of the exposure allowed a reliable assessment of safety in pediatric patients. The safety profile of bosutinib in pediatric patients was consistent with what has been described in the adult CML studies.

The FDA's Assessment:

FDA concurs with the Applicant's results regarding duration of treatment. Median duration of treatment in this application is significantly shorter than that of the randomized study in newly diagnosed adult participants with Ph+ CML (median 55 months, range 0.3-60 months) and that of the single study in adult participants with refractory/resistant disease (median 26 months) that led to approval of bosutinib. The difference in duration of treatment is inherent in the study design and plan, and the pediatric participants who have not discontinued therapy will continue treatment for this chronic disease. As previously mentioned, up to 10 years of follow-

up for safety is planned.

Relevant characteristics of the safety population:

The Applicant's Position:

Baseline characteristics and conditions, and use of concomitant medications were consistent with the patient population under study.

The FDA's Assessment:

The FDA agrees with the statement. The efficacy and safety population were the same, and the baseline characteristics were described in Section 8.1.2.

Adequacy of the safety database:

The Applicant's Position:

The overall size of the safety data set and the extent of exposure at the proposed dose level were sufficient to characterize the safety of bosutinib for the proposed indication of treatment of pediatric patients with ND CML or R/I CML.

The participant population in the BCHILD Study with respect to age, gender, and other demographic, disease, and baseline characteristics is consistent with what is expected for the proposed indication, enabling these results to be generalized to patients with ND CML or R/I CML. Further details are provided in Section 8.2.

The FDA's Assessment:

The size and diversity of the study population is acceptable for safety analysis.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the clinical safety review. No safety update is required.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Categorization of Adverse Event

The Applicant's Position:

AEs were collected as specified in the BCHILD Study protocol. AEs were coded using MedDRA version 25.1 and were summarized by treatment arm.

The safety of study treatment was evaluated on the basis of the:

- AEs and laboratory parameters were graded using NCI-CTCAE version 4.03
- Frequency of deaths, SAEs, and other clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose interruption and/or reduction)
- Changes in laboratory variables
- Frequency and type of AEs by demographic subgroups (age, race, geographic region)

AESIs were reported in the following categories: Myelosuppression, Liver, GI, Cardiac, Vascular, Renal, Effusion, and Rash.

The FDA's Assessment:
FDA agrees with the Applicant's categorization of AEs.

Routine Clinical Tests

Each treatment cycle lasted for 28 days. In Cycle 1 visits were conducted on Day 1, 8, 14, and 22, with an additional ECG conducted on Day 15 (Phase 2) and pre-dose escalation. Additional visits were conducted at the beginning of each cycle for Cycles 2-7 and at the beginning of every 3rd cycle for Cycles 8 and greater. Safety assessments were collected as follows:

- Physical examination, adverse event assessment, symptom assessment, vital signs, and laboratory safety assessments including hematology, blood chemistry, and liver function were performed at each visit.
- Urinalysis was conducted at the beginning of Cycle 1 and every 3 cycles thereafter (Cycle 4, 7, etc)
- Electrocardiograms were collected on Day 14 and the beginning of Cycle 2, 3, and 4. Echocardiograms and assessments of bone growth were conducted every 12 months after the start of therapy.
- Estradiol in girls and testosterone in boys was monitored every 6 months starting with Cycle 7.
- Menarcheal status and pregnancy testing, as applicable, were collected at visits associated with the beginning of a new cycle

The Applicant's Position:
The routine clinical safety tests carried out were consistent with clinical practices, appropriate for the population under study. All of the laboratory tests were routine safety assessments in this study population.

The FDA's Assessment:
FDA agrees with the monitoring plan and finds it adequate for this participant population.

8.2.4. Safety Results

Deaths

Data:
There were no on-treatment deaths. One participant in the 300 mg/m^2 cohort died 15 months after the last dose of bosutinib.

The Applicant's Position:
There were no deaths reported within 28 days after last dose of study treatment.

The FDA's Assessment:
The FDA agrees with Applicant's summary of deaths. No patients died during study treatment or within 28 days of the last dose. One participant died from meningitis 15 months after discontinuation of study drug. It is likely that the death is related to complications from the underlying disease and not to bosutinib.

Serious Adverse Events

Data:

24.5% participants had SAEs. The most frequently reported SAE was Vomiting (3 participants, 6.1%), while other SAEs were experienced in ≤2 participants by PT (Table 27). No fatal SAEs were reported.

The frequency of SAEs was highest in the Phase 1 300 mg/m^2 cohort (66.7%, Table 27).

Table 27. Applicant – Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Number of Participants Evaluable for Adverse Events	Phase 1 (300mg/m²) (N=6)	Phase 1 (350mg/m²) (N=11)	Phase 1 (400mg/m²) (N=11)	Phase 2 CP1L (300mg/m²) (N=21)	Total (N=49)
Number (%) of Participants with Serious Adverse Events[a]: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Participants with any event	4 (66.7)	3 (27.3)	2 (18.2)	3 (14.3)	12 (24.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	2 (9.5)	2 (4.1)
Febrile neutropenia	0	0	0	1 (4.8)	1 (2.0)
Thrombocytopenia [1]	0	0	0	1 (4.8)	1 (2.0)
GASTROINTESTINAL DISORDERS	1 (16.7)	1 (9.1)	1 (9.1)	1 (4.8)	4 (8.2)
Vomiting	1 (16.7)	1 (9.1)	1 (9.1)	0	3 (6.1)
Diarrhoea	0	0	0	1 (4.8)	1 (2.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (16.7)	1 (9.1)	0	0	2 (4.1)
Pyrexia	1 (16.7)	1 (9.1)	0	0	2 (4.1)
INFECTIONS AND INFESTATIONS	3 (50.0)	0	0	2 (9.5)	5 (10.2)
Appendicitis	0	0	0	1 (4.8)	1 (2.0)
Device related infection	1 (16.7)	0	0	0	1 (2.0)
Lower respiratory tract infection viral	1 (16.7)	0	0	0	1 (2.0)
Pneumonia	1 (16.7)	0	0	0	1 (2.0)
Skin infection	0	0	0	1 (4.8)	1 (2.0)
Upper respiratory tract infection	1 (16.7)	0	0	0	1 (2.0)

Table 27. Applicant – Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Number of Participants Evaluable for Adverse Events	Phase 1 (300mg/m²) (N=6)	Phase 1 (350mg/m²) (N=11)	Phase 1 (400mg/m²) (N=11)	Phase 2 CP1L (300mg/m²) (N=21)	Total (N=49)
Number (%) of Participants with Serious Adverse Events[a]: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1 (9.1)	0	1 (2.0)
Head injury	0	0	1 (9.1)	0	1 (2.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (16.7)	0	0	0	1 (2.0)
Pain in extremity	1 (16.7)	0	0	0	1 (2.0)
NERVOUS SYSTEM DISORDERS	0	1 (9.1)	0	0	1 (2.0)
Headache	0	1 (9.1)	0	0	1 (2.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (16.7)	0	0	0	1 (2.0)
Pulmonary hypertension	1 (16.7)	0	0	0	1 (2.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (9.1)	1 (9.1)	1 (4.8)	3 (6.1)
Rash maculo-papular	0	1 (9.1)	1 (9.1)	0	2 (4.1)
Urticaria	0	0	0	1 (4.8)	1 (2.0)

Note: Descending order of the incidences is presented at the level of preferred term within each system organ class based on the incidences of "Total" column.
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report two or more different adverse events within the higher level category.
Treatment-emergent adverse events (TEAE) were defined as any event increasing in severity from baseline or any new event starting during bosutinib therapy or within 28 days of the last dose of study treatment.
a. Serious adverse events (SAEs) are counted at MedDRA preferred term/Cohort with each individual SAE counted only once per participant per cohort.
[1] For this summary, the following clustered terms for cytopenias: Thrombocytopenia (PT=Thrombocytopenia; Platelet count decreased),
Anaemia (PT=Anaemia; Haemoglobin decreased), Neutropenia (PT=Neutropenia; Neutrophil count decreased), Leukopenia (PT=Leukopenia; White blood cell count decreased),
Lymphopenia (PT=Lymphopenia; Lymphocyte count decreased) are used. PT=preferred term.
MedDRA v25.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22DEC2022 (10:44) Source Data: adae Table Generation: 20JAN2023 (18:05) (Data cutoff date : 19SEP2022) Output File: ./csr1/BCHILD_CSR2023/adsae_s001
Table 14.3.2.2.2 Bosutinib is for Pfizer internal use.

The Applicant's Position:
No new safety issues were identified from a review of the SAEs.

The FDA's Assessment:
Treatment-emergent serious adverse events in Study BCHILD by dose and disease status were evaluated and confirmed. In participants with ND disease, SAEs were less common in pediatric participants compared to those reported in adult participants (14% vs. 22% respectively) while in R/I participants the frequencies of SAEs were similar (32% vs. 30% respectively). No additional safety concerns beyond those reported in adults were reported in pediatric patients.

Dropouts and/or Discontinuations Due to Adverse Effects
Data:

53.1% participants had TEAEs leading to dose delay, dose reduction, or permanent treatment discontinuation (discontinuation of treatment is discussed further in Section 8.1.2).

20.4% participants had TEAEs leading to permanent treatment discontinuation. The most frequently reported TEAE leading to permanent treatment discontinuation was ALT increased (3 participants, 6.1%), while other TEAEs were reported in ≤2 participants by PT.

49.0% participants had at least 1 dose delay. The cohort with the highest percent of subjects requiring at least one dose delay was the Phase 1 350 mg/m^2 cohort (54.5%), and the cohort with the lowest percent of subjects requiring at least one dose delay was the Phase 1 400 mg/m^2 cohort (36.4%). The median time to first dose delay ranged from 26 days in the Phase 2 300 mg/m^2 cohort to 143 days in the Phase 1 300 mg/m^2 cohort.

28.6% participants had at least 1 dose reduction. The cohort with the highest percent of subjects requiring at least one dose reduction was the Phase 1 350 and 400 mg/m^2 cohorts (36.4%), the cohort with the lowest percent of subjects requiring at least one dose delay was the Phase 1 300 mg/m^2 cohort (16.7%). The median (range) time to first dose reduction ranged from 18 days in the Phase 1 350 mg/m^2 cohort to 123 days in the Phase 2 300 mg/m^2 cohort.

The Applicant's Position:
AEs leading to permanent treatment discontinuation were generally consistent with the known safety profile of bosutinib. No new safety signals were identified.

The FDA's Assessment:
Analyzing the data provided, FDA confirms the frequencies of dose discontinuation due to AE in 2 participants or more and includes increased ALT in 3 (6%), and increased AST, diarrhea, fatigue, and maculo-papular rash in 2 (4%) participants each. The median time to first dose reduction was 36 days (minimum 8 days in a participant who received 350 mg/m^2 and maximum 227 days in a participant in phase 2 who received 300 mg/m^2) and differs from these reported by the Applicant. The different values do not significantly change the safety evaluation, but discontinuation and its causes should be acknowledged in the context of long-term therapy. The median time to first dose delay was 28 days.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Adverse Events Leading to Delay, Reduction, or Permanent Discontinuation from study treatment are summarized in Table 28.

Table 28. Applicant – Summary of Adverse Events Leading to Delay, Reduction, or Permanent Discontinuation From Study Treatment by MedDRA System Organ Class and Preferred Term (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Number of Participants Evaluable for AEs[a]	Phase 1 (300mg/m²) (N=6)	Phase 1 (350mg/m²) (N=11)	Phase 1 (400mg/m²) (N=11)	Phase 2 CP1L (300mg/m²) (N=21)	Total (N=49)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Participants with events	3 (50.0)	6 (54.5)	5 (45.5)	12 (57.1)	26 (53.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	2 (18.2)	8 (38.1)	10 (20.4)
Thrombocytopenia [1]	0	0	2 (18.2)	7 (33.3)	9 (18.4)
Neutropenia [1]	0	0	1 (9.1)	3 (14.3)	4 (8.2)
GASTROINTESTINAL DISORDERS	1 (16.7)	3 (27.3)	3 (27.3)	4 (19.0)	11 (22.4)
Diarrhoea	0	2 (18.2)	2 (18.2)	3 (14.3)	7 (14.3)
Abdominal pain	1 (16.7)	2 (18.2)	1 (9.1)	2 (9.5)	6 (12.2)
Vomiting	0	3 (27.3)	2 (18.2)	0	5 (10.2)
Abdominal pain upper	0	0	0	1 (4.8)	1 (2.0)
Nausea	0	0	1 (9.1)	0	1 (2.0)
Oral pain	1 (16.7)	0	0	0	1 (2.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	1 (9.1)	1 (4.8)	2 (4.1)
Fatigue	0	0	1 (9.1)	1 (4.8)	2 (4.1)
INFECTIONS AND INFESTATIONS	1 (16.7)	1 (9.1)	0	0	2 (4.1)
Otitis externa	1 (16.7)	0	0	0	1 (2.0)
Rhinovirus infection	0	1 (9.1)	0	0	1 (2.0)
INVESTIGATIONS	0	3 (27.3)	2 (18.2)	1 (4.8)	6 (12.2)
Alanine aminotransferase increased	0	3 (27.3)	2 (18.2)	1 (4.8)	6 (12.2)
Aspartate aminotransferase increased	0	2 (18.2)	0	1 (4.8)	3 (6.1)
Bilirubin conjugated increased	0	0	1 (9.1)	0	1 (2.0)
Blood alkaline phosphatase increased	0	1 (9.1)	0	0	1 (2.0)
Blood creatine phosphokinase increased	0	1 (9.1)	0	0	1 (2.0)
Blood creatinine increased	0	1 (9.1)	0	0	1 (2.0)
METABOLISM AND NUTRITION DISORDERS	0	1 (9.1)	0	1 (4.8)	2 (4.1)

Table 28. Applicant – Summary of Adverse Events Leading to Delay, Reduction, or Permanent Discontinuation From Study Treatment by MedDRA System Organ Class and Preferred Term (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Number of Participants Evaluable for AEs[a]	Phase 1 (300mg/m²) (N=6)	Phase 1 (350mg/m²) (N=11)	Phase 1 (400mg/m²) (N=11)	Phase 2 CP1L (300mg/m²) (N=21)	Total (N=49)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Decreased appetite	0	1 (9.1)	0	0	1 (2.0)
Hyperuricaemia	0	0	0	1 (4.8)	1 (2.0)
PSYCHIATRIC DISORDERS	1 (16.7)	0	0	0	1 (2.0)
Delirium	1 (16.7)	0	0	0	1 (2.0)
RENAL AND URINARY DISORDERS	0	0	0	1 (4.8)	1 (2.0)
Haematuria	0	0	0	1 (4.8)	1 (2.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (16.7)	2 (18.2)	3 (27.3)	1 (4.8)	7 (14.3)
Rash maculo-papular	0	1 (9.1)	3 (27.3)	0	4 (8.2)
Urticaria	0	1 (9.1)	0	1 (4.8)	2 (4.1)
Erythema nodosum	1 (16.7)	0	0	0	1 (2.0)

Note: Descending order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the incidences of "Total" column.
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a Participant may report two or more different
adverse events within the higher level category.
[1] For this summary, the following clustered terms for cytopenias: Thrombocytopenia (PT=Thrombocytopenia; Platelet count decreased),
Anaemia (PT=Anaemia; Haemoglobin decreased), Neutropenia (PT=Neutropenia; Neutrophil count decreased), Leukopenia (PT=Leukopenia; White blood cell count decreased),
Lymphopenia (PT=lymphopenia and PT=lymphocyte count decreased) are used.
a. Includes treatment-emergent adverse events leading to delay, reduction and adverse events leading to permanently discontinuation of study treatment.
PT= preferred term. MedDRA v25.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22DEC2022 (10:44) Source Data: adae Table Generation: 19JAN2023 (14:04) (Data cutoff date : 19SEP2022) Output File: ./csr1/BCHILD CSR2023/adae dr s184
Table 14.3.1.1.2 Bosutinib is for Pfizer internal use.

The Applicant's Position:

AEs leading to dose delays, reduction, or permanent discontinuation were generally consistent with the known safety profile of bosutinib. The rate of permanent treatment discontinuations associated with AEs was low and no new safety signals were identified.

The FDA's Assessment:
Slightly more than half the patients (53%) had AEs leading to discontinuation, dose reduction or interruption. Discontinuation was relatively low at 10 (20%) patients. Dose reduction occurred in 15 (30%) patients and interruption occurred in 20 (41%) patients. Dose modifications were slightly more common among patients with R/I disease (50%) compared to ND disease (42%). The frequencies and the specifics of the AEs leading to DC, dose reduction or interruption are similar or better than the known results in adult patients.

Significant Adverse Events

Data:
53.1% of participants had TEAEs leading to the dose delay, dose reduction or permanent treatment discontinuation. No trend in TEAEs was observed across dose cohorts.

The most frequent TEAEs (occurring in ≥10% of participants) leading to dose delay, dose reduction or permanent treatment discontinuation were Thrombocytopenia (18.4%), Diarrhoea (14.3%), ALT increased and Abdominal pain (each 12.2%), and Vomiting (10.2%).

20.4% of participants had TEAEs leading to permanent treatment discontinuation. The most frequently reported TEAEs leading to permanent treatment discontinuation was ALT increased (3 participants, 6.1%), while other TEAEs were experienced in ≤2 participants by PT.

The Applicant's Position:
The safety profile of bosutinib in all pediatric participants was acceptable and generally consistent with what has been described previously in the adult CML trials. Most AEs associated with bosutinib treatment were manageable with dose reductions/dose interruptions or supportive medication. No new safety signals were identified in pediatric participants as of the data cutoff.

The FDA's Assessment:
The analysis of significant adverse events was reviewed and confirmed.

Treatment Emergent Adverse Events and Adverse Reactions
Data:
Adverse events are summarized in Table 29.

The most frequently reported TEAEs (≥50% of participants, all grades) were Diarrhoea (81.6%), Abdominal pain (61.2%), and Vomiting (55.1%). Other frequently reported TEAEs (≥20% of participants, all grades) included Nausea (49.0%), Thrombocytopenia (36.7%), Headache (34.7%), Pyrexia (30.6%), ALT increased (30.6%), Rash maculo-papular and Fatigue (both 28.6%), Decreased appetite (26.5%), Pain in extremity (22.4%), Abdominal pain upper and Constipation (both 20.4%). The most frequently reported Grade 3 or 4 TEAEs (≥10% of

participants) were Thrombocytopenia (18.4%), ALT increased (14.3%), Diarrhoea (12.2%), and Neutropenia (10.2%).

Table 29. Applicant – Summary of Adverse Events (All Causalities) (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Number (%) of Participants	Phase 1 (300mg/m²) n (%)	Phase 1 (350mg/m²) n (%)	Phase 1 (400mg/m²) n (%)	Phase 2 CP1L (300mg/m²) n (%)	Total n (%)
Participants evaluable for adverse events	6	11	11	21	49
Participants with TEAEs	6 (100.0)	11 (100.0)	11 (100.0)	21 (100.0)	49 (100.0)
Participants with drug related TEAEs	6 (100.0)	11 (100.0)	11 (100.0)	20 (95.2)	48 (98.0)
Participants with serious TEAEs	4 (66.7)	3 (27.3)	2 (18.2)	3 (14.3)	12 (24.5)
Participants with Maximum Grade 3 or 4 TEAEs	3 (50.0)	6 (54.5)	6 (54.5)	18 (85.7)	33 (67.3)
Participants with Maximum Grade 5 TEAEs	0	0	0	0	0
Participants permanently discontinued from study treatment due to adverse events	1 (16.7)	4 (36.4)	2 (18.2)	3 (14.3)	10 (20.4)
Participants with delay, reduction or permanent discontinuation from study treatment due to adverse events[a]	3 (50.0)	6 (54.5)	5 (45.5)	12 (57.1)	26 (53.1)

Participants are counted only once in each row.
Treatment-emergent adverse events (TEAE) were defined as any event increasing in severity from baseline or any new event starting during bosutinib therapy or within 28 days of the last dose of study treatment.
a. Includes treatment-emergent adverse events leading to delay, reduction and adverse events leading to permanently discontinuation of study treatment.
MedDRA v25.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22DEC2022 (10:44) Source Data: adae Table Generation: 19JAN2023 (13:15) (Data cutoff date : 19SEP2022) Output File: ./csr1/BCHILD CSR2023/adae ns s020
Table 14.3.1.2.1 Bosutinib is for Pfizer internal use.

The Applicant's Position:
AESI frequencies were generally consistent with the known safety profiles of bosutinib, and no new safety signals were identified.

The FDA's Assessment:
FDA review of the data agrees with the frequencies of adverse events noted in the text by the Applicant, except for abdominal pain, which is accurate in the label but not in the text above. The difference most likely stems from the use of grouped terms in the label. Summary of adverse events is consistent with the knows toxicity of bosutinib.

Additional analysis of AE by cohort and by age:

Table 30. Adverse Reactions (10% or Greater) in Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Ph+ CML-CP Resistant or Intolerant to Prior Therapy Who Received Bosulif in BCHILD by cohort group

Preferred Term	Phase 1 Cohort 1		Phase 1 Cohort 2		Phase 1 Cohort 3		Phase 2 Cohort 4		Total	
Dose	300 mg/m^2 N=6		350 mg/m^2 N=11		400 mg/m^2 N=11		300 mg/m^2 N=21		N=49	
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
Diarrhea	5 (83)	1 (17)	10 (91)	1 (9)	10 (91)	1 (9)	15 (71)	3 (14)	36 (73)	6 (12)
Abdominal pain (GT)	4 (67)	0	11 (100)	1 (9)	9 (82)	0	12 (57)	1 (5)	30 (61)	2 (4)
Vomiting	5 (83)	1 (17)	8 (73)	1 (9)	6 (55)	1 (9)	8 (38)	0	27 (55)	3 (6)
Nausea	6 (100)	0	6 (55)	0	5 (46)	0	7 (33)	17 (5)	24 (49)	4 (2)
Rash (GT)	6 (100)	0	5 (46)	1 (9)	10 (91)	3 (27)	3 (14)	0	24 (49)	4 (8)
Hepatic dysfunction (GT)	1 (17)	0	5 (46)	3 (27)	5 (46)	2 (18)	7 (33)	2 (10)	18 (37)	7 (14)
Fatigue (GT)	4 (67)	0	3 (27)	1 (9)	3 (27)	0	8 (38)	1 (5)	18 (37)	2 (4)
Headache	3 (50)	0	3 (27)	1 (9)	5 (46)	0	6 (29)	0	17 (35)	1 (2)
Pyrexia	4 (67)	1 (17)	5 (36)	0	4 (36)	0	2 (10)	1 (5)	15 (31)	8 (4)
Decreased appetite	3 (50)	0	2 (18)	0	4 (36)	0	4 (19)	1 (5)	13 (27)	4 (2)
Constipation	3 (50)	0	1 (9)	0	3 (27)	0	3 (14)	0	10 (20)	0
Respiratory tract infection (GT)	4 (67)	1 (17)	1 (9)	0	1 (9)	0	0	0	6 (12)	1 (2)
Neutropenia	0	0	0	0	2 (18)	2 (18)	5 (24)	3 (14)	7 (14)	5 (10)
Thrombocyto-penia	0	0	0	0	0	1 (9)	12 (57)	8 (38)		

GT: grouped preferred terms. See Section 19.4 for definitions of grouped terms.

Table 31. Adverse Reactions (10% or Greater) in Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Ph+ CML-CP Resistant or Intolerant to Prior Therapy Who Received Bosulif in BCHILD by patient's age group

	≥1 to <6 N=6		≥6 to <12 N=13		≥12 to <18 N=30		Total N=49	
Preferred Term								
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
Pyrexia	5 (83)	1 (17)	5 (38)	0	5 (17)	1 (3)	15 (31)	8 (4)
Diarrhea	4 (67)	0	12 (92)	3 (23)	24 (80)	3 (10)	40 (82)	6 (12)
Abdominal pain	4 (67)	0	11 (85)	1 (8)	21 (70)	1 (3)	36 (73)	2 (4)

Rash	4 (67)	1 (17)	5 (38)	0	13 (43)	3 (10)	22 (49)	4 (8)
Fatigue	3 (50	1 (17)	3 (23)	0	12 (40)	1 (3)	18 (37)	2 (4)
Decreased appetite	3 (50)	0	3 (23)	0	7 (23)	1 (3)	13 (27)	4 (8)
Headache	2 (25)	0	4 (31)	1 (8)	11 (37)	0	17 (35)	1 (2)
Respiratory tract infection	2 (25)	1 (17)	2 (15)	0	2 (7)	0	6 (12)	1 (2)
COVID-19	2 (25)	0	0	0	0	0	2	0
Pain in extremity/ bone pain	2 (25)	1 (17)	4 (31)	0	5 (17)	0	11 (22)	1 (2)
Hepatic dysfunction (GT)	1 (17)	1 (17)	5 (38)	4 (31)	12 (40)	2 (7)	18 (37)	7 (14)
Vomiting	5 (83)	1 (17)	9 (69)	1 (8)	13 (43)	1 (3)	27 (55)	3 (6)
Neutropenia	0	0	1 (8)	1 (8)	6 (20)	4 (13)	7 (14)	5 (10)
Platelet count decrease	1 (17)	0	2 (15)	1 (8)	15 (50)	6 (46)	18 (37)	7 (14)

GT: grouped preferred terms. See Section 19.4 for definitions of grouped terms.

In general, the overall AEs and their frequencies were similar to those expected and reported in the label for the use of bosutinib in adult patients. There were no new safety signals in the pediatric population.

Safety by dose does not show dose-dependent toxicity within the range that had been tested (300-400 mg/m^2). The analysis of toxicity by age seem to indicate that patients age ≥1 to <6 had relatively higher toxicity than patients older than 6 who had the same toxicity as seen in adult patients. Nevertheless, patient number in the group of less than 6 years was too low to draw meaningful conclusions. Post marketing monitoring will be important to clarify the effect of age on toxicity.

Comparison between patients with R/I disease and patients with ND disease may not be accurate considering the shorter follow up of patients on Phase 2 who were accrued only after completion of Phase 1.

Laboratory Findings
Data:

The most frequent (≥50% of participants, all grades) hematology laboratory abnormalities reported on treatment were anaemia (61.2%), platelet count decreased (57.1%) and white blood cell decreased (57.1%)"

The most frequent shifts from Grade ≤2 at baseline to Grade 3 or 4 postbaseline (≥10% of participants) for hematology laboratory results were platelet count decreased (18.4%) and neutrophil count decreased (10.2%).

The most frequent (≥50% of participants, all grades) chemistry laboratory abnormalities reported on treatment were creatinine increased (93.9%), AST increased (65.3%), and ALT increased (63.3%), of which the percentage of participants with events was similar across Phases 1 and 2 cohorts.

The most frequent shifts from Grade ≤ 2 at baseline to Grade 3 or 4 at postbaseline (≥10% of participants) in chemistry laboratory test values were ALT increased (14.3%).

No potential Hy's law cases were identified during the study.

The Applicant's Position:
Hematology and chemistry laboratory test abnormalities were generally consistent with the known safety profile of bosutinib.

No potential Hy's Law cases were reported. There were no notable liver function test findings that would necessitate a change in the current information in the label.

The FDA's Assessment:
Based on review of the data, FDA concurs with the statements and frequencies of laboratory adverse events in this section. A table of the frequency of laboratory abnormalities that worsened from baseline is included in the label.

Vital Signs
Data:
The most frequent vital signs changes of potential clinical concern were DBP <55 mmHg, which was experienced in 44.9% of participants. 14.3% of participants experienced DBP <55 mmHg on at least 2 separate consecutive study visits.

The Applicant's Position:
Vital signs observations in the BCHILD study were generally consistent with the known safety profile of bosutinib.

The FDA's Assessment:
FDA concurs with the Applicant's analysis of decreased DBP. Despite this observation, hypotension was not frequently reporting in adults or children.

Electrocardiograms (ECGs)
Data:
At each collection timepoint 12-lead ECGs were collected in triplicate approximately 5 minutes apart. In Phase 1 and 2 ECGs were obtained at screening and on Day 14 at predose and 6 hours

post-dose. Additional ECGs were collected pre-dose on Day 1 of Cycle 2, 3, and 4, and pre-dose at the time of any dose escalation. In Phase 2, additional ECGs were collected pre-dose on Day 15 of Cycle 1. ECG data was transferred to a central reviewing cardiologist for re-evaluation.

A shift from QTcF ≥450 to 480 msec at baseline to <450 msec was reported in 1 (2.0%) participant. There was no QTcF value of 450 msec or higher observed during the treatment.

Shifts from <450 msec at baseline to ≥450 to 480 msec in QTcB (derived from the uncorrected QT and heart rate using central lab data) were reported in 12 (24.5%) participants, most of whom (7 of 12 participants) were in the Phase 2 300 mg/m^2 cohort; and a shift from >480 to 500 msec at baseline to ≥450 to 480 msec was reported in 1 (2.0%) participant.

The Applicant's Position:
There were no notable ECG findings in the data from the BCHILD study that would necessitate a change in the current information in the label.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of ECG findings.

QT
Data:
No formal QT studies were done.

The Applicant's Position:
Not Applicable

The FDA's Assessment:
FDA concurs that no formal QT study was submitted as part of this sNDA.

Immunogenicity
Data:
Not applicable

The FDA's Assessment:
The FDA concurs that immunogenicity is not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

There are no submission-specific safety issues to present.

Data:
No new safety signals were identified in the BCHILD study.

The Applicant's Position:
Not applicable to this submission.

The FDA's Assessment:
FDA concurs that no specific safety issues were submitted.

Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability
Data:
Not applicable to this submission.

The Applicant's Position:
No COA analyses were performed that informed safety/tolerability outcomes. Exploratory analyses of PRO endpoints associated with efficacy are presented in Section 8.1.

The FDA's Assessment:
FDA concurs that PRO endpoints were exploratory and are reviewed in Section 8.1.2.

8.2.6. Safety Analyses by Demographic Subgroups

Data:
Due to a limited sample size, meaningful analyses cannot be conducted based on subgroups of age, gender, or race.

The Applicant's Position:
The small number of participants in the different subgroups does not allow for definitive conclusions to be made among demographic subgroups.

The FDA's Assessment:
FDA evaluated toxicity by age (Table 31); see comments above for summary. FDA agrees that the subgroups were small and definitive conclusions cannot be reached.

8.2.7. Specific Safety Studies/Clinical Trials

Data:
No new information in this submission.

The Applicant's Position:
Safety summaries were included as part of the BCHILD Study; no additional safety-specific studies were performed.

The FDA's Assessment:
FDA concurs that no additional safety studies were conducted in pediatric patients.

8.2.8. Additional Safety Explorations

Data:
No new information for bosutinib is presented in this submission.

The FDA's Assessment:
FDA agrees that no additional safety explorations were reviewed.

Pediatrics and Assessment of Effects on Growth
Data:
DEXA and bone age X-ray assessment were collected at Screening and every 12 months after the start of therapy. Blood tests (IGF-1, Free T4, TSH, LH, FSH for girls, estradiol for girls, and testosterone for boys) were collected at Screening, the start of Cycle 7, and every 6 months after the start of Cycle 7.

The Applicant's Position:
As of the data cutoff for this submission, the collected growth and bone metabolism data are not mature to allow meaningful analysis yet. A limited number of participants (especially in participants with ND Ph+ CML enrolled more recently) have data available for more than Cycle 12/13.

The monitoring of the growth and bone metabolism parameters is ongoing and planned to continue till 28 days after the last dose of study drug. More data are expected to be collected and available for analysis at a later stage.

The FDA's Assessment:
FDA agrees that it is premature to analyze information on bosutinib effects on growth. FDA will issue a PMR that includes a requirement to follow the patients for at least 5 years from beginning of treatment to monitor growth and development through physical examination, radiological studies, and obtaining biological markers. See additional information in Section 13.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Data:
There were no AEs of drug abuse or cases of withdrawal symptoms.

The Applicant's Position:
Treatment of overdose with bosutinib should consist of general supportive measures. There is no antidote for bosutinib.

No AEs associated with drug abuse or withdrawal of bosutinib were reported.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

8.2.9. Safety in the Postmarket Setting
Safety Concerns Identified Through Postmarket Experience
Data:
Bosutinib is not approved for the treatment of pediatric patients with newly-diagnosed or R/I Ph+ CML. Postmarketing experience with bosutinib is limited to adult patients.

The Applicant's Position:
There is no postmarketing experience in pediatric participants.

The FDA's Assessment:
The FDA agrees that there is no postmarketing experience with on label use of bosutinib in pediatric patients as it has not been approved for that indication. Postmarketing experience is mostly in adults; however, the most recent PSUR includes spontaneous reports of rare off-label use in pediatric patients. Postmarketing reports were not provided by age and included only an age range for which reports were received (ages 7 to 95 years).

Expectations on Safety in the Postmarket Setting
The Applicant's Position:
Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application.

The FDA's Assessment:
FDA agrees with the Applicant's statement; however, due to the short follow-up, especially in Phase 2 patients, FDA will issue a PMR that includes follow-up reporting on the patients for at least 5 years from beginning of treatment, as detailed in Section 116.

8.2.10. Integrated Assessment of Safety
Data:

Not applicable

The Applicant's Position:
Not applicable

The FDA's Assessment:
FDA agrees that no integrated assessment of safety is provided as the BCHILD study is the provides the only safety information in pediatric patients.

SUMMARY AND CONCLUSIONS
8.3. Statistical Issues
The FDA's Assessment:
Study BCHILD enrolled 49 pediatric patients with newly diagnosed or relapsed/intolerant CP Ph+ CML. This trial is a two-part study. The primary objectives of each part of Study BCHILD were safety and PK. Efficacy was a secondary objective in each part of Study BCHILD.

(b) (4)

'Study BCHILD (b) (4) efficacy outcomes were considered to be of high magnitude and sufficient durability to be clinically meaningful. The reviewer notes that the efficacy endpoints captured are commonly accepted measures of efficacy in CML and were specified as secondary endpoints in the protocol.

In N=21 newly diagnosed CP Ph+ CML patients, the major (MCyR) and complete (CCyR) cytogenetic responses were 76.2% (95% CI: 52.8, 91.8) and 71.4% (95% CI: 47.8, 88.7), respectively. The MMR among patients with ND CP Ph+ CML was 28.6% (95% CI: 11.3, 52.3). The median duration of follow-up was 14.2 months (range: 1.1, 26.3 months) in patients with ND CP CML.

The major (MCyR) and complete (CCyR) cytogenetic responses among N=28 patients with R/I CP Ph+ CML were 82.1% (95% CI: 63.1, 93.9) and 78.6% (95% CI: 59.0, 91.7), respectively. The MMR among patients with R/I CP Ph+ CML was 50.0% (95% CI: 30.6, 69.4). The MR4.5 (defined as BCR-ABL/ABL IS ≤ 0.0032%) was 17.9% (95% CI: 6.1, 36.9). Among 14 patients with R/I CP CML who achieved MMR, two patients lost MMR after 13.6 months and 24.7 months on treatment. The median duration of follow-up for overall survival was 23.2 months (range: 1.0, 61.5 months) in patients with R/I CP Ph+ CML.

The analysis of durability of response is limited due to the wide range of follow up among cohorts in this ongoing study. By the data cutoff date, only 33.3% patients in Phase 1 300 mg/m² cohort were ongoing on study treatment, whereas still 95.2% patients in Phase 2 cohort are still ongoing.

8.4. Conclusions and Recommendations

<u>The FDA's Assessment:</u>

The approval and benefit:risk assessment are primarily based on the clinical efficacy and safety data from Study BCHILD, (b) (4)

Study BCHILD included 49 pediatric patients with newly diagnosed or relapsed/intolerant CP Ph+ CML treated with bosutinib and showed complete cytogenetic response in 71.4% and 78.6% patients, respectively, and MMR in 28.6% and 50% patients, respectively. Only 2 patients with R/I disease lost their MMR responses. The analysis of durability of response was limited due to the wide range of follow up between cohorts in this ongoing study.

The analysis of the toxicity of bosutinib on study BCHILD showed it to be similar to that observed and documented in the label for adult patients, with the major toxicities included GI toxicity, rash, and hepatotoxicity. There were no deaths of patients on study and SAEs in the ND patients were less common compared to those reported in adult participants and in R/I participants the frequencies of SAEs were similar between adults and children. The most common drug discontinuation due to AE remained hepatotoxicity. The most frequent hematologic and chemistry laboratory abnormalities that worsened from baseline included decreased platelets and white blood cells, creatinine increase, and AST and ALT increase, and were generally consistent with the known safety profile of bosutinib. No additional warning & precaution is required, although frequencies of the specific AE, SAE, and lab abnormalities were updated in the label.

The long-term safety and the effect of bosutinib on growth and development were not established due to the length of follow-up and a PMR was sent to the sponsor.

The updated label includes the efficacy and safety of bosutinib in pediatric patient that was collected on the BCHILD study. Considering the overall data assessment, the updated indication includes pediatric patients 1 year of age and older with chronic phase Ph+ chronic myelogenous leukemia, newly diagnosed or resistant or intolerant to prior therapy.

X X

Xin Wang, PhD
Primary Statistical Reviewer

Jonathon Vallejo, PhD
Statistical Team Leader

X X

Kamar Godder, MD
Primary Clinical Reviewer

Lori Ehrlich, MD, PhD
Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants because the application did not raise significant efficacy or safety issues for the proposed indications.

10. Pediatrics

The Applicant's Position:
Exemption from the PREA (21 U.S.C. 355c) requirements to conduct additional pediatric assessments, pursuant to Section 505B(k)(1) of the FD&C Act, applies to bosutinib and the pediatric sNDA because Orphan Drug Designation has been granted to bosutinib for the treatment of chronic myelogenous leukemia (reference designation request # 08-2748; received 24 February 2009).

The FDA's Assessment:
Pediatric safety and efficacy information was presented in S-025 and in this review to support the pediatric indication of bosutinib for the treatment of patients 1 year of age and older with CP Ph+ CML, newly diagnosed or resistant or intolerant to prior therapy. This submission is for pediatric assessment for patients ≥ 1 year old. Bosutinib has orphan designation for the treatment of CML and is exempt from pediatric investigations under PREA.

The BCHILD study was the subject of a Pediatric Written Request (PWR) issued under BPCA. FDA agrees that the terms of the PWR were met. Review by the pediatric exclusivity board granted Pediatric Exclusivity. See the annotated response to the pediatric written request for details on the review of the fulfillment of the PWR.

11. Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Indication 1	(b) (4)	The FDA modified the indication as follows: BOSULIF is a kinase inhibitor indicated for the treatment of: • adult and pediatric participants 1 year of age and older with chronic phase Ph+ chronic myelogenous leukemia (CML), newly diagnosed or resistant or intolerant to prior therapy. • adult participants with accelerated or blast phase Ph+ CML with resistance or intolerance to prior therapy.
Dosage and Administration 2	Included the recommended dosing schedule (Table 1) and food volume (Table 2) for pediatric patients. Included the recommended dose adjustments for myelosuppression (Table 3). Included dose escalation language for pediatric patients. Included dose adjustments for non-hematologic adverse reactions for pediatric patients.	In section 2.1 FDA generally agreed but added clarification regarding oral intake. In section 2.4, FDA added a separate table for dosage adjustments for renal and hepatic impairment in pediatric patients that includes BSA banding and pediatric dosing to align with a similar table for adult patients.
Dosage Forms and Strengths 3	Included the recommended capsule form and strengths.	FDA concurs.
Contraindications 4	None.	FDA concurs.
Warnings and Precautions 5	Addition of BCHILD information in the Warnings and Precautions for Gastrointestinal toxicity, Hepatic toxicity, Cardiovascular toxicity, Fluid retention and Renal toxicity.	Deleted table that provided data on eGFR shift in pediatric patients and added the information provided in the text.

Adverse Reactions 6	Adverse reactions (≥10%) in pediatric patients with ND Ph+ CML-CP or R/I Ph+ CML-CP and CML-AP in Single-Arm Trial (Table 11). Select laboratory abnormalities that worsened from baseline in pediatric patients with ND Ph+ CML-CP or R/I Ph+ CML-CP and CML-AP (Table 12).	FDA concurs with the adverse reaction data table, but moved information on adverse reactions that report lab abnormalities to laboratory table and modified values in to delineate worsening from baseline.
Use in Specific Populations 8	(b) (4)	Modified (b) (4) Added that pediatric dosing is BSA-based and that compared to adults, BSA-normalized apparent clearance was higher in pediatric patients.
Description 11	Included details on the composition of the capsules.	FDA concurs with the changes but removed the (b) (4) statements.
Clinical Pharmacology 12	Included details on the pharmacokinetics in pediatrics.	FDA modified this section as follows: In section 12.2, a statement that the time course of bosutinib pharmacodynamic response has not been fully characterized as per 21 CFR 201.57(c)(13)(i)(B) was added. In section 12.3, (b) (4) emoved. In the *Pediatric Patients* subsection, descriptive statistics of AUC, C_{max}, and C_{trough} in pediatric patients with CP Ph+ CML were added. Other changes were made throughout to align with current labeling practice.
Clinical Studies 14	Efficacy results in pediatric patients with ND CP and R/I Ph+ CML are included in Table 16 including MCyR, CcyR, MMR, (b) (4), MR4.5.	For clarity, the section was re-organized to report both participants with ND and those with R/I in the same section. The table was removed and results of MCyR, CCyR, MMR, and MR4.5 were reported in text.
How Supplied/Storage and Handling 16	Included storage and handling conditions for the capsules.	FDA generally concurs with the changes but made some edits to include instructions to store and dispense the capsules in the original container and added instructions about the (b) (4)

		and child resistant closures.
Patient Counseling Information 17	Addition of dosage and administration information.	FDA modified this section to align with changes made in the USPI.
PPI	Patient Information updated.	FDA modified the PPI to align with changes made in the USPI.

The Applicant's Position:
The Applicant proposes to update the US Prescribing Information for bosutinib within the Sections denoted in the table above.

The FDA's Assessment:
The USPI and Patient Package Insert (PPI) were revised by FDA as described in the table above; see the labeling attached to the approval letter for final agreed upon labeling. The PPI was reviewed and revised by the FDA's Patient Labeling Team and Review Team. Revisions were made throughout the PPI for clarity, readability, consistency with the USPI and with data on other TKIs approved in pediatric patients, employing current labeling policies and practices. For further details, refer to the Patient Labeling Team's review filed with NDA 203341. Instructions for Use was added to provide detailed instructions on opening the capsules for administration in applesauce or yogurt.

12. Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
There are no additional risk management strategies needed beyond recommended labeling. The review teams agreed that labeling is sufficient to address safety concerns for treatment with bosutinib in pediatric patients with ND or R/I Ph+ CML in chronic phase.

13. Postmarketing Requirements and Commitment

The FDA's Assessment:
Justification for PMR:
Philadelphia chromosome positive (Ph+) Chronic myelogenous leukemia (CML) in children is a rare chronic disease, with serious and life-threatening consequences. To achieve response, pediatric patients are required to receive long term therapy, during years that are critical for them to attain their growth and puberty.

BCR-ABL Tyrosine kinase inhibitors (TKIs) are known to induce a delay in puberty and growth. Bosutinib, a TKI inhibitor, may cause delay in growth and development, specifically in pre-

pubertal patients. Considering that pediatric patients with Ph+ CML receive continuous therapy for many years, long-term evaluation of growth and development will assess signals of serious risk of growth delay related to the use of the drug.

The safety of bosutinib was evaluated in a single arm study in pediatric patients with newly diagnosed and those with refractory or those that were intolerant to at least one tyrosine kinase inhibitor (TKI) (study BCHILD; ITCC-054/COG AAML1921). The median duration of exposure was 12.2 months (range: 0.2 to 60.0 months). Twenty five percent of the patients developed severe adverse event. The most common safety issues in the single arm study include infection, gastrointestinal disorders, cytopenias, rash, and pyrexia.
Considering the drug was administered for a median of 12.2 months only, the goal of this PMR is to evaluate and provide data to assess the serious potential risk of growth and developmental delay and the safety of long-term administration of bosutinib

PMR Language: Conduct Study BCHILD (ITCC-054/COG AAML1921) to identify, characterize, and determine the incidence of the serious potential risks of growth and developmental delay and worsening of serious adverse reactions including but not limited to gastrointestinal disorders, hematologic toxicity, and infectious adverse events with prolonged exposure (>12 months) to bosutinib in pediatric patients with chronic phase chronic myeloid leukemia (CML). All patients enrolled in Study BCHILD (ITCC-054/COG AAML1921) must be evaluated for growth and development milestones and serious adverse events annually for at least 5 years from the initiation of bosutinib. Include assessments of growth parameters, parameters of bone metabolism and growth, Tanner stage, hormones associated with growth and pubertal development, and serious adverse events. Include incidence rates, time to onset, and outcomes.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes _x_ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _x_ No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _x_ No

14. Division Director (DHOT) (NME ONLY)

X

15. Division Director (OCP)

X

16. Division Director (OB)

X

17. Division Director (Clinical)

X

R. Angelo de Claro, MD
Division Director (DHM1)

18. Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19. Appendices

19.1. References

The Applicant's References:

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19.2. Financial Disclosure

The Applicant's Position:

The integrity of BCHILD Study data was not affected by the financial interest of the investigators.

The FDA's Assessment:

FDA reviewed the financial disclosures document and found no concerns of lack of integrity.

Covered Clinical Study (Name and/or Number):* BCHILD (ITCC-054/AAML1921)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 181		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant) NO DUE DILIGENCE WAS COLLECTED (NOT APPLICABLE)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Not applicable, no new information is provided in the current submission

The FDA's Assessment:
Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:
The Applicant developed a pediatric population PK (PPK) model using data from 41 patients aged 1 to <18 years in Study BCHILD.

FDA assessment determined that the Applicant's model had worse fit as age decreased and did not adequately characterize the impact of age, BSA, or both on bosutinib PK. The Applicant's pediatric PPK model is therefore inadequate for the purposes of characterizing covariate effects on bosutinib PK or predicting bosutinib exposure in pediatric patients with Ph+ CML.

The clinical pharmacology PK assessment in Section 6.2.2.1 evaluates bosutinib exposure derived from noncompartmental analysis (NCA) because the NCA results are more likely to accurately characterize exposure across the range of age and BSA in pediatric patients.

19.4.1.2 PPK Assessment Summary
The Applicant's Position:

(b) (4)

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(b) (4)

[redacted]

The FDA's Assessment:

FDA found the Applicant's PPK model inadequate for the purposes of characterizing bosutinib PK and predicting bosutinib exposure in pediatric patients. The results of the Study BCHILD NCA (refer to Section 6.2.2.1) are more likely to describe bosutinib exposure accurately in pediatric patients with Ph+ CML. A PPK model with adequate characterization of bosutinib PK

in pediatric patients with Ph+ CML has not been identified at this time.

PPK Model Development

(b) (4)

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(b) (4)

In conclusion, the Applicant's pediatric PPK model is inadequate for the purposes of characterizing covariate effects on bosutinib PK or predicting bosutinib exposure in pediatric patients with Ph+ CML. (b) (4)

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

The E-R efficacy analysis utilized individual bosutinib exposure derived from the pediatric PPK model, which was determined to be inadequate for predicting exposure in pediatric patients (refer to Section 19.4.1). Therefore, the Applicant's E-R efficacy analysis may be confounded by poor characterization according to age and BSA, and the accuracy of the E-R efficacy analysis is highly uncertain.

Although the pediatric E-R efficacy analysis should not be used to support any conclusions regarding bosutinib exposure and efficacy in pediatric patients with CP Ph+ CML, no clear associations were identified between PPK model-predicted exposure and rates of cumulative CCyR, MMR, or MR2 for the proposed pediatric indications.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

(b) (4)

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The FDA's Assessment:

Individual patient exposure for the E-R efficacy analysis was calculated using the Applicant's final pediatric PPK model. As discussed in Section 19.4.1, the PPK model is inadequate for predicting bosutinib exposure in pediatric patients. Therefore, the Applicant's E-R efficacy analysis may be confounded by poor characterization according to age and BSA, and the accuracy of the E-R efficacy analysis is highly uncertain. The Applicant's E-R efficacy analysis may only be used for exploratory purposes and cannot be used to support any conclusions regarding bosutinib exposure and efficacy in pediatric patients with CP Ph+ CML. The efficacy of bosutinib for the proposed pediatric indication is to be based on clinical efficacy data (refer to Section 8.1).

(b) (4)

(b) (4)

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

The E-R safety analysis utilized individual bosutinib exposure derived from the pediatric PPK model, which was determined to be inadequate for predicting exposure in pediatric patients (refer to Section 19.4.1). Therefore, the Applicant's E-R safety analysis may be confounded by poor characterization according to age and BSA, and the accuracy of the E-R safety analysis is highly uncertain.

Although the pediatric E-R safety analysis should not be used to support any conclusions regarding bosutinib exposure and safety events in pediatric patients with CP Ph+ CML, no clear associations were identified between PPK model-predicted exposure and Grade ≥3 TEAE, Grade ≥2 diarrhea, Grade ≥2 nausea, or any TEAE leading to dose adjustment in Study BCHILD patients.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:

(b) (4)

[redacted]

8 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

The FDA's Assessment:

Individual bosutinib exposures for the E-R safety analysis were calculated using the Applicant's final pediatric PPK model. As discussed in Section 19.4.1, the pediatric PPK model is inadequate for prediction of bosutinib exposure in pediatric patients. Therefore, the Applicant's E-R safety analysis may be confounded by poor characterization according to age and BSA, and the accuracy of the E-R safety analysis is highly uncertain. The Applicant's E-R safety analysis may only be used for exploratory purposes and cannot be used to support any conclusions regarding bosutinib exposure and safety events in pediatric patients with CP Ph+ CML.

(b) (4)

[redacted]

(b) (4)

(b) (4)

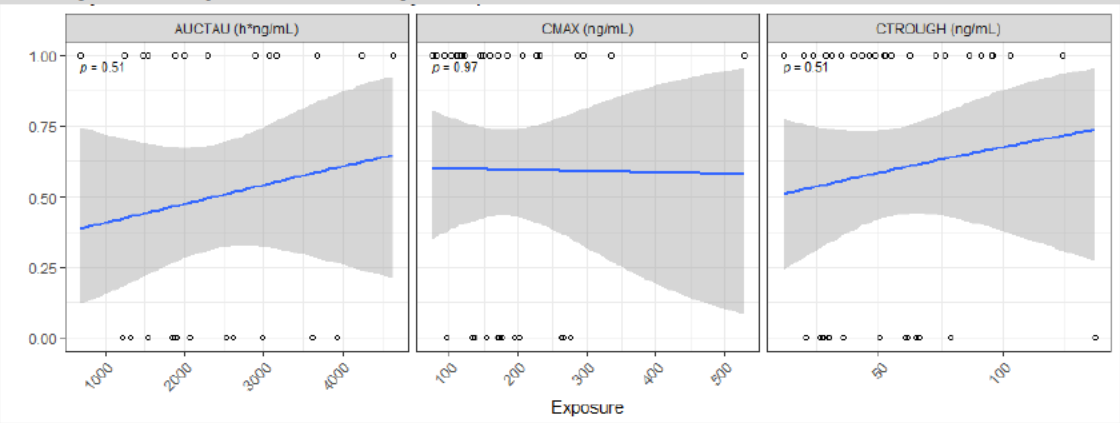
However, the E-R safety analysis results are highly uncertain due to the use of the pediatric PPK model to calculate exposure metrics, given the model's significant issues and inadequacies which are discussed in Section 19.4.1. The E-R safety analysis does not support any conclusions regarding exposure and probability of safety events in pediatric patients with Ph+ CML.

As discussed in Section 6.2.2.1, the NCA is more likely to accurately calculate individual exposure in patients aged 1 to <18 years compared to the pediatric PPK analysis. Therefore, the Reviewer conducted additional E-R safety analysis using the NCA-derived steady state exposure (i.e., Day 14 AUC_{tau}, C_{max}, and C_{trough}). E-R safety data and NCA-derived steady state AUC_{tau} were available in 26 Study BCHILD patients, while E-R safety data and NCA-derived steady state C_{max} and C_{trough} were available in 37 Study BCHILD patients.

No statistically significant E-R safety associations were identified between NCA-derived steady state exposure and Grade ≥3 TEAE (Figure 24), Grade ≥2 diarrhea, Grade ≥2 nausea, Grade ≥2 rash, Grade ≥2 vomiting, Grade ≥2 elevated ALT (Figure 25), Grade ≥2 elevated AST, or any TEAE leading to dose adjustment (Figure 26) according to univariate logistic regression. However, the number of events for some safety events was relatively small (see Table 46). Additionally, the confidence intervals for the logistic regression were wide due to the relatively small sample size. The E-R safety analysis may not have included an adequate number of patients to detect E-R safety associations in pediatric patients with Ph+ CML.

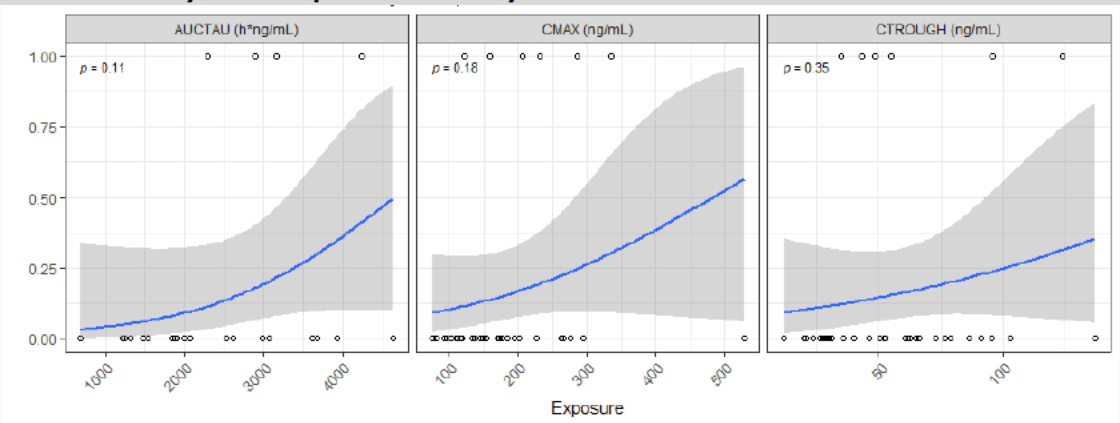
Ultimately, E-R safety data are very limited in pediatric patients with ND or R/I CP Ph+ CML, but E-R analysis did not identify any safety concerns with the proposed dosage.

Figure 24. Univariate Logistic Regression of Grade 3 and Above TEAE versus NCA-derived Steady State Exposure in Study BCHILD Patients



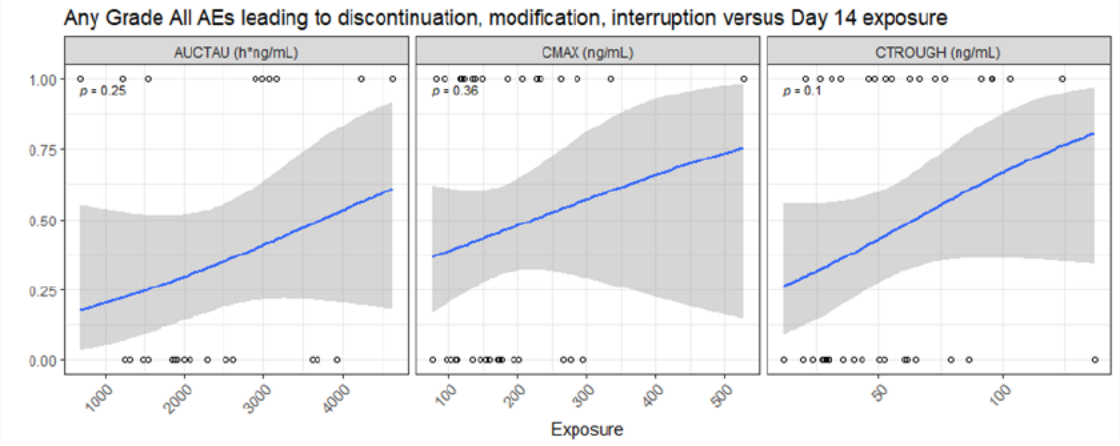
Steady state exposure calculated on Day 14.
AUCtau = AUC over one dosage interval; Cmax = maximum concentration; Ctrough = trough concentration; NCA = noncompartmental analysis; TEAE = treatment emergent adverse event.
Source: Reviewer's analysis of Applicant's E-R safety dataset (cutoff date 13Jun2022)

Figure 25. Univariate Logistic Regression of Grade 2 and Above ALT Elevation versus NCA-derived Steady State Exposure in Study BCHILD Patients



Steady state exposure calculated on Day 14.
ALT = alanine transaminase; AUCtau = AUC over one dosage interval; Cmax = maximum concentration; Ctrough = trough concentration; NCA = noncompartmental analysis.
Source: Reviewer's analysis of Applicant's E-R safety dataset (cutoff date 13Jun2022)

Figure 26. Univariate Logistic Regression of TEAE Leading to Dose Adjustment versus NCA-derived Steady State Exposure in Study BCHILD Patients



Steady state exposure calculated on Day 14. Dose adjustment refers to treatment drug discontinuation, dose modification, or dose interruption.
AUCtau = AUC over one dosage interval; Cmax = maximum concentration; Ctrough = trough concentration; NCA = noncompartmental analysis; TEAE = treatment emergent adverse event.
Source: Reviewer's analysis of Applicant's E-R safety dataset (cutoff date 13Jun2022)

19.4.2.5. Overall Benefit-Risk Evaluation Based on E-R Analyses

The Applicant's Position:

(b) (4)

The FDA's Assessment:

Although E-R data are very limited in pediatric patients with ND or R/I CP Ph+ CML, E-R analysis did not identify any efficacy or safety concerns with the proposed dosage.

The Applicant's pediatric E-R efficacy and pediatric E-R safety analyses (Section 19.4.2) utilized model-predicted exposure from the Applicant's pediatric PPK model, which was determined to be inadequate for the purpose of predicting exposure across the pediatric age range of 1 to <18 years (refer to Section 19.4.1 for details). Therefore, the pediatric E-R analyses may not

have acceptable accuracy and cannot support any conclusions regarding E-R associations in pediatric patients.

The Reviewer's independent E-R safety analysis did not find any safety concerns between with Grade ≥3 TEAE, Grade ≥2 diarrhea, Grade ≥2 nausea, or any TEAE leading to dose adjustment and the NCA-derived exposures following the proposed dosage. However, the number of Study BCHILD patients with adequate PK data for NCA may have been too small to detect any meaningful E-R safety associations.

FDA disagrees with the Applicant's statement (b) (4)

(b) (4)

19.5. Additional Safety Analyses Conducted by FDA

The following grouped terms (GT) were used for FDA analyses of safety, consistent with the combined terms used by the Applicant.

Abdominal Pain**:** Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, Gastrointestinal pain, Hepatic pain

Anemia**:** Anemia, Hemoglobin decreased, Hemoglobinemia, Hemolytic anemia, Normocytic anemia, red blood cell counts decreased.

Fatigue**:** Asthenia, Fatigue, Malaise.

Hepatic dysfunction**:** Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase, Aspartate aminotransferase increased, Bilirubin conjugated increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatomegaly, Hepatosplenomegaly, Hyperbilirubinaemia, Jaundice, Liver function test abnormal, Liver function test increased, Ocular icterus, Transaminases increased, Hepatic function abnormal, Drug-induced liver injury, Hepatic steatosis, Hepatitis, Hepatitis toxic, Hepatobiliary disease, Hepatocellular injury, Hepatotoxicity, Liver disorder, Liver injury.

Neutropenia**:** Neutropenia, Neutrophil count decreased, Agranulocytosis.

Rash: Acarodermatitis, Acne, Angular cheilitis, Blister, Dermatitis, Dermatitis acneiform, Dermatitis bullous, Dermatitis exfoliative generalized, Dermatitis psoriasiform, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Dyshidrotic eczema, Eczema, Eczema asteatotic, Erythema, Erythema annulare, Erythema nodosum, Exfoliative rash, Genital rash, Lichen planus, Lichenoid keratosis, Palmar erythema, Palmar-plantar erythrodysesthesia syndrome, Perivascular dermatitis, Photosensitivity reaction, Pigmentation disorder, Pruritus allergic, Psoriasis, Punctate keratitis, Pyoderma gangrenosum, Pyogenic granuloma, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Seborrheic dermatitis, Seborrheic keratosis, Skin depigmentation, Skin discoloration, Skin disorder, Skin exfoliation, Skin hyperpigmentation, Skin hypopigmentation, Skin irritation, Skin lesion, Skin plaque, Skin reaction, Skin toxicity, Stasis dermatitis.

Respiratory tract infection: Respiratory tract infection includes the following preferred terms: Nasopharyngitis, Respiratory tract congestion, Respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract congestion, Upper respiratory tract infection, Upper respiratory tract inflammation, Viral upper respiratory tract infection

Thrombocytopenia: Platelet count decreased, Thrombocytopenia.

NDA 203341 S025 BOSULIF (bosutinib) tablets; NDA 217729 BOSULIF capsules

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Shwu-Luan Lee, PhD	OOD/DHOT	Sections: 5	Select one: ☑ Authored ☐ Approved
	Signature: Shwu-luan Lee -S Digitally signed by Shwu-luan Lee -S Date: 2023.08.23 11:51:33 -04'00'			
Nonclinical Team Leader	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	Select one: ☑ Authored ☑ Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S Date: 2023.08.23 12:22:25 -04'00'			
Clinical Reviewer	Kamar Godder, MD	OOD/DHM1	Sections: 2, 3, 4, 7-13, 19.2,19.5	Select one: ☑ Authored ☐ Approved
	Signature: Kamar Godder -S Digitally signed by Kamar Godder -S Date: 2023.08.24 17:57:27 -04'00'			
Clinical Team Leader	Lori Ehrlich, MD, PhD	OOD/DHM1	Sections: 1-4, 7-13, 19.2, 19.5	Select one: ☑ Authored ☑ Approved
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Clinical Pharmacology Reviewer	Ritu Chadda, PhD	OCP/DCPI	Sections: 6	Select one: ☑ Authored ☐ Approved
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Clinical Pharmacology Team Leader	Ruby Leong, PharmD	OCP/DCPI	Sections: 6	Select one: ☐ Authored ☑ Approved
	Signature: Ruby Leong -S Digitally signed by Ruby Leong -S Date: 2023.08.23 14:11:37 -04'00'			
Pharmacometrics Reviewer	Robyn Konicki, PharmD	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Robyn E. Konicki -S Digitally signed by Robyn E. Konicki -S Date: 2023.08.24 08:41:17 -04'00'			

Associate Director of Pharmacokinetics	Jiang Liu, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☐ Authored ☑ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2023.08.24 09:14:43 -04'00'			
Statistical Reviewer	Xin Wang, PhD	OB/DBIX	Sections: 8	Select one: ☑ Authored ☐ Approved
	Signature: Xin Wang -S Digitally signed by Xin Wang -S Date: 2023.08.24 10:33:14 -04'00'			
Statistical Team Leader	Jonathon Vallejo, PhD	OB/DBIX	Sections: 8	Select one: ☐ Authored ☑ Approved
	Signature: Jonathon J. Vallejo -S Digitally signed by Jonathon J. Vallejo -S Date: 2023.08.24 16:25:27 -04'00'			
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	Select one: ☑ Authored ☐ Approved
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Cross-Disciplinary Team Leader (CDTL)	Lori Ehrlich, MD, PhD	OOD/DHM1	Sections: All	Select one: ☑ Authored ☐ Approved
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Division Director	R. Angelo de Claro, MD	OOD/DHM1	Sections: All	Select one: ☐ Authored ☑ Approved
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LORI A EHRLICH
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