27 March 2025
EMA/195854/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bosulif

International non-proprietary name: Bosutinib

Procedure No. EMEA/H/C/002373/X/0058/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Term
1L	first line
%CV	percent coefficient of variation
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AP	accelerated phase
AST	aspartate aminotransferase
AUC	area under concentration-time curve
AUC_{24}	area under concentration-time curve over 24 hours
AUC_{inf}	area under concentration-time curve to infinity
AUC_{last}	area under concentration-time curve to last measured
AUC_{tau}	area under the concentration-time curve over dosing interval tau
BBSA	baseline body surface area
BCR-ABL	breakpoint cluster region protein/Abelson murine leukemia viral oncogene
BMD	bone mineral density
BP	blast phase
BSA	body surface area
CCyR	complete cytogenetic response
c-KIT	proto-oncogene encoding receptor tyrosine kinase KIT (also known as CD117)
CL	clearance
CL/F	apparent clearance
C_{max}	maximum observed concentration
CML	chronic myelogenous leukemia
CHR	complete hematologic response
CI	confidence interval
CO	clinical overview
COG	Children's Oncology Group
CP	chronic phase
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	pre-dose concentration
CTX	Type I collagen
DLT	dose limiting toxicity
DEXA	dual-energy X-ray absorptiometry
EC	European Commission
ECG	electrocardiogram
EFS	event-free survival
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
E-R	exposure-response
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GI	gastrointestinal
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplant
ICF	Informed Consent Form
IGF-1	insulin-like growth factor 1
IIV	inter-individual variance
k_a	first-order absorption rate constant
KDIGO	Kidney Disease Improving Global Outcomes
LH	luteinizing hormone
LS	lumbar spine
LVEF	left ventricular ejection fraction
MAA	Market Authorization Application
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MMR	major molecular response (≥3-log reduction from standardized baseline)
MR[number]	molecular response ≥[number]-log reduction from standardized baseline
N, n	number of participants
ND	newly diagnosed
NOAEL	no observed adverse effect level
OS	overall survival

PA	protocol amendment
PCyR	partial cytogenetic response
PD	pharmacodynamics
PDGF-R	platelet-derived growth factor receptor
Ph+	Philadelphia chromosome-positive
PIP	Pediatric Investigation Plan
PK	pharmacokinetics
PMAR	pharmacometrics analysis report
PND	postnatal day
PopPK	population PK
PT	preferred term
PWR	pediatric written request
QD	once daily
R/I	resistance or intolerance
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SDS	standard deviation score
SmPC	Summary of Product Characteristics
SOC	system organ class
$T_{1/2}$	time to half C_{max}
T4	thyroxine
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
T_{lag}	time to lag
T_{max}	time to first occurrence of C_{max}
TSH	thyroid stimulating hormone
UK	United Kingdom
US	United States
USPI	US Prescribing Information
VAS	visual analog scale
V/F	apparent volume of distribution
WT	wild-type

1. Background information on the procedure

1.1. Submission of the dossier

Pfizer Europe MA EEIG submitted on 8 March 2024 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new pharmaceutical form (hard capsules) associated with two new strengths (50 mg and 100 mg) grouped with an extension of indication (C.I.6.a) to include treatment of paediatric patients greater than or equal to 1 year of age with newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) for BOSULIF, based on interim results from study ITCC-054/AAML1921 (BCHILD); this is a phase 1/2, multicenter, international, single-arm, open-label study of bosutinib in pediatric patients with newly diagnosed chronic phase or resistant/intolerant Ph+ chronic myeloid leukemia. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC were to be updated. The Package Leaflet was updated accordingly. Version 7.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the Product Information.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0336/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0336/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0336/2023.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig

The Rapporteur appointed by the PRAC was:

The application was received by the EMA on	8 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 July 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	25 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 July 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	08 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	15 November 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	25 June 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	12 December 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	25 February 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 February 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 March 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Bosulif on	27 March 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Chronic myelogenous leukaemia (CML) is a hematopoietic stem cell disease characterized by a proliferation of granulocytes and their immature myeloid precursors including blast cells. The disease is causally linked to a characteristic cytogenetic abnormality resulting from a reciprocal translocation of the long arms of chromosomes 9 and 22. The shortened chromosome 22, known as the Philadelphia chromosome (Ph), is detected in at least 95% of patients with CML

2.1.2. Epidemiology

CML in childhood is relatively rare, accounting for fewer than 3% of all paediatric leukaemias, 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.

2.1.3. Biologic features, Aetiology and pathogenesis

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 signalling pathways that mediate myeloproliferation, resistance to apoptosis and genetic instability.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The natural history and clinical presentation of Ph+CML in children is not significantly different from that of adults with CML, although published studies are small.

Untreated CML commonly progresses in 3 phases: chronic phase (CP), accelerated phase (AP), and blast phase (BP). The majority of patients are diagnosed during CP, which is characterized by an increased number of leukocytes and/or platelets and a bone marrow blast count less than 15%. If untreated, the initial CP lasts approximately 3 to 5 years. Progress often occurs through the AP to a terminal BP. AP may be marked by 1 or more of the following: increasing splenomegaly and leukocytosis, an increase of blasts to 15% to 29%, an increase of basophils to 20% or greater, thrombocytopenia, and clonal evolution. In BP, for which the median survival is 2-4 months, 30% or more of blood and bone marrow cells are blasts, and myeloid precursors may also form tumours in the lymph nodes, skin, and bone. Patients with BP are the most refractory to treatment and can be divided into 1 of 2 categories: those with myeloid disease and those with lymphoid disease. The rate of response to standard induction chemotherapy for patients in the myeloid BP is approximately 20%, and the rate of complete remission is less than 10%. For patients in the lymphoid BP, the rate of response is approximately 50%, but remissions are transient.

In the era before tyrosine kinase inhibitor (TKI) therapy, hematopoietic stem cell transplant (HSCT) was the standard of care for children with CML, with 3- to 5-year event-free survival (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.

However, 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.

2.1.5. Management

In children as in adults, a TKI is considered to be the preferred first-line therapy for CML. Favourable results from Phase 1 and 2 studies with imatinib in paediatric patient populations support its use as a first-line therapy for paediatric CML, with 96% of children achieving CHR and 69% achieving complete cytogenetic response (CCyR) after 1 year. With the recent approval of dasatinib, some paediatric oncologists favour this drug due to its good tolerability profile, the rapid deep response, and the availability of an oral solution.

For children whose disease fails or progresses or who are intolerant of imatinib, there are presently 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-alpha or hydroxyurea.

In practice, most people now switch to second-line therapy if the response criteria as defined by European Leukemia Net are not met.

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 human leukocyte antigen (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 a challenge. 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.

Available CML-TKIs

The other second-generation inhibitor, 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.

Side effects of imatinib in children occur with the same or lower frequency and tend to be less severe than in adults. Frequent side effects include myelosuppression, nausea, fluid retention, muscle cramps, bone pain, skin rash, diarrhoea, lethargy, and weight gain. Dasatinib seems to be better tolerated in children than in adults.

Nevertheless, it is agreed that an unmet need remains for treatment options in paediatric patients with newly diagnosed (ND) and resistance or intolerance (R/I) CML which are available in population-appropriate administrations, and which demonstrate clinically meaningful response and survival outcomes, with tolerable short- and long-term toxicities specifically relevant to paediatric patients.

2.2. About the product

Bosutinib is an orally active Src/Abl kinase inhibitor with potent antiproliferative and proapoptotic activity in cultured CML cells, and antiproliferative activity in primitive progenitor CML cells from patients. Bosutinib also inhibits proliferation of murine myeloid cells expressing WT Bcr-Abl and most clinically relevant mutated forms of Bcr-Abl.

Bosutinib received approval in the EU for the treatment of adults with ND CP Ph+ CML and CP, AP, and BP Ph+ CML previously treated with 1 or more TKI(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Bosutinib has been developed as an immediate release capsule for oral administration of 25-, 50-, and 100-mg strengths as an age-appropriate presentation. Based on a dose refinement strategy summarized within the SCP leveraging modelling and simulation, only the 50- and 100-mg capsule strengths would be required to support the product label as outlined in the table below:

Table 1. Bosutinib Tablet and Capsule Strengths and Intended Use in Different Indications

Drug Product and Dose Strengths	Intended Use
25-mg capsule	Not required
50-mg capsule	Support starting dose and dose modification increments for smaller pediatric patients 1L (ND) and 2L (R/I) CML
100-mg capsule	Support starting dose and dose modification increments for larger pediatric patients and adults who cannot swallow intact tablets 1L (ND) and 2L (R/I) CML
100-mg tablet	Increment needed to enable dose reduction and escalation in adult and larger pediatric patients (who can swallow intact tablets) 1L and 2L Ph+ CML
400-mg tablet	Starting dose in adult 1L (ND) CML, larger pediatric patients
500-mg tablet	Starting dose in adult 2L+, (R/I) CML, larger pediatric patients

2.3. Type of Application and aspects on development

The study was managed by Erasmus MC (the sponsor) and Children's Oncology Group (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.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard capsules containing 50 mg and 100 mg of bosutinib (as monohydrate).

Other ingredients are:

hard capsule content: mannitol (E421), microcrystalline cellulose (E460), croscarmellose sodium (E468), poloxamer 188, povidone (E1201), magnesium stearate (E470b); hard capsule shells: gelatin, titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (E172); printing ink: shellac

(E904), propylene glycol (E1520), ammonia solution concentrated (E527), black iron oxide (E172) and potassium hydroxide (E525).

The product is available in high-density polyethylene (HDPE) bottle and polypropylene closure with heat induction seal as described in section 6.5 of the SmPC.

2.4.2. Active Substance

No new information has been provided with the exception of an additional site of manufacture.

The active substance documentation is identical to that previously approved for the authorised dosage form and is acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as opaque hard gelatin capsules containing either 50 mg or 100 mg of bosutinib as bosutinib monohydrate.

The 50 mg hard capsules (size 2) are presented as white body/orange cap (approximate length: 18 mm) with "BOS 50" printed on the body and "Pfizer" printed on the cap in black ink.

The 100 mg hard capsules (size 0) are presented as white body/brownish-red cap (approximate length: 22 mm) with "BOS 100" printed on the body and "Pfizer" printed on the cap in black ink.

The aim of the pharmaceutical development was to develop an age-appropriate presentation in addition to the currently approved film-coated tablets. The quality target product profile (QTPP) was defined as an immediate release capsule to be administered once daily and developed to be acceptable for the intended paediatric population.

There are no changes to the active substance as compared to the approved film-coated tablets. The 50 and 100 mg hard capsules are produced from a common blend. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The suitability of the new dosage form in the intended paediatric population has been investigated. The capsules 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 soft food as a vehicle to facilitate administration. In-vitro compatibility studies have been conducted to investigate the impact of mixing of the capsule content with apple sauce or yogurt and no significant change in assay, dissolution, degradation products and homogeneity was demonstrated for up to 120 min.

Comparative dissolution profiles for the approved tablets and proposed capsules have been provided indicating a rapid dissolution.

A bioequivalence study was performed showing bioequivalence between the 100 mg tablet and the proposed 100 mg capsules formulation. The 100 mg capsules used in the bioequivalence study have the same composition as the proposed commercial capsules but were manufactured at a different manufacturing site and had different batch size compared to the proposed batch size. Comparative dissolution profiles were provided for batches manufactured at the two manufacturing sites for all strengths in 0.1 N HCl (pH 1.2). Although, dissolution profiles comparisons at pH 4.5 and 6.8 and QC

media were not provided, this was justified based on the overall presented information and on the in vivo bioequivalence study performed. The justification was considered acceptable.

The development of the dissolution method has been sufficiently described. Discriminatory power has been discussed, formulations with different composition were manufactured and discriminatory power could not be demonstrated. The manufacturing process development and has been described in sufficient detail. The process consists in conventional high shear wet granulation and encapsulation. A common blend is used across the capsule strengths. A detailed control strategy including critical and non-critical process parameters has been provided and considered acceptable.

The primary packaging is high-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat induction seal (HIS). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site: Pfizer Manufacturing Deutschland GmbH, Mooswaldallee 1, 79090 Freiburg, Germany. Satisfactory GMP documentation has been provided.

The manufacturing process consists of the following main steps: wet granulation, dry milling and encapsulation process. The process is considered to be a standard manufacturing process.

Critical process parameters and in-process controls are sufficiently described. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), dissolution (UV), uniformity of dosage Units (HPLC) and microbial quality (Ph. Eur.).

The proposed release and shelf-life specifications are in line with relevant ICH guidelines. They were set considering batch and stability data and are considered acceptable. The applicant has omitted water content testing in the finished product specification and justified the omission, which was found acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented information it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. No additional reference standards have been introduced.

Batch analysis results are provided for numerous batches at commercial scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification

2.4.3.4. Stability of the product

Stability data from three commercial scale batches per each strength of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches of Bosulif hard capsules are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition, supportive data from one batch per each strength has been provided for batches produced at the commercial site stored for up to 36 months at long-term and intermediate conditions and for up to 6 months under accelerated conditions.

Samples were tested for appearance, assay, degradation products, dissolution, water content and microbial quality in line with the release specification. The analytical procedures used are stability indicating. No significant changes have been observed, and results remains within the specification.

In addition, one batch per each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Slight changes have been observed when samples were exposed to light out of their primary packaging. No changes have been observed for samples exposed to light in their primary packaging. It was concluded that the finished product is stable to light when kept in the primary packaging. Special storage condition "Store in the original package in order to protect from light" has been included in the SmPC (section 6.4).

In-use stability studies were performed on 2 batches per each strength The 50 mg strength was stored for up to 90 days at 25 °C/ 60% RH and 30 °C/ 75% RH, and the 100 mg strength for up to 180 days at both storage conditions. A special storage condition "Do not store above 30 °C" has been included in the SmPC upon CHMP request.

Based on available stability data, the proposed shelf-life of 3years and special storage conditions "Do not store above 30 °C. Store in the original package in order to protect from light" as stated in the SmPC (sections 6.3, 6.4) are acceptable.

2.4.3.5. Adventitious agents

Gelatine obtained from bovine or porcine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, no Major Objections and few Other Concerns have been raised. All questions have been adequately addressed.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

There were no new pharmacology/pharmacokinetic/toxicology studies performed for the current dossier.

2.5.2. Pharmacology

No new pharmacology studies were provided within this application. The pharmacology of bosutinibhas therefore not been re-assessed.

2.5.3. Pharmacokinetics

No new pharmacokinetic studies were provided within this application. The pharmacokinetic of bosutinib has therefore not been re-assessed.

2.5.4. Toxicology

No new toxicology studies were provided within this application. The previously submitted juvenile animal study and one non-clinical study found in literature presenting experimental data about bosutinib treatment in juvenile animals (4-week old male Wistar rats)(Ulmer et al, 2013) were relevant to this application and have been assessed and briefly summarized below. Other toxicity studies have not been re-assessed.

Study WIL-655073 (13GR351) "An Oral (Gavage) Toxicity Study of PF-05208763 in Juvenile Rats

The objective of this study was to evaluate potential adverse events of oral administration of PF-05208763 (bosutinib) on neonatal growth and development in juvenile male and female rats when treated from postnatal day 7 through postnatal day 27 or 28, inclusively.

Dosages of 3, 10, 30 and 75 mg/kg/day were administered to juvenile male and female rats. Bosutinib was **not** tolerated at dosage levels ≥10 mg/kg/day. Severe adverse clinical signs lead to termination of these dose groups. Only the 3 mg/kg dose group exhibited no test-article-related clinical observations, such as body weight effects, gross necropsy or histopathologic observations, or changes in finale body or organ weights, or femur lengths. Only in females slightly higher aspartate aminotransferase (AST)

and serum potassium levels were noted. Both, AST and potassium levels fully reversed during the recovery period and no histopathological changes related to the higher serum levels were found. Therefore, his phenomenon is noted to be not of clinical significance. The no-observed-adverse-effect level (NOAEL) for juvenile toxicity was determined to be 3 mg/kg/day with values on PND7 of Cmax 1,160 ng/mL and area under the serum concentration vs. time curve for 0-24 hours (AUC24) 20,100 ng•h/mL. Cmax on post-natal day (PND) 28 was 5.28 ng/mL. The high systemic exposure on PND7 (which were maintained through at least the first 10 days of the study) was attributed to the limited liver metabolic capability in pre-weaning rats as the systemic exposure in post-weaning rats on day28 was subtherapeutic. Since the metabolic pathway for bosutinib is fully mature by one year of age in humans, the high exposure on PND7 is not expected to have an impact on the clinical setting. The results from this study do not warrant changes in the product information.

Further, one non-clinical study (Ulmer et al, 2013) was found in literature that presented experimental data about bosutinib treatment in juvenile animals (4-week-old male Wistar rats). Within this study off target effects of TKIs on bone growth were evaluated. The cited study compared blood levels of IGF-1 and IGFBP-3 after treatment of various TKIs in juvenile rats and paediatric patients. As a result, it was shown that independent from the treatment duration patients exhibited IGF-1 and IGFBP-3 levels almost exclusively in the very low range compared to age-matched references. No clear pattern of rising or falling IGF-1 and IGFBP-3 levels was observed. In rats, compared to controls, serum IGFBP-3 was significantly lowered for all TKIs tested, at all concentrations applied, and at all ages under investigation. It was concluded that growth and GH- related parameters should be monitored regularly in paediatric patients with CML on TKIs.

2.5.5. Ecotoxicity/environmental risk assessment

This extension of the MA and extension of indication for bosulif is not expected to result in an increase in the environmental exposure of the active substance bosutinib. Therefore, a revised environmental risk assessment is not deemed necessary in this submission.

2.5.6. Discussion and conclusion on non-clinical aspects

Based on the results from rat juvenile toxicity studies, growth effects are being further explored in the result of study ITCC-054/AAML1921 which the company has committed to provide soon after approval. These safety related issues are also to be reported in the future PSURs. At this point in time based on the results from rat juvenile toxicity studies, growth effects are not expected in humans.

Bosutinib is already used in existing marketed products and no significant increase in environmental exposure is anticipated. Therefore, Bosutinib is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Methods

The PK evaluation submitted for this extension of indication comes from one investigator-sponsored pivotal study (BCHILD) in children of 1-17 years of age with R/I and newly diagnosed CML which was conducted in 29 sites in 8 countries in Europe and the US. It includes the sampling data from 45 paediatric patients (ages 1 to <18 years), including 18 with ND CML and 27 with R/I CML, and popPK and exposure-response modelling from these paediatric patient data. A separate PopPK model was developed for the paediatric population, including n=41 patients aged 1-17 years. A 1-compartment model with first order absorption and elimination including a lag time best described the paediatric data. The model has been further re-fined during the procedure including parameters (allometric scaling for volume) in order to be more adequate to describe the PK in the paediatric population

In addition, 3 studies in adult healthy volunteers were performed for bridging between formulations, food effect and palatability. (studies B1871061, B1871062, and B1871063). All clinical samples were analyzed within the established stability period of the analyte. Further studies supporting pharmacology of bosutinib in paediatric patients are studies B1871051, B1871057, B1871012 and B1871021.

PK parameters were analysed by standard NCA methods

Bioequivalence and Food Effect

Studies B1871061, B1871062, B1871063

The MAH provided three phase 1 studies in order to support their submission and aiming to assess bioavailability (including the effect of food) and bioequivalence of the bosutinib capsules to the tablet formulation.

Study B1871061: A phase 1, open-label, randomised, 2-period, 2-sequence, crossover study to evaluate the bioequivalence of bosutinib paediatric capsule and the commercial tablet formulations in healthy participants under fed condition.

Following an overnight fast of at least 10 hours, on Day 1 of each period, participants received a high-fat, high-calorie breakfast prior to dosing which had to be completely consumed within 20 minutes.

Study B1871062: A phase 1, randomised, 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. The purpose of study B1871062 was to bridge the 25- to 100-mg capsule strengths in approximately 28 healthy participants under fed condition and assess the effect of a high-fat, high-calorie meal on bosutinib exposures using the capsule formulation.

For treatments A and B (see table below), following an overnight fast of at least 10 hours, on Day 1 of each period, participants received a high-fat and high-calorie breakfast prior to dosing which had to be completely consumed within 20 minutes. For Treatment C, participants were dosed after an overnight fast of at least 10 hours.

Study B1871063: A phase 1, open-label, randomised, 3-Period, 6-Sequence, crossover, single-dose 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.

Following an overnight fast of at least 10 hours, on Day 1 of each period, participants received a high-fat and high-calorie breakfast prior to dosing which had to be completely consumed within 20 minutes.

PK Results

Table 2. PK parameters of study B1871061, B1871062, and B1871063

Study Number	Treatment: Dose Dosage Form Route of Administration and Food Status (Number of participants)	Mean PK Parameters				
		AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
B1871061	A: 100 mg (100 mg x 1) capsule PO under fed condition (N = 63[a], 54 [b])	432.7 (32)	371.5 (41)	16.47 (39)	6.00 (1.00 – 12.0)	31.43 ± 8.2561
	B: 100 mg (100 mg x 1 tablet) PO under fed condition (N = 62[a], 56 [b])	457.1 (33)	389.7 (38)	17.08 (34)	6.00 (1.00 – 8.00)	33.81 ± 9.1516
B1871062	A: 100 mg (100 mg x 1 capsule) PO under fed condition. (N = 30[a], 21 [b])	591.3 (32)	455.6 (40)	17.80 (40)	6.00 (4.00 – 12.0)	47.22 ± 11.753
	B: 100 mg (25 mg x 4 capsules) PO under fed condition. (N = 31[a], 20 [b])	591.7 (39)	446.4 (45)	16.68 (38)	6.00 (3.00 – 8.00)	46.01 ± 13.434
	C: 100 mg (100 mg x 1 capsule) PO under fasted condition (N = 12[a], 4 [b])	479.4 (30)	301.6 (52)	10.75 (58)	6.00 (3.00 – 8.02)	43.28 ± 7.6939
B1871063	A: Contents of 500 mg (100 mg × 5) bosutinib capsules mixed with 45 mL of applesauce PO under fed condition (N = 16[a], 16 [b])	3312 (28)	3150 (28)	126.5 (31)	6.00 (2.00 – 8.02)	36.46 ± 3.7067
	B: Contents of 500 mg (100 mg × 5) bosutinib capsules mixed with 45 mL of full fat yogurt PO under fed condition (N = 17[a], 17 [b])	3205 (23)	3055 (23)	126.1 (27)	6.00 (2.00 – 8.00)	36.30 ± 4.6893
	C: 500 mg (100 mg × 5) bosutinib intact capsules PO under fed condition (N = 17[a], 17 [b])	3161 (32)	3009 (33)	132.0 (33)	6.00 (3.00 – 12.0)	36.02 ± 4.9889

a. AUC_{last}, AUC_{inf}, and C_{max} are geometric means (geometric%CV); T_{max} is median (range); $t_{1/2}$ is arithmetic mean ±Std.dev.
a. Number of participants included in summary statistics for AUC_{last}, C_{max} and T_{max}
b. Number of participants included in summary statistics for AUC_{inf} and $t_{1/2}$ calculations

Table 3. Statistical Summary of Treatment Comparisons Across Bioequivalence and Relative Bioavailability Studies for Capsule Dosage Form

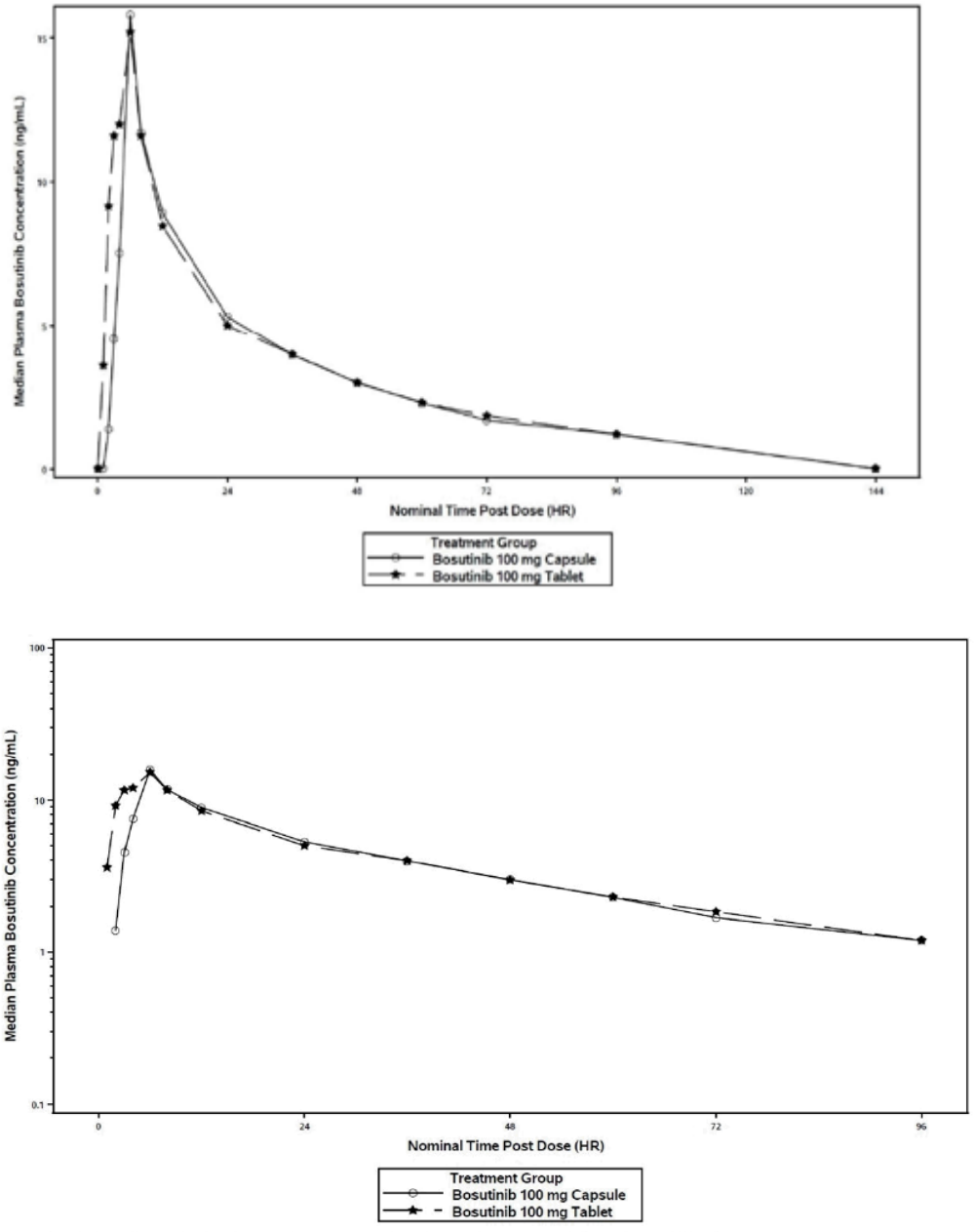
	Adjusted Geometric Means			
Parameter (Units)	**Test**	**Reference**	**Ratio (Test/Reference) of Adjusted Means a**	**90% CI for Ratio a**
Bosutinib 100 mg Capsule (Test) vs. Bosutinib 100 mg Tablet (Reference) Under Fed Conditions (B1871061 A vs B)				
AUC_{inf} (ng·hr/mL)	429.1	462.3	92.83	(89.06 - 96.77)
AUC_{last}(ng·hr/mL)	374.0	397.4	94.12	(90.33 - 98.06)
C_{max} (ng/mL)	16.43	17.18	95.61	(90.07 – 101.48)
Bosutinib 4*25 mg capsule (Test) vs. Bosutinib 1*100 mg capsule (Reference) (B1871062 B vs A)				
AUC_{inf} (ng·hr/mL)	586.9	591.9	99.17	(93.72 – 104.93)
AUC_{last}(ng·hr/mL)	451.6	459.8	98.21	(93.83 – 102.80)
C_{max} (ng/mL)	16.77	17.89	93.77	(90.08 – 97.61)
Bosutinib 100 mg capsule fed (Test) vs. Bosutinib 100 mg capsule fasted (Reference) (B1871062 A vs C)				
AUC_{inf} (ng·hr/mL)	606.1	446.0	135.90	(109.28 – 169.01)
AUC_{last}(ng·hr/mL)	457.3	311.7	146.70	(117.88 – 182.58)
C_{max} (ng/mL)	17.82	10.96	162.54	(130.25 – 202.84)
Bosutinib capsule (100 mg x 5) opened and mixed with applesauce (Test) vs. Bosutinib intact capsule (100 mg x 5) (Reference) (B1871063 A vs C)				
AUC_{inf} (ng·hr/mL)	3360	3161	106.27	(97.76 – 115.53)
AUC_{last}(ng·hr/mL)	3198	3011	106.23	(97.54 – 115.68)
C_{max} (ng/mL)	128.5	132.8	96.82	(86.37 – 108.53)
Bosutinib capsule (100 mg x 5) opened and mixed with yogurt (Test) vs. Bosutinib intact capsule (100 mg x 5) (Reference) (B1871063 B vs C)				
AUC_{inf} (ng·hr/mL)	3222	3161	101.93	(93.97 – 110.56)
AUC_{last}(ng·hr/mL)	3074	3011	102.08	(93.95 – 110.91)
C_{max} (ng/mL)	126.6	132.8	95.39	(85.34 – 106.61)

Fed: high-fat, high-calorie breakfast.
a. The ratios (and 90% CIs) are expressed as percentages.

<u>B1871061</u>

Median plasma bosutinib concentration-time profiles on linear and semi-log scale following a single oral dose of bosutinib 100 mg capsule and 100 mg tablet are presented in Figure below.

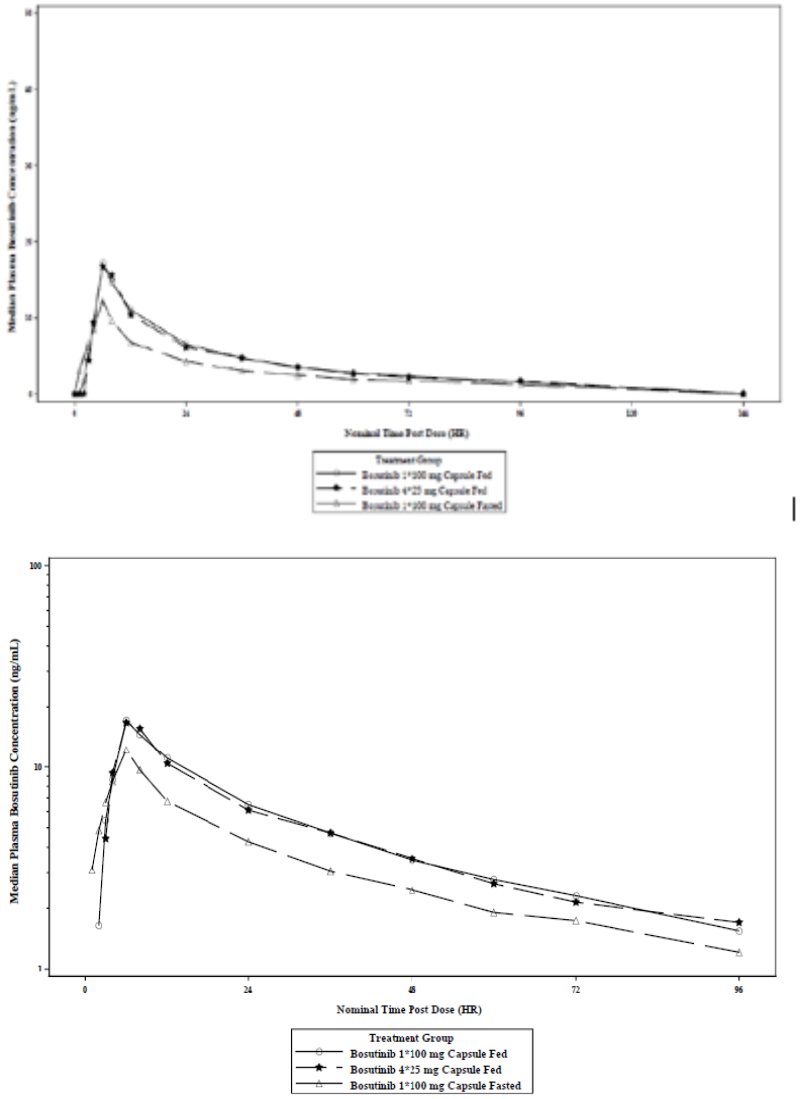
Figure 1. Median plasma bosutinib linear (upper plot) and semi-log (lower plot) concentration-time profile following single oral 100 mg doses of bosutinib



B1871062

Median bosutinib concentration-time profiles on linear and semi-log scale for all treatment groups are presented in Figure below.

Figure 2. Median plasma bosutinib concentration-time profile (upper panel) and semi-log (lower panel) scales following single oral doses. Protocol B1871062

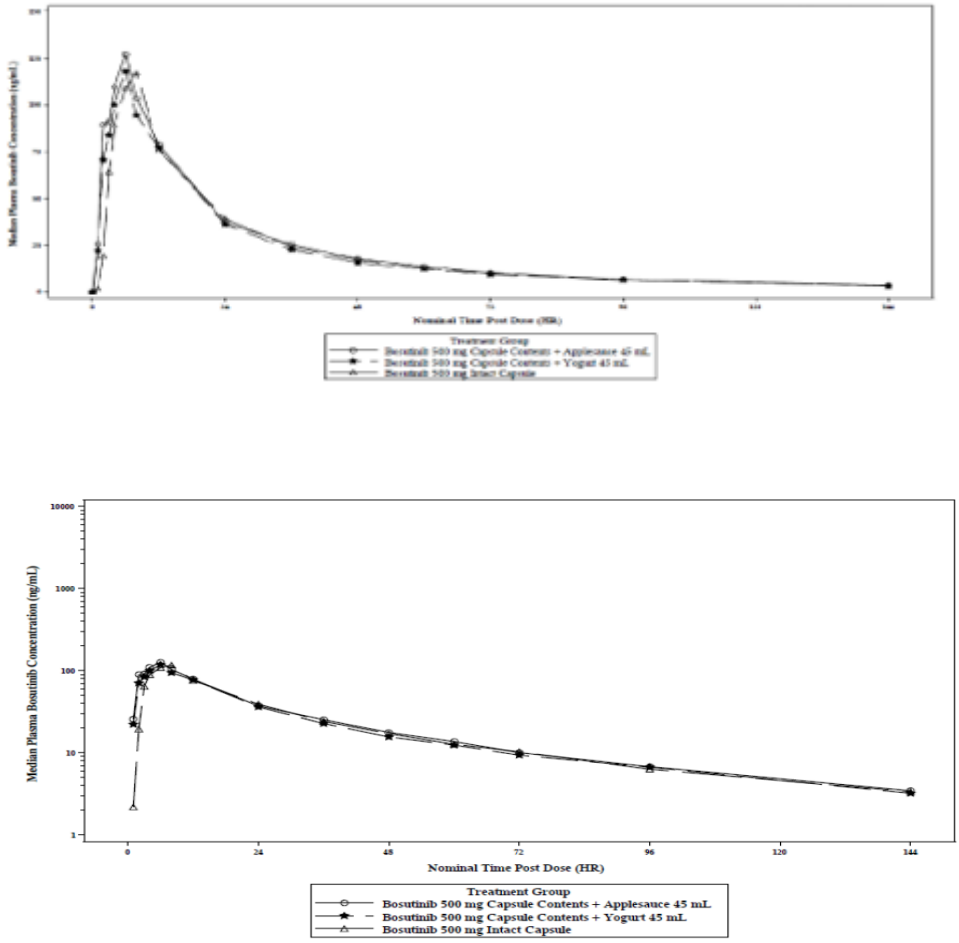


B1871063

Median plasma bosutinib concentration-time profiles for bosutinib 500 mg intact capsule and 500 mg bosutinib capsule contents mixed with either applesauce or yogurt are presented in Figure below, with

corresponding mean plasma bosutinib concentration-time plots on linear (upper plot) and semi-log scales (lower plot).

Figure 3. Median plasma bosutinib linear (upper plot) and semi-log (lower plot) concentration-time profile following single oral doses. Protocol B1871063



Food intake in BCHILD study

Effect of food

Bosutinib C_{max} increased 1.8-fold and AUC increased 1.7-fold when bosutinib tablets were given with a high-fat meal to healthy subjects compared to administration under fasted condition. In a separate study, bosutinib hard capsule administration under the fed condition resulted in exposures approximately 1.5 – 1.6-fold higher than administration under fasted conditions.

Dispersibility

In vitro disintegration test results were provided to support the administration method recommendations in the BCHILD study. A dispersion in water made with bosutinib tablets (100 mg) and capsules (25 and 50 mg) in a 10-mL syringe resulted in a recovery of ≥96.5 % of dose and was stable for 2 hours at room temperature. The dose recovery of bosutinib prepared from a dispersion made with 100 mg tablets in a 10-mL syringe and passed through a nasogastric tube was ≥97.4 %.

Palatability

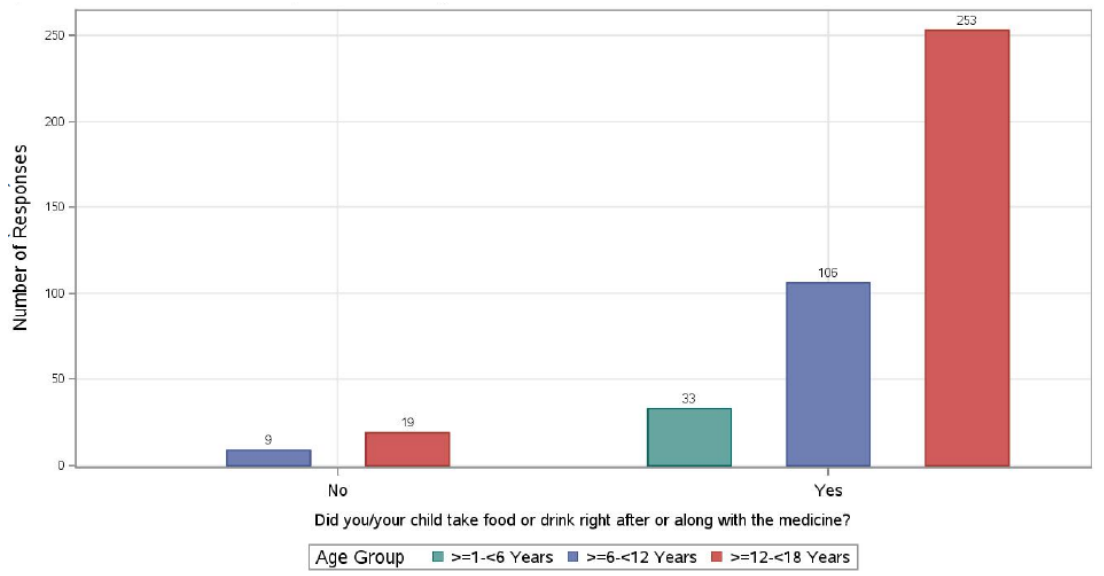
Two single-centre studies (B1871051, B1871057) investigated the palatability of proposed paediatric formulations in adult healthy volunteers. In study 51 the sensory attributes (overall liking, mouth feel,

bitterness, sourness, saltiness, and tongue/mouth burn) was in general significantly worse with liquid formulation (liquid 10 mg/mL with bosutinib). In study 57 the sensory attributes were in general worst with "bosutinib 50 mg × 4 caps in apple sauce". It was considered bad taste (mean VAS score ≥60) for overall liking and bitterness while all other products were considered good (mean VAS score <60) for each sensory attribute. Capsules in water were favourable.

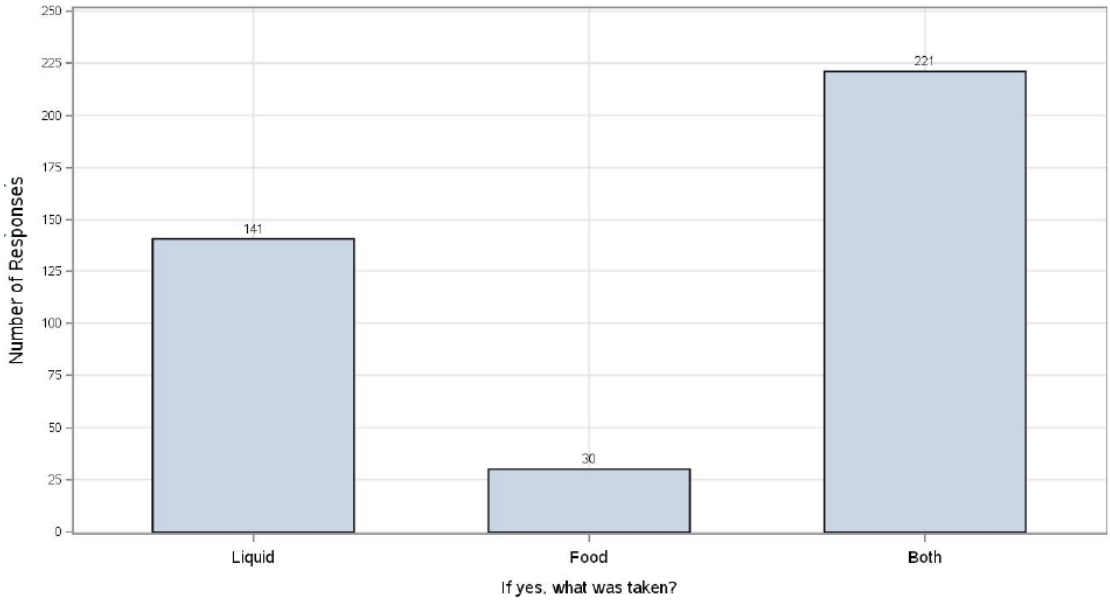
In the BCHILD study, a palatability questionnaire was utilised. Most participants chose to swallow the intact dosage forms (capsules and tablets) and found this acceptable, only some patient added it to soft-food (apple sauce or yoghurt) or few were administered after dissolution via oral syringe or nasogastric tube. The palatability responses indicated that dosing with soft food was acceptable.

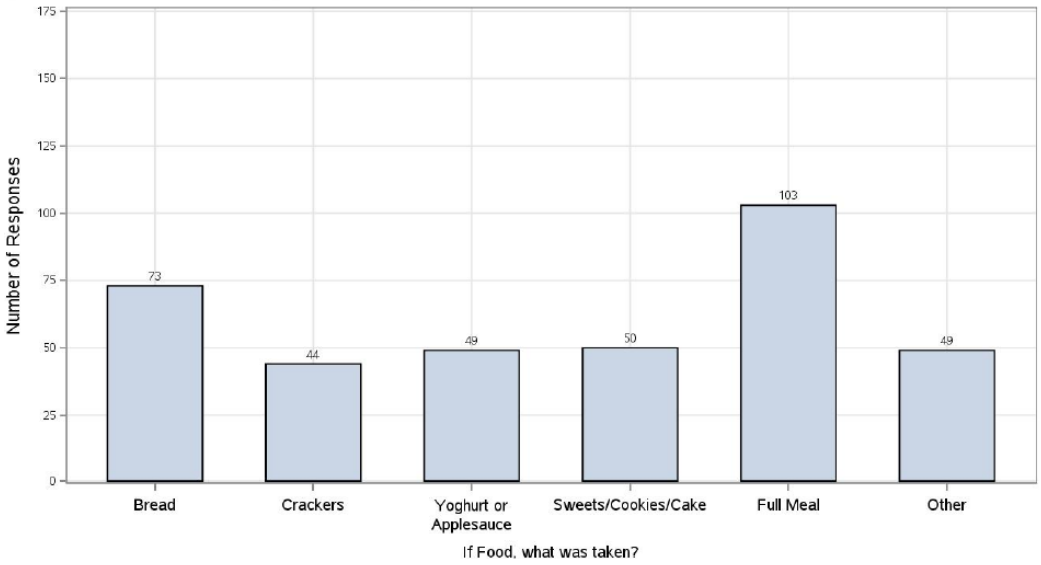
The following figures summarize the information about food and drink intake together with the dose, as responded to the palatability questionnaire by the patients or caregivers. Please note that not all dose and age groups of phases 1 and 2 submitted responses.

Figure 4. Palatability questionnaire: food and drink effect



Note: Participants are grouped by age at study entry.





Dose proportionality and time dependencies

On basis of provided data analysing AUC in the dose range 100 to 600 mg (including data of studies B1871061, B1871062, B1871063, B1871012, B1871021), dose proportionality can be concluded as the slope β = 1.170, i.e. within the acceptance criteria of 0.8 to 1.25. The lower limit of β 90% CI is above 1 (1.098) indicating a trending over-proportional kinetic.

The analyses are based on the data cutoff date of 19.09.2022.

Pharmacology from B-Child study

Table 4. Summary of BCHILD study in paediatric patients with ND CML or R/I CML

Study Name (Pivotal/Supportive)	Primary Pharmacokinetic Objectives	Primary Pharmacokinetic Endpoints	Treatment Regimen (Formulation)	Number of PK Participants (Dose level, age group)	PK sampling included in this application
BCHILD (ITCC-054/AAML1921, B187-WI202099)/ ERASMUS MC and COG/ A Phase 1/2 Study of Bosutinib in Pediatric Patients With Newly Diagnosed Chronic Phase or Resistant/Intolerant Ph+ Chronic Myeloid Leukemia FPFV: 14 November 2016/ Ongoing[a], data cutoff: 19 September 2022 for Interim CSR	Phase 1 Part: • To determine the RP2D of bosutinib $RP2D_{R/I}$ and $RP2D_{ND}$ pediatric patients with CML, based on the pharmacokinetic, safety and tolerability profile of bosutinib observed at various dose levels in pediatric patients with CML who were resistant or intolerant to prior TKI therapy. Phase 2 Part: • To assess the PK of bosutinib at the $RP2D_{ND}$ and $RP2D_{R/I}$ in pediatric participants with ND or R/I Ph + CML. • To assess the population PK of bosutinib.	Phase 1 Part: • PK parameters of bosutinib: C_{max}, T_{max}, AUC_{tau}, C_{trough}, CL/F. • Dose normalized PK parameters: C_{max}, AUC_{tau}, C_{trough}; BSA adjusted CL/F. Phase 2 Part: • Bosutinib C_{max}, T_{max}, AUC_{tau}, C_{trough}, CL/F. • PopPK parameters of bosutinib including clearance and volume of distribution based on combined PK data from Phase 1 and Phase 2. • Dose normalized PK parameters: C_{max}, AUC_{tau}, C_{trough}; BSA adjusted CL/F.	**Phase 1:** Bosutinib (Route: Oral; Dose Regimens: 300 mg/m² QD, 350 mg/m² QD, 400 mg/m² QD). **Phase 2:** Bosutinib (Route: Oral; Dose Regimen: 300 mg/m² QD) **Available dose forms:** 25 mg capsule 50 mg capsule 100 mg tablet 500 mg tablet	Dose Level 300 mg/m² (ND + R/I): N = 20[b], 21[c] 350 mg/m² (R/I): N = 6[b], 11[c] 400 mg/m² (R/I): N = 8[b], 9[c] Age group 1 to <6 years: N = 4[b], 5[c] 6 to < 12 years: N = 12[b], 11[c], 12 to <18 years: N = 18[b], 25[c]	Intensive PK sampling.[d] Cycle 1 Day 14 (C1D14) 0h, 1h, 3h, 6h, 8h[e], 24h[f] (C1D15 predose), C2D1, C3D1, C4D1 Ad hoc: Dose escalation, drug-related SAE

a. "Ongoing" studies include completed or terminated studies with no final CSR as of the data cutoff (includes ongoing studies as well as studies in which patients enrollment and follow-up have been completed, but the analysis and CSR are in progress).
b. Number of participants contributing to NCA summary statistics.
c. Number of participants included in PopPK analysis.
d. Intensive PK samples on Cycle 1 Day 14 to be collected in all Phase 1 participants and first 3 Phase 2 participants in each age group (1 to <6 years, 6 to <12 years, 12 to <18 years).
e. Eight-hour sample collected only for Phase 1 participants.
f. Twenty-four hours after Day 14 dose, and just prior to Day 15 dosing administration.

In Phase 1 (Dose-Finding Part), 6 patients with R/I CML were enrolled and received a starting dose of 300 mg/m² (Dose Level 1) and 2 patients with a starting dose of 350 mg/m² (DL2) given QD continuously with a meal. Patients stayed on their assigned dose-level until a RP2D was established.

After establishing the RP2D, patients still on study were allowed to be dose escalated or de-escalated to the RP2D, provided that there were no major safety concerns and in consultation with the sponsor only. For the Phase 2 part, based on clinical study protocol version 4.0, dated 10 October 2019, in addition to patients with R/I CML, patients with ND CML were enrolled. For the R/I CML patients, the dose escalation levels were expanded to 400 mg.

Bosutinib was to be administered orally QD with a meal. For patients who could not swallow whole tablets or capsules, the following instructions were provided to the caregivers/parents:

- only the tablets can be dissolved and used for NG administration,
- tablets and/or capsules can be used for dosing orally using a syringe,
- only the capsules can be opened and sprinkled onto soft food-stuff (either apple sauce or yoghurt).

Mixing the capsules on apple sauce or yogurt was not considered a substitute of a proper meal.

The first dose level was planned as equivalent to 100% of the adult starting dose (500 mg) and rounded up to 300 mg/m^2 BSA. The BSA calculation was to be repeated at the beginning of every 3rd cycle (Cycle 4, 7 etc), and the dose adapted if BSA changed ≥10%. Daily dose was not to exceed the maximum adult equivalent per dose group (see Tables below).

Table 5. Bosutinib Dosing Table for R/I patients (both Phase 1 and Phase 2)

Rounded Doses to Match Available Dose Strengths

Body Surface Area (m²)	Actual Daily Dose in mg						
	200mg/m²	250mg/m²	300mg/m²	350mg/m²	400mg/m²	450mg/m²	500mg/m²
0.3	50	75	100	100	125	125	150
0.4	75	100	125	150	150	175	200
0.5	100	125	150	175	200	225	250
0.6	125	150	175	200	250	275	300
0.7	150	175	200	250	275	325	350
0.8	150	200	250	275	325	350	400
0.9	175	225	275	325	350	400	450
1.0	200	250	300	350	400	450	500
1.1	225	275	325	375	450	500	550
1.2	250	300	350	425	475	550	600#
1.3	250	325	400	450	525	575	600#
1.4	275	350	425	500	550	600#	600#
1.5	300#	375	450	525	600#	600#	600#
1.6	300#	400#	475	550	600#	600#	600#
1.7	300#	400#	500#	600#	600#	600#	600#
1.8	300#	400#	500#	600#	600#	600#	600#
1.9	300#	400#	500#	600#	600#	600#	600#
2.0	300#	400#	500#	600#	600#	600#	600#
2.1	300#	400#	500#	600#	600#	600#	600#
2.2	300#	400#	500#	600#	600#	600#	600#
2.3	300#	400#	500#	600#	600#	600#	600#
2.4	300#	400#	500#	600#	600#	600#	600#

Note: dosages were rounded off to allow dosing with the available formulations. Please take into account that only tablets can be dissolved for administration through a NG tube, and that only capsules can be opened for sprinkling on food stuff, or a combination of tablets and capsules can be used for oral administration with a syringe.
Dosages do not exceed the maximum adult equivalent.

Table 6. Bosutinib Dosing Table for ND patients (Phase 2 only)

Rounded Doses to Match Available Dose Strengths

Body Surface Area (m^2)	Actual Daily Dose in mg			
	200mg/m^2	250mg/m^2	300mg/m^2	350mg/m^2
0.3	50	75	100	100
0.4	75	100	125	150
0.5	100	125	150	175
0.6	125	150	175	200
0.7	150	175	200	250
0.8	150	200	250	275
0.9	175	225	275	325
1.0	200	250	300	350
1.1	225	275	325	375
1.2	250	300	350	425
1.3	250	325	400	450
1.4	275	350	425	500#
1.5	300#	375	450	500#
1.6	300#	400#	475	500#
1.7	300#	400#	500#	500#
1.8	300#	400#	500#	500#
1.9	300#	400#	500#	500#
2.0	300#	400#	500#	500#
2.1	300#	400#	500#	500#
2.2	300#	400#	500#	500#
2.3	300#	400#	500#	500#

Table 7. Age at enrolment in BCHILD study

	Phase 1 (300mg/m^2) (N=6)	Phase 1 (350mg/m^2) (N=11)	Phase 1 (400mg/m^2) (N=11)	Phase 2 CP1L (300mg/m^2) (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)

The denominator to calculate percentages is N, the number of participants in the safety analysis set within each cohort.

Table 8. ***Descriptive Summary of Bosutinib PK Parameters (Cycle 1 Day 14) BCHILD study***

Parameter (Unit)[a]	Phase 1 (300 mg/m²) (N=6)	Phase 1 (350 mg/m²) (N=8)	Phase 1 (400 mg/m²) (N=9)	Phase 2 CP1L (300 mg/m²) (N=17)	Phase 1 + Phase 2 CP1L (300 mg/m²) (N=23)
N	5	6	8	15	20
AUC_{tau} (ng.hr/mL)	2203 (31)	2516 (38)	2661 (32)	1911 (48)	1980 (44)
C_{max} (ng/mL)	188.5 (26)	221.2 (52)	198.1 (35)	136.6 (44)	148.0 (42)
T_{max} (hr)	3.00 (2.92 , 6.00)	3.30 (1.00 , 6.00)	3.01 (2.87 , 8.00)	3.13 (1.00 , 8.00)	3.11 (1.00 , 8.00)
CL/F (L/hr)	153.4 (34)	129.1 (51)	192.8 (46)	207.7 (44)	192.5 (43)
BSA-adjusted CL/F (L/hr/m²)	135.2 (30)	133.4 (36)	136.7 (21)	147.2 (50)	144.1 (45)
C_{trough} (ng/mL)	46.58 (71)	46.33 (50)	48.88 (93)	48.77 (48)	48.22 (52)
C_{trough}(dn) (ng/mL/mg/m²)	0.1582 (67)	0.1370 (45)	0.1345 (76)	0.1745 (53)	0.1703 (55)
C_{max}(dn) (ng/mL/mg/m²)	0.6334 (25)	0.6586 (49)	0.5439 (24)	0.4849 (45)	0.5184 (42)
AUC_{tau}(dn) (ng.hr/mL/mg/m²)	7.393 (30)	7.494 (36)	7.312 (21)	6.794 (50)	6.939 (45)

N:Total number of participants received treatment and had at least one bosutinib PK parameter reported.
n:Number of participants contributing to the summary statistics.
a. Geometric mean (geometric CV%) for all parameters except for Tmax where median (minimum, maximum) are presented.

Figure 5. Mean Plasma Bosutinib Concentration-Time Profiles Cycle 1 Day 14; BCHILD study

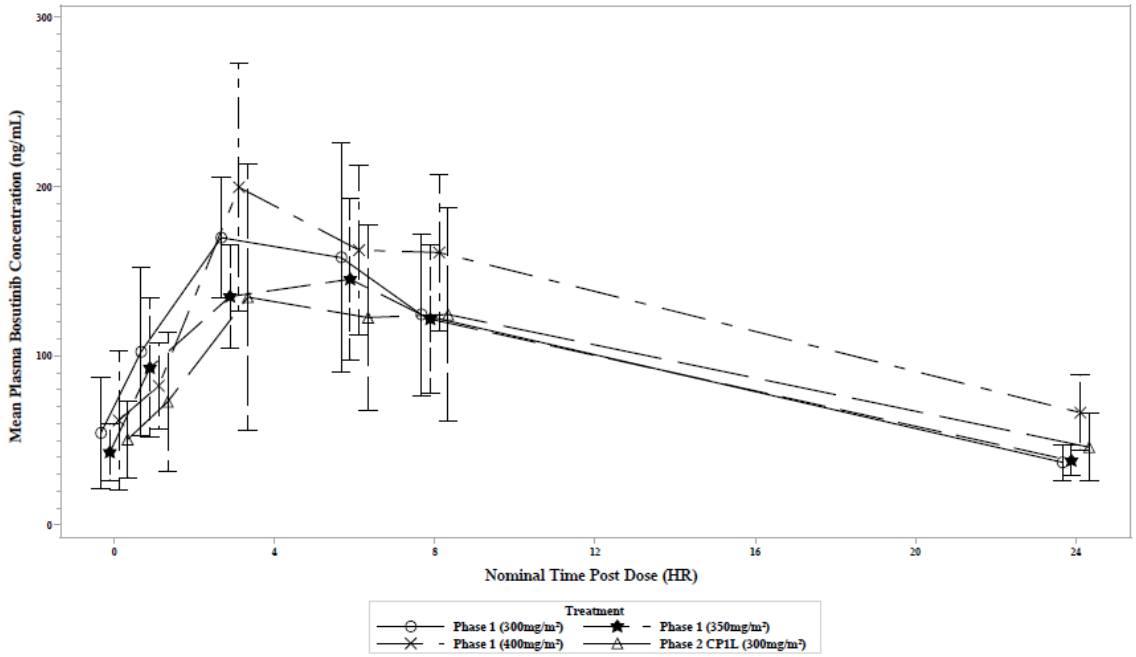
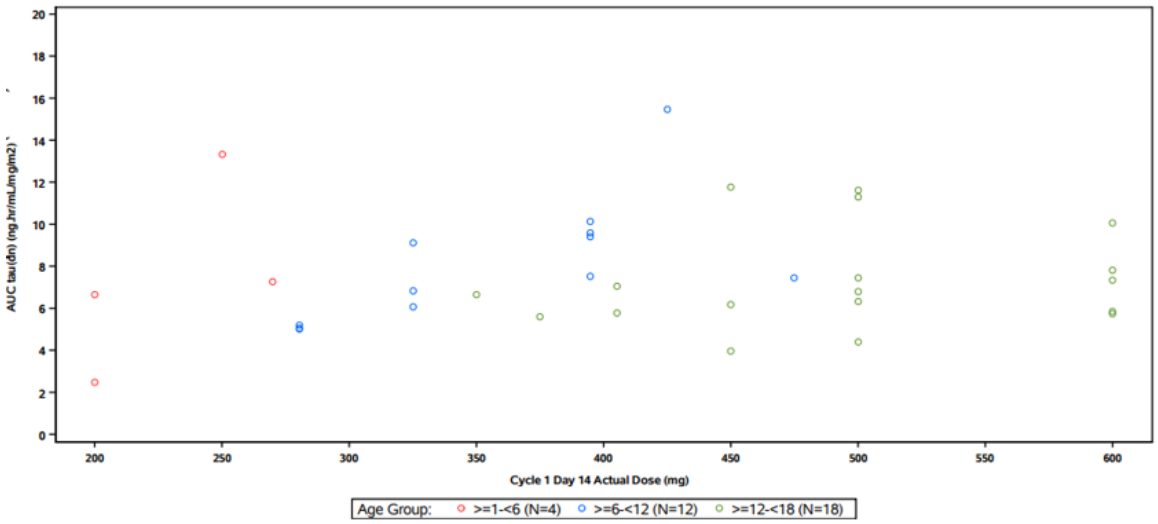


Figure below provides the dose-normalized AUC exposures for paediatric patients per defined age groups within the BCHILD study.

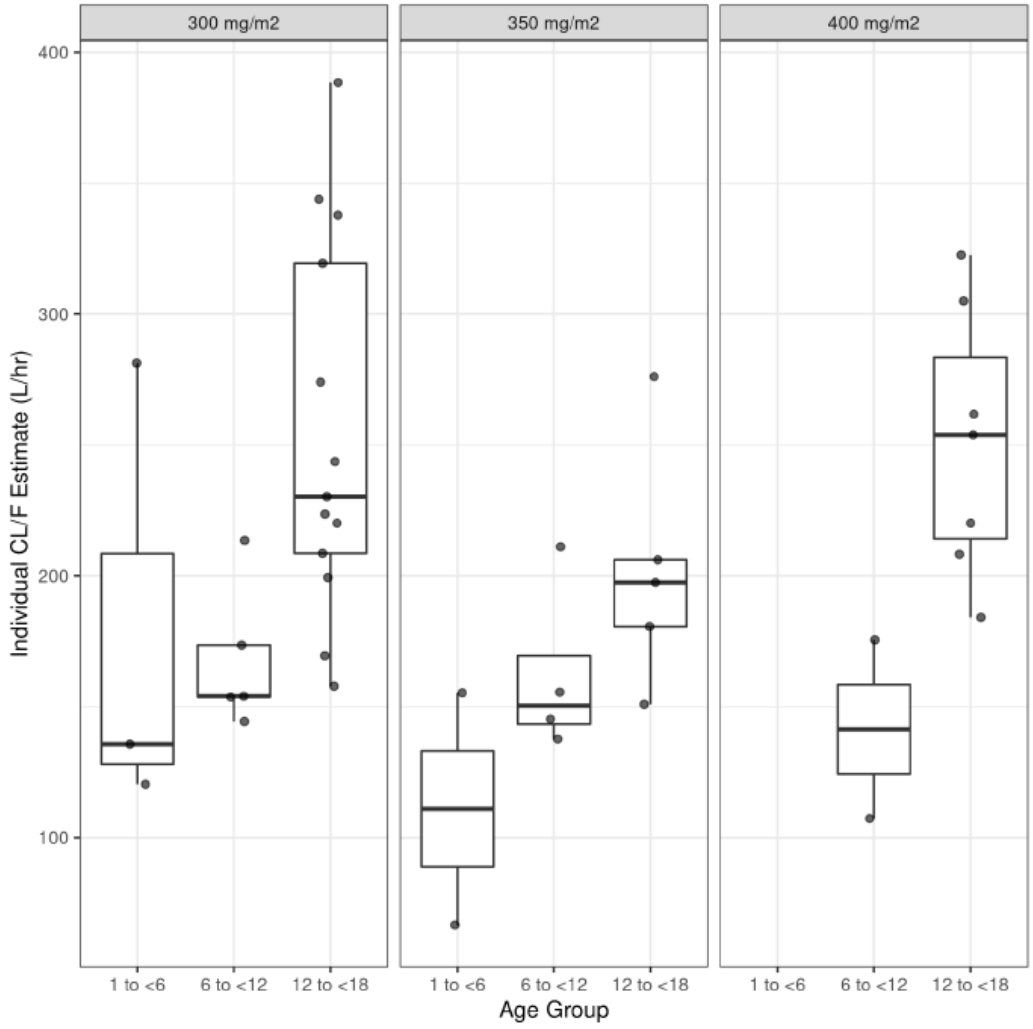
Figure 6. Dose Normalized AUC Exposures for Paediatric Patients



Pop-PK analysis

Based on the PopPK analysis (PMAR-1516), Figure 7 shows the anticipated increase in post hoc CL/F estimates across age range for each BSA-based dose level.

Figure 7. Post hoc CL/F Estimates versus Age Categorization Stratified by Dose Level



Paediatric exposures by age group were generated and dose normalized to 300 mg/m^2 and summarized in Table below for comparison to adult exposures.

Table 9. Observed Steady State PK Parameters Across Paediatric Age Groups From the BCHILD Study Normalized to 300 mg/m^2 Compared to Simulated Adult Steady State Exposures at 400 mg

Age Group	PK Parameter	Mean	SD	Geomean	CV	Median	Range
≥1 - <6 years* (N = 4)	AUC_T (h*ng/mL)	2227	1340	1894	78.9	2084	744 - 3996
	C_{max} (ng/mL)	220	163	182	78.0	168	87 - 456
	C_{trough} (ng/mL)	55.5	21.4	52.3	42.4	55.5	33 - 78
≥6 - <12 years* (N = 12)	AUC_T (h*ng/mL)	2421	891	2291	34.9	2243	1509 - 4638
	C_{max} (ng/mL)	196	72.8	185	36.7	183	102 - 369
	C_{trough} (ng/mL)	53.8	31.9	45.6	66.7	46.5	18 - 105
≥12 - <18 years* (N = 18)	AUC_T (h*ng/mL)	2193	708	2094	31.8	2016	1188 - 3531
	C_{max} (ng/mL)	155	49.5	148	31.1	146	90 - 282
	C_{trough} (ng/mL)	52.3	27.4	45.9	58.1	49.5	15 - 126
Adult#	AUC_T (h*ng/mL)	2510	850	2370	33.69	2370	350 - 6240

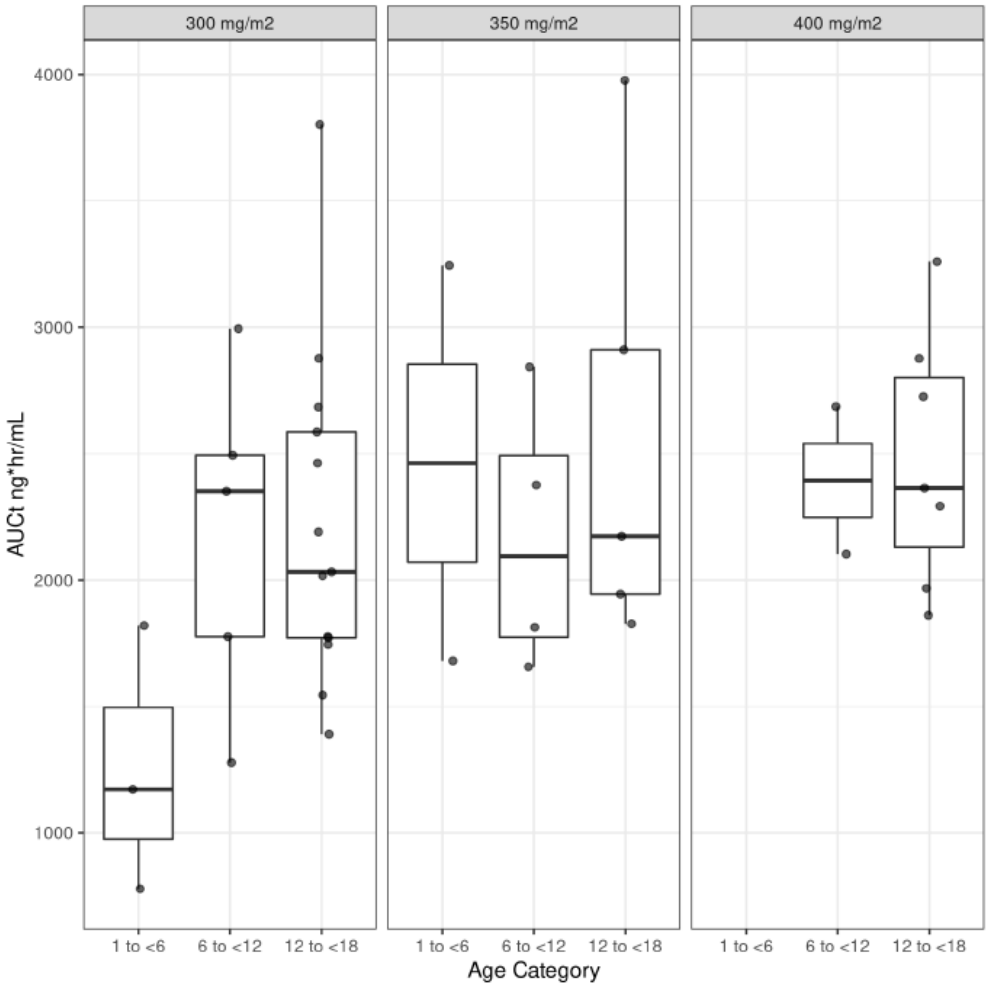
Table 9. Observed Steady State PK Parameters Across Paediatric Age Groups From the BCHILD Study Normalized to 300 mg/m² Compared to Simulated Adult Steady State Exposures at 400 mg

Age Group	PK Parameter	Mean	SD	Geomean	CV	Median	Range
	C_{max} (ng/mL)	134	41.5	127.37	31.05	127	29.29 - 313.47
	C_{trough} (ng/mL)	73.3	29.0	67.92	39.46	68.3	4.71 - 202

*Exposures normalized to 300 mg/m2 from BCHILD study, Source: CP1:FI-58313046; k

Figure 8 shows the overlap of simulated AUCt for the analysed paediatric patients on day 28 after administration of a 400 mg/m² dose across the three pre-specified age categories and stratified by BBSA-based dose level the patients received in the BCHILD study. The 1 to < 6 age category for the patients in the 300 mg/m² dose group from study BCHILD is visibly lower than the other age categories. There is slight overlap, but the lower average value may be due to the limited number of patients (3) in that group as well as the lowest AUCt estimate relative to the other patients.

Figure 8. AUCt Comparison for Paediatric Patients on Day 28 Across Age Categories Stratified by WI202099 Dose Level for a 400 mg/m² Dose



2.6.2.2. Pharmacokinetics-Pharmacodynamics (PK/PD)

Relationship between PK and PD

Exploratory exposure-response (E-R) for efficacy endpoints within the ND and R/I populations in the BCHILD study did not indicate any trends of increased CCyR and/or MMR response rate by exposure metrics in the ND population. However, there was a trend of higher plasma exposures in select exposure metrics in R/I participants who achieved CCyR and/or MMR (data not shown).

Visual inspection of exposure metrics with grade of AEs of special interest from adult studies did not reveal an E-R relationship for Diarrhoea Grade ≥2, Nausea Grade ≥2, TEAE Grade ≥3, or AEs leading to discontinuation, modification, or interruption; and no covariates were identified (data not shown).

Dose justification

Modelling and simulation were used to simplify paediatric dose instructions and provide consistency between paediatric and adult dosing recommendations via a dose-banding approach. The starting dose by BSA bracket targeted 80 – 125% of the calculated dose level. The proposed recommended regimen is shown in Table below and includes the following considerations:

- Captures all body size bands for the label which correlate with age brackets.
- Provides the ability to round to the nearest 50 mg from calculated dose for patients with BSAs <0.9 m^2 and the nearest 100 mg for patients with BSAs corresponding to ≥0.9 m^2.
- Reduces need for frequent dose adjustments based on BSA changes.
- No patients will be taking >4 capsules per dose (as supported by 50- and 100-mg capsule strengths and 100-, 400-, and 500-mg tablet strengths).
- All patients with BSA corresponding to age 10 years and over would be able to start with 1 pill per day (tablet) without mixing tablets and capsules.
- Provides a consolidated table across pediatric indications (common BSA cut-offs) for label simplicity.

Table 10. Proposed Bosutinib Starting Dose Instructions for Paediatric Patients

BSA (m^2)	ND Calculated Dose (300 mg/m^2 dose level)	ND Recommended Dose	R/I Calculated Dose 400 mg/m^2 dose level)	R/I Recommended Dose
0.55 – <0.63	165 - < 189 mg	200 mg	220 – <252 mg	250 mg
0.63 - <0.75	189 - <225 mg	200 mg	252 - <300 mg	300 mg
0.75 - <0.9	225 - <270 mg	250 mg	300 - <360 mg	350 mg
0.9 - <1.1	270 - <330 mg	300 mg	360 - < 440 mg	400 mg
≥1.1	≥330 mg	400 mg[a]	≥440 mg	500 mg[a]

a. maximum starting dose (corresponding to maximum starting dose in adult indication)

A violin plot and a scatter plot (Figures below) have been generated for AUCt exposure metrics on Day 28 for adults and compared with the BSA-based dose regimen and associated dose banding-based approach. As expected based on the fit-for-purpose paediatric popPK model, the exposure projections for virtual paediatric patients using the 1 compartment paediatric popPK model are lower than those from adults using the adult 2 compartment popPK model.

Figure 9. Day 28 Simulated Paediatric Exposures for 400 mg/m2 Dose Group using BSA-Banded Dose Instruction versus BSA-Calculated Dose in a Virtual Population Compared to the Adult Population (Violin Plot)

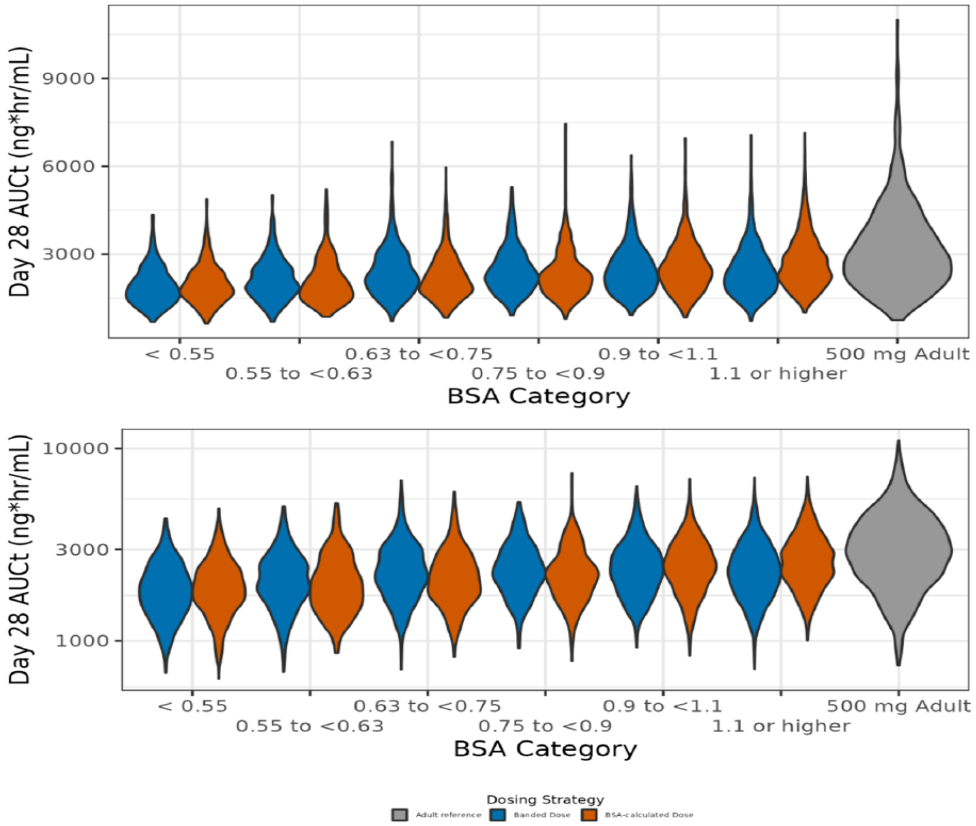
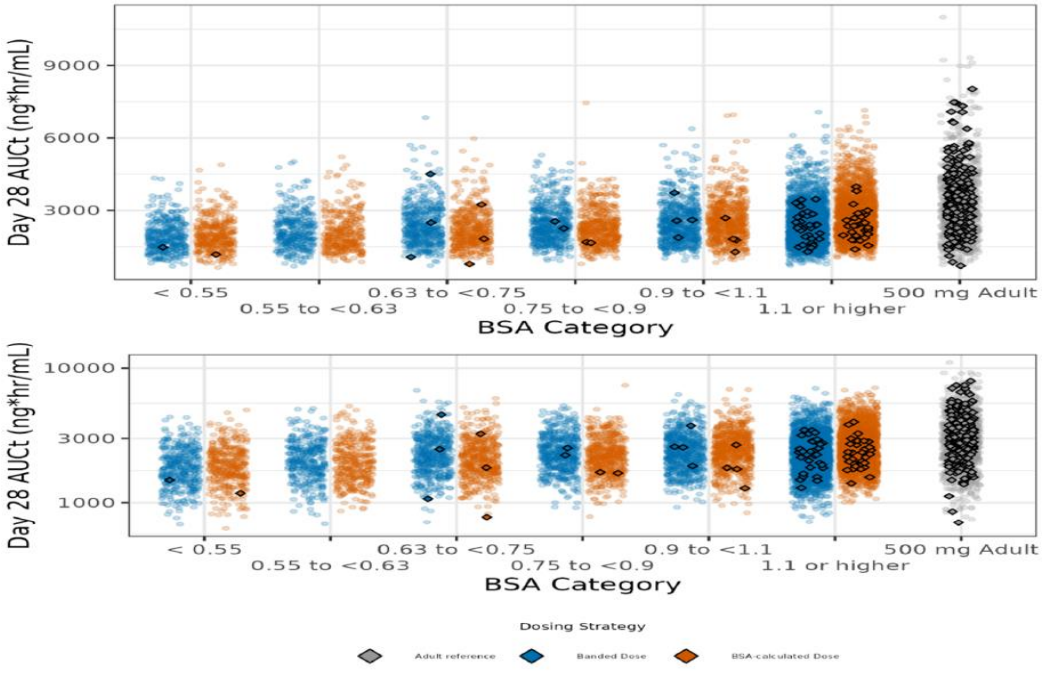
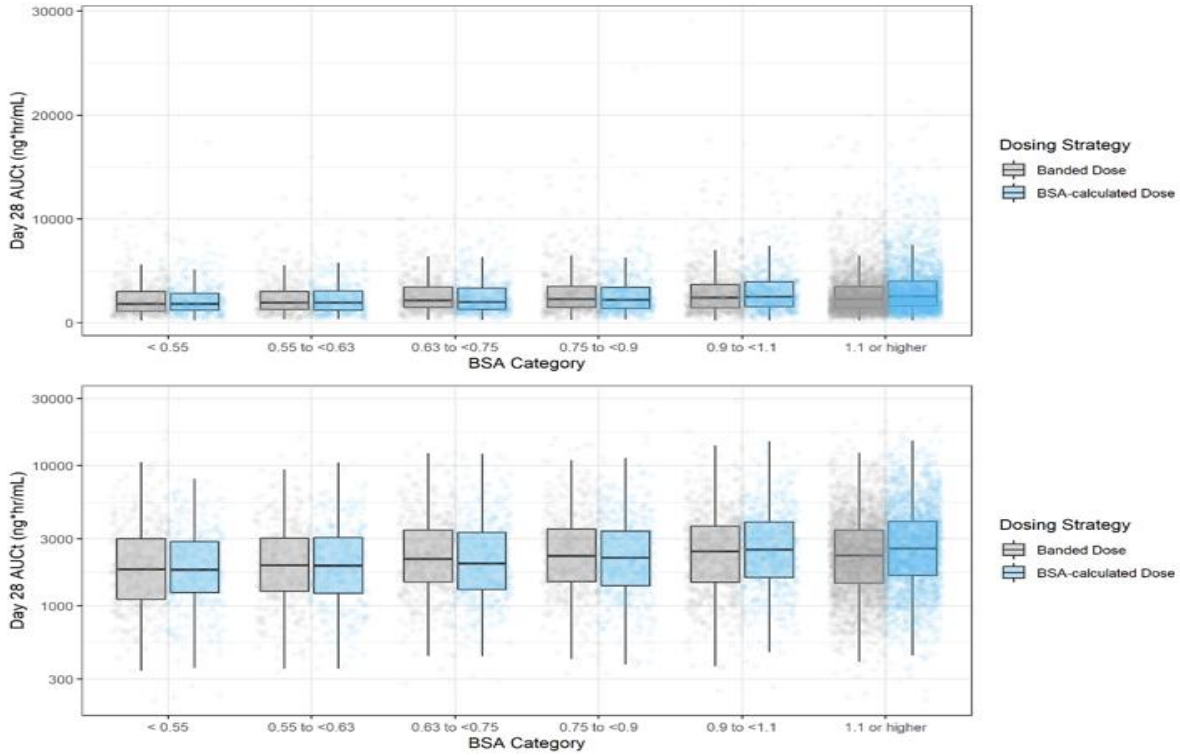


Figure 10. Day 28 Simulated Paediatric Exposures for 400 mg/m^2 Dose Group using BSA-Banded Dose Instruction versus BSA-Calculated Dose in a Virtual Population - and Compared to the Adult Population (upper Scatterplot)





2.6.3. Discussion on clinical pharmacology

The determination of bosutinib in human plasma in the submitted studies showed adequate performance. Intreim study report (ISR) assessments were conducted and met the acceptance criteria for all studies.

Since it was not possible to conduct a popPK analysis with the combined dataset of adult and paediatric patients (due to differing typical values), a separate PopPK model was developed for the paediatric population, including n=41 patients aged 1-17 years. A 1-compartment model with first order absorption and elimination including a lag time best described the paediatric data. During the procedure the model was updated with allometric scaling for volume which improved the model fit. Overall, the simulations conducted with the updated model, show that exposure in the different paediatric age groups, even if lower, are within a similar range as for adults. This is still valid for maximal doses with the additional 100mg. Nevertheless, the doses and resulting exposures for the age group 1-6 years are still uncertain because of the uncertainties in the ontogeny function for the main metabolizing enzyme CYP3A4. Since due to limited data available in the paediatric population in the submission, an ontogeny function cannot be estimated, different published (and one inhouse) ontogeny equations were proposed. These differed between similar to 3.5-fold enzyme activity compared with adults at the age of around 2 years. Also at the age of 6 years, a difference by 2-fold in enzyme activity was still existent. It was not possible to define which equation was most appropriate. On this aspect the paediatric model has several limitations, therefore, it is not considered appropriate to derive dosing recommendations based on this model for the youngest age group (1-6 years). Considering this, the initially claimed indication has been restricted further to patients from 6 years and above.

Individual exposures derived from the popPK model were used in a subsequent exposure-response analysis for efficacy and safety. Results were demonstrating no relationship, probably due to very limited data. Since the overall approach was PK bridge, the exposure-response analysis is not considered pivotal.

In study B1871061, bioequivalence between the 100 mg commercial tablets and the 100 mg capsule formulation for the paediatric population in healthy volunteers under fed condition was shown.

In study B1871062, bioequivalence between 4 x 25 mg capsule and 1 x 100 mg capsule in healthy volunteers under fed condition was shown and dissolution testing was successful between strengths at all necessary pH values. From a clinical and a quality perspective, a strength waiver for the 50 mg capsule is acceptable., From the initial marketing authorisation application of bosutinib it is known that it exhibits dose proportional increases in AUC and Cmax, between 200 to 600 mg. On the basis of the new provided data -linearity can be assumed down to 100 mg . The SmPC was adapted accordingly.

A food effect was evaluated in this study as well, comparing the exposure of a 100 mg dose (capsule) under fed condition to a 100 mg dose (capsule) under fasted condition. A trend of increased exposure with food is observed with the presented results. The MAH provided literature data which might allow an extrapolation from adult patients to a pediatric population with regard to changes in pH-values or bile salt concentrations. Although these factors alone might not give a permission of transferring the data in the respective case, a correlation to the fat-content in meals can be assumed. This possibly correlates to a better solubility of bosutinib.

In study B1871063 it was shown, that bosutinib 500 mg capsule contents mixed with applesauce or yogurt (test treatments) exhibit comparable pharmacokinetics to the 500 mg bosutinib intact capsule under fed condition in healthy adult participants.

Results of different *in vitro* tests of dispersibility and disintegration for tablets and capsules were provided i.e. dispersion in water, for syringe and nasogastric tube and storage and recovered contents are within the required limits. It was clarified that the MAH does not pursue the administration of tablets after dispersion for syringe and nasogastric tube.

The dedicated food effect studies submitted to date only investigated the PK effects of a high-fat meal vs. fasted state. Bosutinib Cmax increased 1.8-fold and AUC increased 1.7-fold when bosutinib tablets were given with a high-fat meal to healthy subjects compared to administration under fasted condition. In a separate study, bosutinib hard capsule administration under the fed condition resulted in exposures approximately 1.5 – 1.6-fold higher than administration under fasted conditions.

Based on this information, the clinical study protocol requirement for study drug intake was that "apple sauce and yoghurt were not considered a full meal" and the proposed new recommendation in SmPC section 4.2 states this accordingly.

From the palatability questionnaire applied in the BCHILD study the MAH concluded that most of the patients swallowed their tablets or capsules whole, but intake with soft food was acceptable.

The BSA-adjusted dose-normalised geo-mean values (CV%) of AUC_{tau} and C_{max} at C1D14, as derived from the NCA analysis of the BCHILD study, suggested a roughly comparable exposure over the BSA-adjusted dose-range tested, although the underlying dataset was very limited and patients were excluded if not having had 8 consecutive doses prior to blood draw or incomplete PK profiles.

However, even more relevant, the calculations did not take into account that the actual doses administered to these paediatric cancer patients of 1-17 years of age varied significantly, from 150 mg to 600 mg, and were hence also lower than the known linear range. The MAH was thus asked to provide an analysis utilising actual doses for the 3 age groups of 1-<6, 6-<12, and 12-17 years separately to show dose-proportionality over the whole range of doses (<200 mg-600mg) each to justify adding "Exposures increased in a dose proportional manner" in the proposed new paediatric paragraph in SmPC section 5.2. As a result from the provided data, the questioned statement can be amended to include the demonstrated linear dose range in paediatrics, and hence the text should read

"Exposures increased in a dose proportional manner between 100 – 600 mg", which is in accordance with previous information.

The PK in the target population comes from the pivotal BCHILD study in children of 1-17 years of age with R/I and newly diagnosed CML. Firstly, the design was to include only R/I patients with up to 350mg/m² BSA QD to establish a RP2D based on PK and safety/tolerability. After the Bosulif EU approval was extended to newly diagnosed CML patients at the lower 400mg QD dose the study design was substantially amended during the study to also include ND patients at a corresponding dose level of 300mg/m². In addition, the design was also amended to include a higher dose escalation level of 400mg/m² in R/I CML patients based on an updated adult popPK model provided in previous procedures. The rationale for the new dose levels were stated by the MAH resulting from extrapolation of exposure (AUC) from adult popPK data and preliminary exposure data from the first 300mg/m² dose level group. As expected, the overall number of paediatric patients was small depending also on the age group, so that PK samples were very limited. From the demographic summary it is also noteworthy that no patient in the 1-<6 years group was treated with the highest new dose level of 400 mg/m².

In addition, the NCA-based PK dataset for establishing the key PK parameters at day 14 excluded patients who did not provide sufficient samples for a proper PK profile or had no sufficient number of continuous doses prior to the steady-state PK analysis at Cycle 1 Day 14. Thereafter, only trough samples at cycles 2-4 were drawn and the cycle 2-4 pre-dose concentrations were provided.

According to the clinical study protocol , the dose had to be adjusted every 3 months, i.e. starting from cycle 4. PK sampling, however, stopped at C4D1 pre-dose, so it is unknown, how the trough levels developed in each patient with their growth during course of the study.

In paediatric patients, median Tmax occurred at approximately 3 hours post-dose (range 1 to 8 hours post-dose). Exposures increased in a dose proportional manner between 100 – 600 mg. The geometric mean AUCtau in the 300 mg/m2 to 400 mg/m2 cohorts was within the range (+/- 20%) of geometric mean AUCtau for the adult dose level in the respective newly-diagnosed and resistant or intolerant Ph+ CML indications, however Cmax and clearance were higher and Cmin was lower in paediatric patients than in adults.

From the conducted analysis it became apparent that pre-dose plasma concentrations were mostly below the adult mean trough concentration after 500 mg of 105 ng/ml, independent of age and dose. Even under consideration of the newly proposed reduced geo-mean C_{trough} parameters for adults for the 400 mg (65 ng/ml) and 500 mg doses (91 ng/ml) from popPK modelling the measured pre-dose concentrations in the children were substantially lower than in adults, 29% and 48% lower for 300 mg/m^2 and 400 mg/m^2 dosing, respectively. In addition, the dose-normalised AUC per age group was compared to those stated in the SmPC for the approved doses of 400 mg and 500 mg in adults, respectively and support the information that the proposed dosing in children results in an AUC in the lower range of the adult exposure.

Also,popPK simulations for AUC for a 400mg/m² dose are very low and variable exposure for patients treated in the smallest age group.

For the developed paediatric popPK model, additional visual predictive checks (VPCs) have been provided stratified by age, dosing group and BSA. These reveal that the model overpredicts Cmin in the youngest age group (1-6 years) and overpredicts Cmax in both younger age groups (1-6 and 6-12 years). Therefore, the model does not yet adequately describe the paediatric data.

With the underlying grouped variation the MAH proposed to update the SmPC data in section 5.2 with concentrations for the 400mg and 500mg dose levels derived from the recent adult popPK model. Of these PK parameters, C_{trough} levels are 68 ng/mL (39%) [128 nM] at 400mg and 91 ng/mL (42%)

[172 nM] at 500mg QD doses. These concentrations are total, i.e. protein-bound. With a protein binding of 96%, the unbound trough concentrations are calculated to 5 nM and 7 nM, suggesting an about 50% target saturation in adults.

Now, the C1D14 geo-mean trough concentrations in the paediatric dose and age groups were approximately 48 ng/ml (range 20-103 ng/ml; total 1L+2L 300 mg/m² group), corresponding to 90.5 nM total or 3.5 nM unbound bosutinib. And ~49 ng/ml (range 12-137 ng/ml) in the 400 mg/m² group. While these means are even lower and without knowledge of response status in these patients, the concentrations measured in the 1-year-old patient were only a quarter of this mean value, i.e. 12-14 ng/ml, so that a sufficient target occupation for efficacy has been questioned. The MAH submitted popPK-derived exposure-response graphs which evaluated several other exposure metrics than those which had previously been established, none of which showed any significant relationship for response/non-response to the measures of cumulative CCyR and cumulative MMR in both populations.

Despite the patient numbers are so limited here, the MAH was asked to evaluate minimal Cmin per patient to his response and discuss results accordingly. From the response it could be derived that children who did not achieve a MMR most often had lowest minimal C_{min} concentrations (between C1D14 and C4). It is also noted that in some adolescents who already received the adult doses of 500mg/600mg pre-dose concentrations were still very low. This is probably due to the much higher clearance in all dose and age groups (192.5 (43) L/h compared to 61.9 (26) L/h in adults) and especially in the eldest group.

In paediatric patients, median T_{max} occurred at approximately 3 hours post-dose (range 1 to 8 hours post-dose). Exposures increased in a dose proportional manner between 100 – 600 mg. The geometric mean AUCtau in the 300 mg/m2 to 400 mg/m2 cohorts was within the range (+/- 20%) of geometric mean AUCtau for the adult dose level in the respective newly-diagnosed and resistant or intolerant Ph+ CML indications, however Cmax and clearance were higher and

As it is acknowledged that it might be difficult to propose a definite threshold of C_{trough}, in view of possible safety and tolerability concerns (e.g. diarrhoea and potential resulting dehydration), a statement in section 4.2 and PL was included to stop treatment especially in cases when adequate clinical responses are awaited for several months, and further dose escalation up to maximum of 100 mg above BSA-adjusted recommended dose is not possible.

Summarizing, the intention of the MAH to provide specific dosing for paediatric newly diagnosed and R/I CML patients is endorsed. However, experimental PK data from the BCHILD study in patients below 6 years of age are and will remain very scarse, so that also the modelling efforts can only be considered limited and cannot support dosing below the age of 6 years.

2.6.4. Conclusions on clinical pharmacology

From a clinical pharmacology point of view this application for the indication in paediatric CML patients aged 6 years and above together with a new "patient-centric" hard capsule formulation is supported.

2.6.5. Clinical efficacy

Data regarding efficacy and safety in the paediatric population is derived from the **BCHILD Trial**.

As per the BCHILD Interim study report data cutoff date (19 September 2022) the study provided data on 49 paediatric patients (ages 1 to < 18 years), including 21 with ND CML and 28 with R/I CML

supporting the use of BOSULIF in paediatric patients 1 year of age and older with ND CP Ph+ CML, or paediatric patients 1 year of age and older with CP, AP, or BP Ph+ CML with R/I to prior therapy.

2.6.5.1. Dose response study(ies)

Phase 1 of this study employed a 6+4 design (no dose limiting toxicity in 6 participants or 1 dose limiting toxicity in 10 participants) and incorporated additional PK information before escalating to the next dose level. If any unacceptable toxicity or any PK results exceeded the acceptable exposure levels for the adult equivalent dose, further dose escalation was prohibited.

The RP2D was defined as the dose that results in equivalent (approximately ±20% of the adult AUC values) PK exposure to 400 mg/day (in participants with ND Ph+ CML) or 500 mg/day (in participants with R/I Ph+ CML) in adults and was considered safe with 0 of 6 or <2 DLTs observed out of 10 evaluable participants.

Based on the acceptable tolerability and lack of exposure-safety relationship across the evaluated dose range, in addition to achieving plasma exposures within the range of targeted plasma exposures from adult experience to enable efficacy extrapolation, the recommended doses for paediatric patients are 300 and 400 mg/m2 once daily following a meal, for the ND and R/I indications, respectively.

2.6.5.2. Main study

BCHILD:: A Phase 1/2 Study of Bosutinib in Pediatric Patients With Newly Diagnosed Chronic Phase or Resistant/Intolerant Ph+ Chronic Myeloid Leukemia, Study ITCC-054/AAML1921.

As perthe BCHILD Interim study report data cutoff date (19 September 2022) the study provided data on 49 paediatric patients (ages 1 to < 18 years), including 21 with ND CML and 28 with R/I CML supporting the use of BOSULIF in paediatric patients 1 year of age and older with ND CP Ph+ CML, or paediatric patients 1 year of age and older with CP, AP, or BP Ph+ CML with R/I to prior therapy.

Table 11. Summary of the BCHILD Study of Bosutinib in Paediatric Participants with ND CML or R/I CML

Protocol Number/ Sponsor/Title/Country/ Study Dates and Status[a]	**Secondary Efficacy Objective(s)**	**Efficacy Endpoint(s)**	**Study Treatment**	**Study Population Data cutoff: 19 September 2022)**
BCHILD Trial (ITCC) 054/AAML1921, B187-WI202099)/ ERASMUS MC and COG/ Title: *"A Phase 1/2 Study of Bosutinib in Paediatric Patients With Newly Diagnosed Chronic Phase or Resistant/Intolerant Ph+ Chronic Myeloid Leukemia"*	**Phase I** To preliminarily evaluate the anti-leukemic activity in paediatric patients with Ph+ CML following resistance or intolerance to one or more TKIs	**Phase I** Overall cumulative disease response: CHR, MCyR (CCyR+PCyR), CCyR, MMR, deep molecular response	**Phase I** Bosutinib (Route: Oral; Dose Regimens: 300 mg/m^2 QD, 350 mg/m^2 QD, 400 mg/m^2 QD).	**Phase 1** 300 mg/m^2 QD: **6** 350 mg/m^2 QD: **11** 400 mg/m^2 QD: **11**
Countries: France, Germany, Italy, Spain, Switzerland, The Netherlands, United Kingdom, United States)	**Phase II** a.)To describe the clinical efficacy of bosutinib in paediatric	**Phase 2:** Overall cumulative disease response by the line of therapy:	**Phase 2:** Bosutinib (Route: Oral; Dose Regimen: 300 mg/m^2 QD)	**Phase 2** 300 mg/m^2 QD: 21

FPFV: 14 November 2016/ Ongoing, data cutoff: 19 September 2022 for Interim CSR	participants with ND Ph+ CML in CP b.)To describe the clinical efficacy of bosutinib in paediatric patients with Ph+ CML in any phase of disease following resistance or intolerance to one or more TKIs[b]	CHR, MCyR (CCyR+PCyR), CCyR, MMR, deep molecular response 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 paediatric patients with Ph+CML by line of therapy		

a. "Ongoing" studies include completed or terminated studies with no final CSR as of the data cutoff (includes ongoing studies as well as studies in which patient enrollment and follow-up have been completed, but the analysis and CSR are in-progress).
b. This exploratory endpoint was added after the final SAP but before database lock. Refer to the BCHILD Report Body Section 3.7.2 for more details.
c. Study populations are defined in the BCHILD SAP Section 6.
d. 50 participants were enrolled and 1 patient was not treated.

As of the safety data cutoff date, 55 paediatric patients (ages 1 to < 18 years), including 24 with ND CML and 31 with R/I CML, were enrolled and received at least one dose of bosutinib.

Methods

- **Study Participants**

The study BCHILD enrolled the following populations:

- Phase 1: (R/I only)
  - Only paediatric participants with Ph+ CML who were R/I to previous TKI treatment were enrolled during the dose-finding part of the study. R/I participants could have been in CP, AP, or BP of CML disease.
- Phase 2:
  - Phase 2 ND: paediatric participants with ND Ph+ CML were enrolled in Phase 2 of the study only if CML was in CP.
  - Phase 2 R/I: paediatric participants with Ph+ CML and R/I to previous TKI treatment could have also been enrolled during Phase 2 of the study. Any phase of CML disease (CP, AP, or BP) was allowed in this cohort.

Paediatric participants with ND Ph+ CP CML or R/I Ph+ CML were enrolled in this study according to the following main inclusion and exclusion criteria:

Main Phase 1

Inclusion Criteria (R/I participants only)

1. Cytogenetic and molecular diagnosis of Ph+ CML at either time of initial CML diagnosis or at time of study screening.
2. Resistance (suboptimal response or failure, as defined by 2013 ELN guidelines5) or intolerance (with or without suboptimal response or failure) to at least 1 prior TKI.
3. Age ≥1 and <18 years at day of signing the informed consent.
4. Lansky performance status ≥50% for participants ≤16 years of age, or Karnofsky scale ≥50% for participants >16 years of age.
5. Adequate bone marrow, renal and liver function.

Exclusion Criteria (R/I participants only):

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

1. Diagnosis of primary Ph+ acute lymphoblastic leukemia.
2. 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.
3. Extramedullary disease only.
4. 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).
5. Any prior treatment with a TKI within 7 days prior to starting bosutinib treatment, or other antitumor or anti-leukemia treatment (with the exception of hydroxyurea and/or anagrelide) within 14 days prior to start of bosutinib treatment.
6. Prior growth factors or biologic agents within 7 days prior to bosutinib treatment.
7. Use of strong or moderate CYP3A4 inhibitors and inducers within 7 days prior and/or concomitant to bosutinib treatment.
8. Use of proton pump inhibitors (Ph-modifying agents) within 7 days prior and/or concomitant to bosutinib treatment.
9. Prior radiotherapy within 3 months prior to bosutinib treatment.
10. Allogeneic stem cell transplantation within 3 months prior to bosutinib treatment.
11. DLI within 1 month prior to bosutinib treatment.
12. Hereditary bone marrow failure disorder.
13. GVHD within 60 days prior to bosutinib treatment.
14. History of clinically significant or uncontrolled cardiac disease.
15. Prolonged QTc (>450 msec, average of triplicate ECGs).

Phase II

Main Phase 2 Inclusion Criteria Participants with Resistant/Intolerant CML:
The inclusion criteria for the participants with R/I in Phase 2 were identical to the Phase 1 inclusion criteria.

Participants with Newly Diagnosed CML

1. Cytogenetic and molecular diagnosis of Ph+ CML at either time of initial CML diagnosis or at time of study screening.

2. 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. Diagnosis of CP CML was defined as per Appendix 16.1.1, Protocol Appendix 1.
3. Age ≥1 and <18 years at day of attaining the informed consent.
4. Lansky performance status ≥50% for participants ≤16 years of age, or Karnofsky scale ≥50% for participants >16 years of age (Appendix 16.1.1, Protocol Appendix 5).
5. Adequate renal function: Participants must have a calculated CrCl ≥ 60 mL/min/1.73 m^2, using the Schwartz formula to estimate GFR (see Appendix 16.1.1, Protocol Appendix 11).
6. Adequate liver function, including
    - AST/ALT ≤2.5×ULN or ≤5×ULN if attributable to disease involvement of the liver
    - Total bilirubin ≤1.5×ULN unless the participant has documented Gilbert syndrome.

<u>Main Phase 2 Exclusion Criteria</u> Participants with Resistant/Intolerant CML:

The exclusion criteria for the R/I cohort in Phase 2 were identical to the Phase 1 exclusion criteria.

Participants with Newly Diagnosed Ph+ CML

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

1. Diagnosis of primary Ph+ acute lymphoblastic leukemia.
2. Extramedullary disease only.
3. 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.
4. Any prior treatment with a TKI or other antitumor or anti-leukemia treatment (with the exception of hydroxyurea and/or anagrelide)
5. Prior growth factors or biologic agents within 7 days prior to bosutinib treatment.
6. Use of strong or moderate CYP3A4 inhibitors and inducers within 7 days prior and/or concomitant to bosutinib treatment.
7. Use of proton pump inhibitors (Ph-modifying agents) within 7 days prior and/or concomitant to bosutinib treatment).
8. Hereditary bone marrow failure disorder.
9. History of clinically significant or uncontrolled cardiac disease.
10. Prolonged QTc (>450 msec, average of triplicate ECGs).

- **Treatments**

Bosutinib is administered orally QD with a meal (approximately at the same time of day, preferably in the morning). It is allowed to open bosutinib capsules and add the capsule contents to a suitable foodstuff (apple sauce or yoghurt) for administration. Mixing the capsules on apple sauce or yogurt is not considered a substitute of a proper meal.

The currently approved commercial bosutinib immediate-release film-coated tablets are available at 100-, 400-, and 500-mg strengths. Bosutinib 100- and 500-mg tablets have been used in clinical studies in paediatric participants. In addition, the bosutinib drug product is formulated as a capsule which can be administered intact or opened and capsule contents mixed with soft foods for oral administration. Strengths of 50- and 100-mg bosutinib are provided in hard gelatin capsules.

The 25 mg capsule was used in clinical studies during development and was also included in the primary and supplemental stability studies for the capsule dosage form. The qualitative and quantitative composition of the bosutinib capsules has remained consistent throughout the clinical studies.

Bosutinib tablets (100 and 500 mg dosage strength) and bosutinib capsules (25 and 50 mg dosage strengths) were supplied by Pfizer. Participants continue to receive bosutinib until up to 2 years from the time of last participant first visit (LPFV) in the same phase, unless disease progression, unacceptable toxicity, withdrawal of consent/assent by caregiver or patient, death, or discontinuation of study by the Sponsor, whichever occurs first.

In Phase 1, the dose of bosutinib depends on the dose cohort (300 mg/m^2, 350 mg/m^2 and 400 mg/m^2 cohort) that the participant (with R/I Ph+ CML) is assigned to; In Phase 2, participants with ND Ph+ CML are dosed according to the recommended-phase-2-dose for newly-diagnosed patient (RP2DND) as established in Phase 1.

The dose was adjusted for the participant's BSA measured during screening. The BSA calculation was 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. Daily dose was not to exceed the maximum adult equivalent per dose group.

Recommendations for dose reduction/ treatment interruption and dose escalation were provided in the study protocol.

- **Objectives and Outcomes/endpoints**

Table 12: Trial objectives and endpoints selected according phases
Phase I

Type	Objective	Endpoints	Reference
Primary			
Safety	• To determine the RP2D of bosutinib for R/I (RP2DR/I) and ND CP (RP2DND) paediatric participants with Ph+ CML, based on the PK, safety, and tolerability profile of bosutinib observed at various dose levels in paediatric 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	Interim data for all endpoints are reported in the ISR.
PK		• PK parameters of bosutinib: Cmax, Tmax, AUCtau, Ctrough, CL/F • Dose normalized PK parameters: Cmax, AUCtau, Ctrough; BSA adjusted CL/Fa	
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 paediatric 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			
Safety	To evaluate the effects of bosutinib on growth and bone metabolism	Parameters of bone metabolism and 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 T4b, TSHb 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 paediatric participants with Ph+ CML following resistance or intolerance to one or more TKIsa	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 paediatric participants with Ph+ CML by line of therapy	

a. Study objective/endpoint that was added after the final SAP but before database lock. Refer to Section 3.7.2 for more details.

b. Hormone associated with growth and pubertal development that is being collected in the US only as requested by FDA.

Phase II

Type	Objective	Endpoints	Reference
Primary			
PK	• To assess the PK of bosutinib at the RP2DND and RP2DR/I in paediatric participants with ND or R/I Ph + CML	• Cmax, Tmax, AUCtau, Ctrough, CL/F • Dose normalized PK parameters: Cmax, AUCtau, Ctrough; BSA adjusted CL/F[a]	Interim data for all endpoints are reported in this CSR
	• 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 paediatric 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 paediatric participants with ND Ph+ CML in CP	• Overall cumulative disease response by the line of therapy: CHR, MCyR (CCyR+PCyR), CCyR, MMR, deep molecular response	
	• To describe the clinical efficacy of bosutinib in paediatric 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 paediatric 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			
Type	Objective	Endpoints	Reference
Safety	• To evaluate the effects of bosutinib on growth and bone metabolism	• Parameters of bone metabolism and growth: including linear growth, bone age, BMD of LS, physical signs of pubertal maturation (Tanner stage and testicular volume of boys), Vitamin D and 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. Refer to Section 3.7.2 for more details.
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.

- **Sample size**

This study does not include any formal sample size determination but is based on feasibility due to the rarity of paediatric CP CML.

A minimum of 60 total evaluable patients including at least 15 patients < 12 years are expected to be enrolled combining phase 1 and phase 2.

At least 35 evaluable patients will be enrolled in phase 2 to fulfil the PIP commitment (approximately 50 total evaluable patients with both phases combined).

- **Randomisation and Blinding (masking)**

The BCHILD trial was an open-label study. Dose level allocation was performed centrally.

- **Statistical methods**

Since the study has not been powered for efficacy, only descriptive analyses will be provided.

These descriptive efficacy analyses are intended to allow extrapolation of efficacy in the paediatric population from data in adults with Ph+ CML. Response rates for cumulative CHR, MCyR, CCyR, MMR and deep molecular response in paediatric patients with Ph+ CML in all phases of diseases are analysed, as well as time to and duration of response (CHR, MCyR, CCyR, MMR), transformation, EFS and OS.

Results

- **Participant flow**

As of the data cutoff date of 19 September 2022, the disposition events summary, including reasons for discontinuation, is presented in the tables below for end of treatment and for end of study respectively:

Table 13. Disposition Events Summary - End of Treatment (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Study Phase **Number (%) of Participants**	**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 (%)**
Disposition phase: Treatment Participants Entered:	6 (100.0)	11 (100.0)	11 (100.0)	21 (100.0)	49 (100.0)
Discontinued	5 (83.3)	7 (63.6)	5 (45.5)	5 (23.8)	22 (44.9)
Reason for discontinuation Patient/guardian withdraws assent/consent to	0	0	0	0	0

undergo further treatment					
Unsatisfactory response or disease progression	2 (33.3)	3 (27.3)	3 (27.3)	2 (9.5)	10 (20.4)
Death	0	0	0	0	0
Lost to Follow-Up	0	0	0	0	0
Study terminated by Sponsor for significant safety or efficacy concerns	0	0	0	0	0

Table 14. Disposition Events Summary - End of Study (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

	Phase 1	**Phase 1**	**Phase 1**	**Phase 2 CP1L**	**Total**
	(300mg/m²)	**(350mg/m²)**	**(400mg/m²)**	**(300mg/m²)**	**(N=49)**
	(N=6)	**(N=11)**	**(N=11)**	**(N=21)**	
Number (%) of	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Participants					
Discontinued	4 (66.7)	3 (27.3)	1 (9.1)	1 (4.8)	9 (18.4)
Protocol	1 (16.7)	3 (27.3)	0	0	4 (8.2)
Completion					
Death	1 (16.7)	0	0	0	1 (2.0)
Lost to Follow-Up	1 (16.7)	0	0	0	1 (2.0)
Withdrawal of	0	0	1 (9.1)	1 (4.8)	2 (4.1)
consent					
Other	1 (16.7)	0	0	0	1 (2.0)
Ongoing	2 (33.3)	8 (72.7)	10 (90.9)	20 (95.2)	40 (81.6)

(Data cutoff date : 19SEP2022)

- **Recruitment**

As of the data cutoff date of 19 September 2022, a total of 52 participants were screened at 29 sites in 8 countries (France, Germany, Italy, Spain, Switzerland, the Netherlands, UK, and USA, of whom 50 were enrolled and 49 were treated.

- **Conduct of the study**

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 protocol versions 3.0 (12 July 2018), 4.0 (instituted in the EU, 10 Oct 2019) and 4.1 (instituted in the US only, 19 Dec 2019), as described in Appendix 16.1.1.

- According to protocol version 4.0, the DL2 for participants with R/I Ph+ CML in Phase 1 was planned to be escalated to 400 mg/m2 (DL2B) instead of 350 mg/m2 (DL2A). However, after occurrence of a DLT in the 350 mg/m2 cohort (See Section 5.2.1.2 for details), the number of participant in Phase 1 DL2A was increased from initially 6 participants to 10 participants before allowing dose escalation to 400 mg/m2 (DL2B).

- Protocol version 4.1 differs from version 4.0 only in the addition of growth and bone metabolism parameters following FDA request. Version 4.1 was not instituted outside of the US.

Changes in the planned analyses for the study that were implemented by SAP amendment(s) are described in Appendix 16.1.9. Relevant changes made after the final SAP and before database lock are described as follows:

- An exploratory objective and endpoints for Phase 1 were added to assess duration of responses, EFS, and OS.
    - When considered confirmed loss, the treatment discontinuation due to death within 28 days of last dose was updated as death due to PD within 28 days of last dose.

- CHR and confirmed loss of CHR were based on the data collected in CRF instead of derived data as defined in the SAP Section 7.3.

- **Baseline data**

Table 15. Demographic Characteristics (Safety Analysis Set) (Protocol ITCC- 054/AAML1921 (B187-WI202099))

	Phase 1 (300 mg/m^2) (N=6)	Phase 1 (350 mg/m^2) (N=11)	Phase 1 (400 mg/m^2) (N=11)	Phase 2 CP1L (300 mg/m^2) (N=30)	Phase 2 R/I (400 mg/m^2) (N=6)
Age (Years), n (%)					
≥1-<6	2 (33.3)	2 (18.2)	0	2 (6.7)	0
≥6-<12	3 (50.0)	4 (36.4)	3 (27.3)	10 (33.3)	1 (16.7)
≥12-<18	1 (16.7)	5 (45.5)	8 (72.7)	18 (60.0)	5 (83.3)
Median (range)	8.50 (1, 17)	11.00 (4, 17)	15.00 (6, 17)	12.50 (5,17)	14.50 (11, 16)
Gender, n (%)					
Male	5 (83.3)	4 (36.4)	7 (63.6)	18 (60.0)	4 (66.7)
Female	1 (16.7)	7 (63.6)	4 (36.4)	12 (40.0)	2 (33.3)
Race, n (%)					
White	0	5 (45.5)	7 (63.6)	22 (73.3)	4 (66.7)
Black or African American	0	1 (9.1)	1 (9.1)	5 (16.7)	1 (16.7)
Asian	0	1 (9.1)	3 (27.3)	1 (3.3)	1 (16.7)
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	2 (6.7)	0
Unknown	6 (100.0)	4 (36.4)	0	0	0
Ethnicity, n (%)					
Hispanic or Latino	0	0	2 (18.2)	7 (23.3)	0
Not Hispanic or Latino	0	8 (72.7)	9 (81.8)	23 (76.7)	6 (100.0)
Unknown	6 (100.0)	3 (27.3)	0	0	0

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).
(Data cutoff date : 19SEP2022)

An Overview about Baseline and Disease Characteristics is provided in the Table below:

Table 16. 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)**
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
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					
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. (Data cutoff date : 19SEP2022)

- **Numbers analysed**

Table 17: Participant Evaluation Groups BCHILD

	Phase 1 (300mg/m²)	Phase 1 (350mg/m²)	Phase 1 (400mg/m²)	Phase 2 CP1L (300mg/m²)	Total (N=50)
	(N=6)	(N=11)	(N=11)	(N=21)	
	n (%)	n (%)	n (%)	n (%)	n (%)
Screened: 52					
Screen Failure: 2					
Full Analysis Set	6 (100.0)	11 (100.0)	11 (100.0)	21 (100.0)	50 (100.0)
Safety Analysis Set	6 (100.0)	11 (100.0)	11 (100.0)	21 (100.0)	49 (98.0)
Not Treated	0	0	0	0	1 (2.0)
Per-Protocol Analysis Set	6 (100.0)	10 (90.9)	10 (90.9)	0	26 (52.0)
PedsQL Analysis Set	5 (83.3)	11 (100.0)	11 (100.0)	21 (100.0)	48 (96.0)
Growth & Bone Metabolism Analysis Set	6 (100.0)	11 (100.0)	11 (100.0)	21 (100.0)	49 (98.0)

Note: Participants who are enrolled but not treated are counted in total column.
Note: Per protocol analysis set is defined for phase 1 includes all enrolled participants who received at least one dose of study treatment and evaluable for RP2D.
(Data cutoff date : 19SEP2022)

Table 18. 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)						
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.
(Data cutoff date : 19SEP2022)

The study treatment compliance was well maintained. Overall median relative dose intensity was 96.71% (range: 93.81%, 115.87%) for the Phase 1 300 mg/m2 cohort, 94.32% (range: 52.31%,

102.75%) for the Phase 1 350 mg/m2 cohort, 91.53% (range: 74.96%, 100.00%) for the Phase 1 400 mg/m2 cohort, and 97.50% (range: 18.18%, 119.46%) for the Phase 2 300 mg/m2 cohort.

- **Outcomes and estimation**

The following secondary endpoint results are relevant for cumulative efficacy assessment in this exploratory trial:

Complete hematologic response (CHR)

Table 19. Summary of CHR (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

Completer Haematological Response	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)
Participants in Analysis					
CHR (n (%))	6 (100.0)	10 (90.9)	8 (72.7)	24 (81.8)	18 (85.7)
(95% CI)[a]	(54.1, 100.0)	(58.7, 99.8)	(39.0, 94.0)	(39.0, 99.8)	(63.7, 97.0)
Median Time to CHR (months)	1.86	1,87	2.27	2.0	1.0
Range (months)	(1.64, 4.76)	(0.95.2.79)	(0.99, 2.79)	(0.95, 4.76)	(0.89, 4.63)

Abbreviations: CHR: Complete Haematological Response
(Data cutoff date : 19SEP2022)

The KM estimate of maintaining CHR at Month 12 was 100% (95% CI: 100%, 100%), 100% (95% CI: 100%, 100%), 87.5% (95% CI: 38.7%, 98.1%) and 100% (95% CI: 100%, 100%) in the Phase 1 300 mg/m2 cohort, Phase 1 350 mg/m2 cohort, Phase 1 400 mg/m2 cohort and Phase 2 300 mg/m2 cohort, respectively.

Cumulative Major Cytogenetic Response (MCyR) (CCyR+PCyR)

Table 20. Summary of 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=11)	Phase 1 Total (R/I) (N=28)	Phase 2 CP1L (300mg/m²) (N=21)
Participants in Analysis					
MCyR (n (%))	6 (100.0)	10 (90.9)	7 (63.6)	23 (82.1)	16 (76.2)
(95% CI)[a]	(54.1, 100.0)	(58.7, 99.8)	(30.8, 89.1)	(63.1, 93.9)	(52.8, 91.8)
CCyR (n (%))	5 (83.3)	10 (90.9)	7 (63.6)	22 (78.6)	15 (71.4)
(95% CI)[a]	(35.9, 99.6)	(58.7, 99.8)	(30.8, 89.1)	(59.0, 91.7)	(47.8, 88.7)
Median Time to MCyR (months	2.76	2.79	2.79	2.78	2.92
Range (months)	(2.56, 8.21)	(2.76, 5.75)	(1,17,3.71)	(1.17,8.21)	(2.73, 8.31
Median Time to CCyR (months	2.76	2.79	2.79	2.78	5.49
Range (months)	(2.56,2.79)	(2.76, 5.75)	(1.71.3.71)	(1.71,8.21)	(2.79,11.01)
Participants still On-Treatment without MCyR, n (%)	0	0	1 (9.1)	1 (3.6)	3 (14.3)

Abbreviations: MCyR - Major Cytogenetic Response, CCyR - Complete Cytogenetic Response.
Note: Major cytogenetic response (MCyR, defined as complete cytogenetic response [CCyR] plus partial cytogenetic response [PCyR]).
Note: Cumulative response is defined as any on-treatment response.
Note: Response is unconfirmed for cytogenetic. To be considered a responder, a participant with a baseline response must have maintenance of response for >= 4 weeks from baseline for cytogenetic response or improvement from baseline must be achieved. Participant with a non-valid or missing baseline assessment must demonstrate the best response, complete cytogenetic response (CCyR) to be considered a responder for the respective endpoint. (Data cutoff date : 19SEP2022)

The KM estimate of maintaining MCyR/CCyR at Month 12 was 100% (95% CI: 100%, 100%) in the Phase 1 300 mg/m2 cohort, Phase 1 350 mg/m2 cohort, and Phase 2 300 mg/m2 cohort. The KM estimate of maintaining MCyR/CCyR at Month 12 was 75.0% (95% CI: 12.8%, 96.1%) in the Phase 1 400 mg/m2 cohort.

Major molecular response (MMR) (including MR4 and MR4.5; "deep molecular response")

Table 21. Summary of Cumulative Molecular Response (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=11)	Phase 1 Total (R/I) (N=28)	Phase 2 CP1L (300mg/m²) (N=21)
Participants in Analysis					
MMR, n (%) | (95% CI)[a]	4 (66.7) (22.3,95.7)	5 (45.5) (16.7, 76.6)	5 (45.5) (16.7, 76.6)	14 (50.0) (30.6, 69.4)	6 (28.6) | (11.3, 52.2)
MR4, n (%) | (95% CI)[a]	2 (33.3) (4.3,77.7)	4 (36.4) (1.0,69.2)	0 (0.0) (0.0, 28.5)	6 (21.4) (8.3,41.0)	1 (4.8) (0.1, 23.8
MR4.5, n (%) | (95% CI)[a]	2 (33.3) (4.3, 77.7)	3 (27.3) 6.0,61.0))	0 (0) (0.0,28.5)	5 (17.9) (6.1,36.9)	0 (0.0) (0.0, 16.1)
Participants still On-Treatment without MMR , n (%)	0	1 (9.1)	2 (18.2)	3 (10.7)	11 (52.4)
Median time to MMR (months)(range in months)	5.01 (2.56, 27.83)	5.55 (2.79, 8.54)	5.59 (2.66, 8.51)		5.67 (2.79, 11.04)

Responses at each specific timepoint (visit) are from peripheral blood if available. If at a specific timepoint results on peripheral blood are not available BM results (if available) are used.
Abbreviations: MMR: Major Molecular Response.
MMR (MR3) is defined as <= 0.1% BCR-ABL1 ratio on international scale (IS) (corresponding to >= 3-log reduction from standardized baseline) with a minimum number of ABL1 assessed by the central laboratory.
MR4 is defined as <= 0.01% BCR-ABL1 ratio on IS (corresponding to >= 4-log reduction from standardized baseline) with a minimum number of ABL1 assessed by the central laboratory.
MR4.5 is defined as <= 0.0032% BCR-ABL1 ratio on IS (corresponding to >= 4.5-log reduction from standardized baseline) with a minimum number of ABL1 assessed by the central laboratory.
Note: Molecular responses are unconfirmed and post-baseline molecular responses are independent of the participant's baseline assessment.
Analysis includes all treated participants.
a. Associated 2-sided 95% CI based on the exact method by Clopper-Pearson.
(Data cutoff date : 19SEP2022)

As duration of therapy in this cohort specifically limits the molecular response assessments of MMR, MR4, and MR4.5, early molecular response, in line with international guidelines for optimal response assessment, was also evaluated in participants with ND Ph+ CML.

Among evaluable (ABL copies ≥10000 at 3 months) participants with ND CML, 9 (81.8% [95% CI: 59.0%, 104.6%]) had a BCR-ABL ratio ≤10% at 3 months. Among evaluable (ABL copies ≥10000 at 6 months) participants with ND CML, 4 (57.1% [95% CI: 20.5%, 93.8%]) had a BCR-ABL ratio ≤1% at 6 months.

Time to and duration of the respective responses by line of therapy

Table 22. Summary of Duration of MMR (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)
Number of Participants with a Response Loss, n (%)	0	1 (20.0)	1 (20.0)	2 (14.3)	0
Number of Participants with PD[b], n (%)	0	0	0	0	0
Number of Participants with Death[b], n (%)	0	0	0	0	0
Number of Participants Censored[c], n (%)	4 (100.0)	4 (80.0)	4 (80.0)	12 (85.7)	6 (100.0)
Prior to Month 6, n (%)	0	1 (20.0)	2(40.0)	3(21.4)	4 (66.7)
Prior to Month 12, n (%)	1 (25.0)	1 (20.0)	3(60.0)	5(35.7)	5 (83.3)
Prior to Month 18, n (%)	2 (50.0)	1 (20.0)	4(80.0)	7(50.0)	6 (100.0)
Prior to Month 24, n (%)	3 (75.0)	3 (60.0)	4 (80.0)	10 (71.4)	6 (100.0)
Duration of MMR[d] (Months)|(95% CI)					
25th Percentile	-- (--, --)	-- (19.2, --)	11.0 (11.0, --)	19.2 (11.0,--)	-- (--, --)
				--)	
Median	-- (--, --)	-- (19.2, --)	-(11.0, --)	-- (11.0, --)	-- (--, --)
75th Percentile	-- (--, --)	-- (19.2, --)	-(11.0, -)	-- (19.2, --	-- (--, --)
Kaplan-Meier Estimate of the Probability of Maintaining MMR, % (95% CI)					
At month 6	100.0 (100.0,100.0)	100.0 (100.0,100.0)	100.0 (100.0,100.0)	100.0) (100.0,100.0)	100.0 (100.0,100.0)
At month 12	100.0 (100.0,100.0)	100.0 (100.0,100.0)	50.0 (0.6, 91.0)	90.0 (47.3,98.5)	100.0 (100.0,100.0)
At month 18	100.0 (100.0,100.0)	100.0 (100.0,100.0)	--(--,--)	90.0 (47.3,98.5)	--(--,--)
At month 24	100.0 (100.0, 100.0)	75.0 (12.8, 96.1)	--(--,--)	72.0 (23.8, 92.8)	--(--,--)

Responses at each specific timepoint (visit) are from peripheral blood if available. If at a specific timepoint results on peripheral blood are not available BM results (if available) are used.
Note: One month is assumed to have 30.4375 days.
Note: The percentiles and rate calculation are based on the Kaplan-Meier Estimate.
Note: The median times and quartiles with associated 2-sided 95% confidence intervals (CIs) based on the Brookmeyer- Crowley log(-log) transformation method.
Note: The Kaplan-Meier rate at the specific time point will be provided together with the associated 2-sided 95% CI based on Greenwood's formula using a log(-log) transformation.
Note: Duration of response is defined as the time period from the date of the earliest demonstration of a response until the earliest date of confirmed loss of that response.
a. Confirmed loss for molecular is defined as the date from the first of 2 consecutive non-responses at least 28 days apart with at least 5x increase from lowest transcript level recorded. If a participant's last assessment is an unconfirmed loss and they discontinue treatment due to progression or die due to disease progression within 28 days of last dose, then the date of the last assessment is the date of confirmed loss.
b. Transformation to AP/BP or death due to disease progression within 28 days of last dose without any prior loss are also considered as confirmed loss.
c. Responders without confirmed loss of response are censored at the last evaluation date.

d. Duration of response in months = (date of confirmed loss of first response – date of first response + 1)
(Data cutoff date : 19SEP2022)

Event-Free Survival (including time to transformation to AP and BP CML) by line of therapy

Table 23. Event-Free Survival (EFS) (Safety Analysis Set) (Protocol ITCC- 054/AAML1921 (B187-WI202099))

EFS (Months)	Phase 1 (300 mg/m²) (N=6)	Phase 1 (350 mg/m²) (N=11)	Phase 1 (400 mg/m²) (N=11)	Phase 1 Total (R/I) (N=28)	Phase 2 CP1L (300 mg/m²) (N=21)
Number of Participants with Events, n (%)	0 (0.0)	1 (9.1)	2 (18.2)	3 (10.7)	0 (0.0)
Number of Participants with Progression, n (%)	0 (0.0)	1 (9.1)	2 (18.2)	3 (10.7)	0 (0.0)
Number of Participants with Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of Participants with	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Transformation to AP or BP, n (%)					
Number of Censored Participants[a], n (%)	6 (100.0)	10 (90.9)	9 (81.8)	25 (89.3)	21 (100.0)
Prior to month 6	0 (0.0)	2 (18.2)	3 (27.3)	5 (17.9)	7 (33.3)
Prior to month 12	1 (16.7)	6 (54.5)	5 (45.5)	12 (42.9)	12 (57.1)
Prior to month 18	3 (50.0)	6 (54.5)	7 (63.6)	16 (57.1)	17 (81.0)
Prior to month 24	4 (66.7)	6 (54.5)	9 (81.8)	19 (67.9)	20 (95.2)
EFS (Months) (95% CI)					
75th Percentile	-- (--, --)	-- (27.5, --)	-- (13.6, --)	-- (--, --)	-- (--, --)
Median	-- (--, --)	-- (27.5, --)	-- (7.9, --)	- (27.5, --)	-- (--, --)
25th Percentile	-- (--, --)	27.5 (27.5, --)	13.6 (7.9, --)	27.5 (7.9, --)	-- (--, --)
EFS Rate, % (95% CI)					
At month 6	100.0 (100.0)	100.0 (100.0)	100.0 (100.0)	100.0 (100.0,	100.0 (100.0)
At month 12	100.0 (100.0)	100.0 (100.0)	87.5 (38.7,98.1	95.2 (70.7,100.0)	100.0 (100.0, 100.0)
At month 18	100.0 (100.0, 100.0 (100.0, 70.0 (22.5,			88.9 (61.8,	100.0 (100.0, 100.0)
	100.0) 100.0) 91.8)			97.2)	
At month 24	100.0 (100.0, 100.0	(100.0, --(--,--)		88.9 (61.8, 97.2)	100.0 (100.0, 100.0)
	100.0) 100.0)			97.2)	
Duration of follow-up (Months)					
Median (Min, Max)	20.06 (9.30, 61.50), ,	10.41 (0.99, 38.34)	11.02 (0.49, 19.38)	14.05 (0.49, 61.50)	9.36 (0.95, 24.80)

Abbreviation: '--' = Non Estimable; AP=Accelerated Phase; BP=Blast Phase.
a. Participants without an event are censored at the last evaluation date. Note: One month is assumed to have 30.4375 days.
Note: The percentiles and EFS rate calculation are based on the Kaplan-Meier Estimate.
Note: The median times and quartiles with associated 2-sided 95% confidence intervals (CIs) based on the Brookmeyer- Crowley log(-log) transformation method.
Note: EFS Rates at the specific time point will be provided together with the associated 2-sided 95% CI based on Greenwood's formula using a log(-log) transformation.
Note: Event-free survival (EFS) is defined as the time period from start of treatment with bosutinib until on-treatment progression, transformation to AP and BP CML or death from any cause, whichever occurs first. Participants without an event are censored at the last evaluation date.
Note: Progression is defined as:
Loss of CHR, Loss of CCyR, for Participants not achieving a CHR: doubling of WBC at least 1 month apart with the second value > 20 x 10^9/L and maintained in subsequent assessments for at least 2 weeks. (Data cutoff date : 19SEP2022)

Time to Accelerated Phase/Blast Phase Transformation

There were no transformations to AP/BP reported in any of the participants in Phase 1 or Phase 2 cohorts.

OS in paediatric participants with Ph+ CML by line of therapy

OS was not mature at the time of data cutoff. The median duration of follow-up was 33.13 months (range: 22.60-61.50 months) for the Phase 1 300 mg/m2 cohort, 25.53 months (range: 19.38-38.57 months) for the Phase 1 350 mg/m2 cohort, 14.39 months (range: 0.95-21.36 months) for the Phase 1 400 mg/m2 cohort, and 14.23 months (range: 1.08-26.35 months) for the Phase 2 300 mg/m2 cohort.

There were no on-treatment deaths. One participant in the 300 mg/m2 cohort died 15 months after the last dose of bosutinib due to a meningitis (not related).

Exploratory

BCR-ABL Mutations: No emergent mutations were detected by the data cutoff.

Paediatric Quality of Life Gastrointestinal Scale: Most responses indicate that participants "never" or "almost never" experienced on-treatment GI symptoms.

Growth and Bone Metabolism: Growth and bone metabolism parameters have been collected for a total of 49 participants who were dosed and had baseline/post-baseline measurement for at least one of the parameters. Hormones of free T4 and TSH were collected in the US sites only.

As of the data cutoff of this CSR, the collected growth and bone metabolism data are not mature to allow meaningful analysis yet. As of the data cutoff of this CSR, 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 to which the company has committed to provide soon through the results of study ITCC-054/AAML1921 and monitoring in the future PSURs.

- **Ancillary analyses**

As of the data cutoff date, 26.5% of participants were reported to receive new anti-CML therapy upon discontinuation of study treatment as shown in table below:

Table 24. Summary of Post Study Anti-CML Therapy (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)
Participants Received New Anti-CML Therapy,n (%)					
Yes	3 (50.0)	6 (54.5)	1 (9.1)	3 (14.3)	13 (26.5)
CML Therapy Type					
Drug					
Dasatinib	1 (16.7)	2 (18.2)	0	1 (4.8)	4 (8.2)
Imatinib	0	1 (9.1)	0	1 (4.8)	2 (4.1)
Nilotinib	1 (16.7)	2 (18.2)	0	0	3 (6.1)
Ponatinib	1 (16.7)	1 (9.1)	1 (9.1)	1 (4.8)	4 (8.2)
HSCT					
Allogeneic	0	2 (18.2)	0	0	2 (4.1)
Autologous	0	0	0	0	0
Syngeneic	0	0	0	0	0

Abbreviations: HSCT = Hematopoietic cell transplantation.

2.6.5.3. Clinical studies in special populations

The BCHILD trial was specifically performed in the paediatric population. No further data have been provided on other special populations in the submitted dossier fo rteh procedure.

2.6.5.4. Supportive studies

A short summary of efficacy in adults is provided here:

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 was 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 BOSULIF 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 and/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.

For further details on the studies mentioned above please refer to the published EPAR for procedure II-25-G and II-50-G published on the Bosulif EMA webpage.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy assessment in the applied extension for the paediatric population is based on efficacy shown in the BCHILD trial. This ongoing Phase 1b/2, multicentre, international, single-arm, open-label study was designed in a dose finding first step and additional efficacy and safety assessment with the recommended dose of bosutinib in psediatric participants with ND CML and paediatric participants with CML who have received at least 1 prior TKI therapy (R/I CML).

Primary objectives of the study (Phases 1 and 2, respectively) was to determine the RP2D of bosutinib for participants with ND Ph+ CML (RP2DND) and participants with R/I Ph+ CML (RP2DR/I), and to assess the PK at RP2DND and RP2DR/I. The efficacy of bosutinib is being evaluated as secondary and

exploratory objectives, which is acceptable considering the very rare target population and the issue that the efficacy endpoints are well established and hard endpoints. Moreover the approach and the study key issues were agreed during consultation with PDCO.

The intended target population is adequately characterised by the inclusion and exclusion criteria; however, limitations and heterogeneity in in demographics was foreseen due to disease's rareness in the paediatric population and acknowledged.

It is acknowledged that the study has been ongoing for several years, the median follow-up varies significantly across individual treatment groups. Considering the very small paediatric subgroup of CML patients and the issue that several other approved TKI products were also including paediatric patients in parallel, feasibility of clinical trials was challenging, but manageable at the end to adequately conclude of the efficacy and safety in the applied subpopulation.

With regard to conduct of the study, several amendments were installed during the study, however, none are considered critical. There were no protocol deviations.

In summary, the study design and conduct was adequate, included population appears representative for the applied indication and raise no major concerns.

Efficacy data and additional analyses

Resistant and intolerant CML cohort (R/I) [Phase1, at least 1 TKI]

In the Phase 1 cohort of the pivotal BCHILD trial subjects with cytogenetic and molecular diagnosis of Ph+ CML, who were resistant (suboptimal response or failure, as defined by 2013 ELN guideline (Baccarani et al, 2013)) or intolerant (with or without suboptimal response or failure) to at least 1 prior TKI were included to identify an adequate dose.

In this R/I cohort, CCyR (MCyR) was achieved/maintained at any time by 83.3% (100%), 90.9% (90.9%), and 63.6% (63.6%) participants in the 300, 350, and 400 mg/m2 cohorts, respectively. Molecular responses achieved at any time in evaluable participants were as high as 66.7% (MMR in the 300 mg/m2 cohort) and 50% in the total R/I population and median time until response reflects a comparable efficacy like in adults. Most participants who achieved a response were able to maintain it for long-term as indicated by KM estimates of 72.0% at Month 24 for the R/I population.

Newly diagnosed CML cohort (Phase2)

Due to the limited duration of therapy at the cut-off data MMR in the Phase 2 cohort was achieved only in 28.6% of the ND populations. However, 76.2% of those with newly diagnosed CML reached major cytogenetic response (MCyR) and nearly all of these subjects reached complete cytogenetic response (CCcR) response. As indicated by a median duration of ~3 months of treatment to reach MCyR as well as for complete haematological response (CHR) the efficacy of bosutinib also in the first line population is not challenged and again similar to that known already from the adult population.

Considering that development of MMR needs longer treatment duration than reaching CHR or MCyR/CCyR and the wide range of follow-up among study participants, full interpretation of the molecular response data was initially not sufficiently possible due to the shorter duration of therapy in the phase 2 population. However, considering the experience available from the adult CML population this is not surprising and does not raise any concern regarding efficacy in this subpopulation.

In summary, the data currently available from the interim analysis of BCHILD trial demonstrated clearly clinically relevant efficacy of bosutinib in paediatric R/I and ND CML participants, similar to that shown already in previous results in adults. Most of the participants attaining (or maintaining, in the instance of R/I) MCyR, CCyR and MMR.

Of the MCyR and CCyR responders, only 2 participants reported response loss: 1 (10.0%) participant in the Phase 1 350 mg/m2 cohort and 1 (14.3%) participant in the Phase 1 400 mg/m2 cohort.

There were no other reports of response loss, PD, or death in any participant with MCyR or CCyR. Most participants achieving a sustainable response and 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.

Although survival estimates are still immature at the time of the data cut-off, it is agreed 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. In established guidelines (e.g. 2013 ELN Guideline; 2020 ELN guideline), it is recognized 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 optimal 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.

Since the above reported findings are taken from the setting of an adult CML population, applicability to a paediatric 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 result in favourable survival outcomes with longer follow-up.

In summary, evidence for efficacy available appears sufficient to justify the intended indication in newly diagnosed paediatric patients and also the R/I subpopulation.

However, treatment start is applied above an age of 1 year which is neither justified by the data nor appears the posology for the youngest children below an age of 6 years sufficiently justified by the available Pop-PK analysis, especially high uncertainties remain with respect to the appropriateness of the included ontogeny function in patients below 6 years. Considering these uncertainties and the difficulties envisaged to further analyse this paediatric subpopulation due to limited patients numbers, the company has restricted the indication where the evidence are clearly supporting the use of Bosulif: the final acceptable indication is therefore now limited to paediatric population from 6 years and above.

2.6.7. Conclusions on the clinical efficacy

The design principles and conduct of the explorative phase 1b/2 trial BCHILD, is considered reliable and provided relevant efficacy results in the R/I and ND CML paediatric population.

Efficacy in the ND and R/I/ paediatric population is sufficiently proven from the data provided. Most recent data lock point data from the BCHILD trial demonstrate clearly efficacy with respect to the standard endpoints (MCyR, CCyR, MMR, MR4) also used in adult trials in CML in resistant/refractory as well as in newly diagnosed paediatric patients with Ph+ CML. The prognostic value for overall life expectance in treated CML is adequately justified.

Efficacy in younger children below the age of 6 years was analysed again but uncertainties remain due to the small number of subjects available in this age range and difficulties to interpret the limited pop PK modelling exposure in this paediatric subpopulation. Therefore, the proposal to allow treatment starting with the age range above of one year remain still challenging from a PK-point of view. By restricting the indication to children of 6 years and above, which are supported by the evidence

provided in the submitted data, no further uncertainties remain and the indication for patients of 6 years and above is considered approvable

2.6.8. Clinical safety

Safety assessment in the paediatric population here applied is based on the results of the BCHILD study. The safety data presented within the dossier use a more recent data cutoff date (27 February 2023) including n=55 subjects.

Safety results are available from 55 paediatric participants (ages 1 to ≤18 years) in the ITCC-054 (BCHILD, B187-WI202099) study (hereafter referred to as the BCHILD study), including 24 with ND CML and 31 with R/I CML.

2.6.8.1. Patient exposure

Of the 55 treated participants, 24 were ND (Phase 2 300 mg/m2 cohort) and 31 were R/I to prior TKIs (all Phase 1 cohorts and Phase 2 400 mg/m2 cohort). The median age of all participants was 13 years (range: 1-17 years). The mean age of all participants was 12.02 years (SD: 4.36 years).

Table 25. Duration of Treatment (Safety Analysis Set) (Protocol ITCC- 054/AAML1921 (B187-WI202099))

Duration of treat-ment (Months)a	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=24)	Phase 2 R/I (400mg/m²) (N=3)	Total (N=55)
N	6	11	11	28	24	3	55
Mean (SD)	28.60 (20.36)	18.88 (15.63)	14.11 (8.96)	19.09 (15.07)	13.62 (8.83)	1.86 (1.68)	15.76 (12.86)
Median (range)	20.09 (9.26, 60.85)	9.86 (0.95, 43.86)	14.32 (0.30, 26.64)	15.47 (0.30, 60.85)	11.48 (0.20, 31.64)	1.97 (0.13, 3.48)	13.47 (0.13, 60.85)
Category (Months)							
<=1	0	1 (9.1)	1 (9.1)	2 (7.1)	1 (4.2)	1 (33.3)	4 (7.3)
>1 - <=2	0	0	0	0	0	1 (33.3)	1 (1.8)
>2 - <=4	0	0	1 (9.1)	1 (3.6)	3 (12.5)	1 (33.3)	5 (9.1)
>4 - <=8	0	4(36.4)	2 (18.2)	6(21.4)	4(16.7)	0	10(18.2)
>8 -<=12	1(16.7)	1 (9.1)	0	2 (7.1)	4 (16.7)	6 (10.9)	6 (10.9)
>12 -<=24	3(50.0)	0	0 5 (45.5)	8 (28.6)	9 (37.5)	0	17 (30.9)
>24	2(33.3)	5 (45.5)	2 (18.2)	9 (32.1)	3 (12.5)	0	12 (21.8)

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.

Table 26. Summary of Study Drug Exposure (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=24)	Phase 2 R/I (400mg/m²) (N=3)	Total (N=55)
Number of Doses						
N	**6**	**11**	**11**	**24**	**3**	**55**
Mean (SD)	862.67 (620.18)	560.55 (485.07)	405.18 (260.91)	409.75 (278.35)	51.33 (47.50)	468.85 (394.82)
Median (range)	593.50 (281.00, 1846.00)	300.00 (22.00, 1328.00)	401.00 (9.00, 790.00)	334.00 (6.00, 963.00)	51.00 (4.00, 99.00)	400.00 (4.00, 1846.00)
Cumulative Dose (mg) [1]						
N	**6**	**11**	**11**	**24**	**3**	**55**
Mean (SD)	326546 (280210)	231680 (215964)	214855 (151209)	174972 (134798)	29525.0 (28599.3)	202892 (178393)
Median (range)	262600 (56100.0, 785875)	112500 (5100.00, 620025)	195200 (5400.00, 455300)	143850 (2850.00, 481500)	26775.0 (2400.00, 59400.0)	146000 (2400.00, 785875)
Dose Intensity (mg/day) [2]						
N	**6**	**11**	**11**	**24**	**3**	**55**
Mean (SD)	337.31 (128.23)	371.76 (117.72)	494.68 (88.42)	399.15 (95.01)	535.54 (79.83)	413.47 (113.48)
Median (range)	374.04 (164.33, 488.16)	366.33 (175.86, 562.47)	496.02 (325.00, 600.00)	437.00 (238.55, 528.60)	560.38 (446.25, 600.00)	428.79 (164.33, 600.00)
Relative Dose Intensity (%) [3]						
N	**6**	**11**	**11**	**24**	**0**	**52**
Mean (SD)	100.03 (9.27)	84.37 (18.10)	89.78 (8.53)	89.89 (18.95)	- (-)	89.87 (16.36)
Median (range)	96.71 (93.81, 118.58)	94.23 (52.31, 103.00)	91.20 (74.96, 100.00)	97.45 (18.18, 113.56)	- (-, -)	94.57 (18.18, 118.58)

n = the number of participants in the safety analysis set within each cohort.
[1] Cumulative dose (mg) = sum of actual dose given (mg).
[2] Dose Intensity (mg/day): Cumulative dose divided by time from first dose date to last zero/non-zero dose date.
[3] Relative Dose Intensity (%): (sum of actual dose given (mg)/sum of planned dose (mg))*100.
Planned dose (mg) is calculated using allocated dose level (mg/m2) with adjustment to collected Body surface area (BSA) every 3rd cycle based on Table9A/B from latest Protocol.

Dose Delays and Dose Reductions

- 49.1% of all participants had at least 1 dose delay, including 50.0%, 54.5%, and 36.4% of participants in the Phase 1 300, 350, and 400 mg/m^2 cohorts.
- 30.9% of all participants had at least 1 dose reduction, including 16.7%, 36.4%, and 36.4% in the Phase 1 300, 350, and 400 mg/m2 cohorts, respectively, 29.2% of participants in the Phase 2 300 mg/m^2 cohort, and 33.3% of participants in the Phase 2 400 mg/m^2 cohort
- Dose Escalations: Only 2 participants reported dose escalations.

2.6.8.2. Adverse events

Table 27. Summary of Adverse Events (All Causalities) (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099))

	Phase 1 300mg/ m² n (%)	Phase 1 (350mg/ m²) n (%)	Phase 1 (400mg/ m²) n (%)	Phase 2 CP1L (300mg/ m²) n (%)	Phase 2 R/I (400mg/ m²) n (%)	Total n (%)
Participants evaluable for adverse events	6	11	11	24	3	55
Participants with TEAEs	6 (100.0)	11 (100.0)	11 (100.0)	23 (95.8)	3 (100.0)	54 (98.2)
Participants with drug related TEAEs	6 (100.0)	11 (100.0)	11 (100.0)	22 (91.7)	3 (100.0)	53 (96.4)
Participants with serious TEAEs	4 (66.7)	3 (27.3)	2 (18.2)	5 (20.8)	0	14 (25.5)
Participants with Maximum Grade 3 or 4 TEAEs	3 (50.0)	6 (54.5)	6 (54.5)	20 (83.3)	2 (66.7)	37 (67.3)
Participants with Maximum Grade 5	0	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 (12.5)	1 (33.3)	11 (20.0)
Participants with delay, reduction or permanent discontinuation from study treatment due to adverse events[a]	3 (50.0)	6 (54.5)	5 (45.5)	13 (54.2)	2 (66.7)	29 (52.7)

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 v26.0 coding dictionary applied.)

The most frequently reported all-causality TEAEs (≥50% of participants, all grades) were Diarrhoea (81.8%), Vomiting (56.4%), Abdominal pain (54.5%), and Nausea (50.9%);

Other frequently reported TEAEs (≥20% of participants, all grades) included Thrombocytopenia (34.5%), Pyrexia (32.7%), Headache (32.7%), ALT increased (29.1%), Rash maculopapular (27.3%), Fatigue (27.3%), Decreased appetite (23.6%), Abdominal pain upper (20.0%), Constipation (20.0%), and Pain in extremity (20.0%).

Dose-Limiting Toxicities and RP2D in Phase 1: Two participants experienced DLTs in Phase 1 Cycle 1: One participant in the Phase 1 350 mg/m^2 cohort had DLTs of Abdominal pain, Diarrhoea and Vomiting, all Grade 3 and 1 participant in the Phase 1 400 mg/m^2 cohort had DLTs of ALT increased, Blood bilirubin increased, and Rash maculo-papular, all Grade 3.

The most frequently reported Grade 3 or 4 TEAEs (≥10% of participants, all grades) were Thrombocytopenia (18.2%), ALT increased (14.5%), and Diarrhoea (12.7%). 8 of 10 participants who had Grade 3 or 4 Thrombocytopenia were in the Phase 2 300 mg/m2 cohort.

Drug-related adverse events

Table 28. Summary of Most Common Drug Related TEAEs (Any Grade in >= 10% or Grade 3/4 in >= 5%) by MedDRA System Organ Class and Preferred Term (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187- WI202099))

Numberof Participants Evaluable for AEs	Phase 1 (300mg/m2) N=6		Phase 1 350 mg/m2 N=11		Phase 1 (400mg/m2) N=11		Phase 2 CP1L 300mg/2 N=24		Phase 2 R/I 400mg/m2 N=3		Total N=55	
Number (%) of Participants: by SOC Preferred Term	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Participants with any even	**6 (100.0)**	**3 (50.0)**	**11 (100-0**	**6 (54.5**	**11 (100.0**	**6 (54.5)**	**22 (91.7)**	**17 (70.8)**	**3 (100.0)**	**2 (66.7)**	**53 (96.4)**	**34 (61.8)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**0**	**0**	**2 (18.2)**	**0**	**6 (54.5)**	**2 (18.2)**	**14 (58.3)**	**10 (41.7)**	**1 (33.3)**	**1 (33.3)**	**23 (41.8)**	**13 (23.6)**
Thrombocytopenia [1]	0	0	2 (18.2)	0	4 (36.4)	1 (9.1)	11 (45.8)	8 (33.3)	1 (33.3)	1 (33.3)	18 (32.7)	10 (18.2)
Anaemia [1]	0	0	1 (9.1)	0	1 (9.1)	0	6 (25.0)	4 (16.7)	1 (33.3)	0	9 (16.4)	4 (7.3)
Neutropenia [1]	0	0	0	0	2 (18.2)	2 (18.2)	5 (20.8)	3 (12.3)	0	0	7 (12.7)	5 (9.1)
GASTROINTESTINAL DISORDERS	**6 (100.0)**	**2 (33.3)**	**10 (90.9)**	**2 (18.2)**	**10 (90.9)**	**2 (18.2)**	**19 (79.2)**	**5 (20.8)**	**3 (100.0)**	**1 (33.3)**	**48 (87.3)**	**12 (21.8)**
Diarrhoea	5 (83.3)	1 (16.7)	9 (81.8)	1 (9.1)	9 (81.8)	1 (9.1)	17 (70.8)	3 (12.5)	3 (100.0)	1 (33.3)	43 (78.2)	7 (12.7)
Vomiting	5 (83.3)	1 (16.7)	8 (72.7)	2(18.2)	6 (54.5)	1 (9.1)	9 (37.5	0	1 (33.3)	8	29 (52.7)	4 (7.3)
Nausea	6 (100.0)	0	6 (54.5)	1 (9.1)	5 (45.5)	0	10 (41.7)	1 (4.2)	1 (33.3)	0	28 (50.9)	2 (3.6)
Abdominal Pain	1 (16.7)	0	10 (90.9)	1 (9.1)	7 (63.6)	0	7 (29.2)	0	1 (33.3)	0	26 (47.3)	1 (1.8)
Upper Abdominal Pain	3 (50.0)	0	1 (9.1)	0	2 (18.2)	0	4 (16.7)	1 (4.2)	0	0	10 (18.2)	1 (1.8)
Constipation	2 (33.3)	0	0	0	1 (9.1)	0	3 (12.5)	0	0	0	6 (10.9)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**5 (83.3)**	**0**	**3 (27.3)**	**1 (9.1)**	**5 (45.5)**	**0**	**8 (33.3)**	**1 (4.2)**	**1 (33.3)**	**0**	**22 (40.9)**	**2 (3.6)**
Fatigue	4 (66.7)	0	2 (18.2)	1 (9.1)	2 (18.2)	0	6 (25.0)	1 (4.2)	1 (33.3)	0	15 (27.3)	2 (3.6)
Pyrexia	3 (50.0)	0	1 (9.1)	0	2 (18.2)	0	1 (4.2)	0	0	0	7 (12.7)	0
INVESTIGATIONS	**3**	**0**	**6**	**3**	**7**	**2**	**10**	**6**	**1**	**0**	**27**	**11**

Numberof Participants Evaluable for AEs	Phase 1 (300mg/m2) N=6		Phase 1 350 mg/m2 N=11		Phase 1 (400mg/m2) N=11		Phase 2 CP1L 300mg/2 N=24		Phase 2 R/I 400mg/m2 N=3		Total N=55	
Number (%) of Participants: by SOC Preferred Term	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Participants with any even	**6 (100.0)**	**3 (50.0)**	**11 (100-0**	**6 (54.5**	**11 (100.0**	**6 (54.5)**	**22 (91.7)**	**17 (70.8)**	**3 (100.0)**	**2 (66.7)**	**53 (96.4)**	**34 (61.8)**
	(50.0)		**(54.5)**	**(27.3)**	**(63.6)**	**(18.2)**	**(41.7)**	**(25.0)**	**(33.3)**		**(49.1)**	**(20.0)**
Alanine aminotransferase increased	1 (16.7)	0	4 (36.4)	3 (27.3)	5 (45.5)	2 (18.2)	6 (25.0)	3 (12.5)	0	0	16 (29.1)	8 (14.5)
Aspartate aminotransferase increased	0	0	3 (27.3)	2 (18.2)	3 (27.3)	0	4 (16.7)	0	0	0	10 (18.2)	2 (3.6)
Blood creatine phosphokinase increased	0	0	2 (18.2)	0	3 (27.3)	0	3 (12.5)	1 (4.2)	1 (33.3)	0	9 (16.4)	1 (1.8)
Blood creatinine increased	2 (33.3)	0	2 (18.2)	0	2 (18.2)	0	1 (4.2)	0	0	0	7 (12.7)	0
Blood alkaline phosphatatase increased	0	0	1 (9.1)	0	1 (9.1)	0	4 (16.7)	0	0	0	6 (10.9)	0
METABOLISM AND NUTRITION DISORDERS	**3 (50.0)**	**0**	**3 (27.3)**	**0**	**6 (54.5)**	**0**	**7 (29.2)**	**2 (8.3)**	**0**	**0**	**19 (34.5)**	**2 (3.6)**
Decreased appetite	2 (33.3)	0	2 (18.2)	0	4 (36.4)	0	4 (16.7)	1 (4.2)	0	0	12 (21.8)	1 (1.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**2 (33.3)**	**0**	**2 (18.2)**	**1 (9.1)**	**4 (36.4)**	**0**	**5 (20.5)**	**1 (4.2)**	**0**	**0**	**13 (23.6)**	**2 (3.6)**
Pain in extremity	2 (33.3)	0	0	0	2 (18.2)	0	4 (16.7)	0	0	0	8 (14.5)	0
NERVOUS SYSTEM DISORDERS	**2 (33.3)**	**1 (16.7)**	**2 (18.2)**	**0**	**4 (36.4)**	**0**	**6 (25.0)**	**2 (8.3)**	**0**	**0**	**14 (25.5)**	**3 (5.5)**
Headache	2 (33.3)	0	1 (9.1)	0	4 (36.4)	0	5 (20.5)	0	0	0	12 (21.8)	0
SKIN AND SU/BCUTANEOUS TISSUE DISORDERS	**5 (83.3)**	**0**	**9 (81.8)**	**2 (18.2)**	**9 (81.8)**	**3 (27.3)**	**7 (29.2)**	**1 (4.2)**	**0**	**0**	**30 (54.5)**	**6 (10.9)**
Rash maculo-papular	0	0	3 (27.3)	1 (9.1)	8 (72.7)	3 (27.3)	2 (8.3)	0	0	0	13 (23.6)	4 (7.3)

Note: Any preferred term reporting greater than or equal to the percentage cutoff on the 'Total' column is included in the table.
Note: Descending order of the incidences is presented at the level of preferred term within each system organ class based on the incidences of 'All Grades' under '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.
[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 v26.0 coding dictionary applied.

Table 29. Comparison of TEAEs in terms of Grade3/4 events between the paediatric and adult population

Derived System Organ Class[a] Preferred Term	Bosutinib Paediatric Population (BCHILD) Total (N=55)		Bosutinib Adult Population Total (N=1372)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any Adverse Event	**54 (98.181)**	**35 (63.636)**	**1349 (98.6)**	**943 (68.3)**
Blood and lymphatic system disorders	**23 (41.818)**	**13 (23.636)**	**692 (50.4)**	**395 (28.8)**
Thrombocytopenia	19 (34.545)			10 (18.181)
Anaemia	10 (18.181)			4 (7.272)
Neutropenia	7 (12.727)			5 (9.090)
Leukopenia	4 (7.272)	1 (1.818)	135 (9.8)	56 (4.1)
Febrile neutropenia	1 (1.818)	1 (1.818)	12 ((0.8)	2 (0.1)
Cardiac disorders	1 (1.818)	0		
Pericardial effusion	1 (1.818)	0	63 (4.6)	20 (1.5)
Ear and labyrinth disorders	**1 (1.818)**	**0**	**28 (2.)**	**0**
Tinnitus	1 (1.818)	0	28 (2.0)	0
Gastrointestinal disorders	**49 (89.090)**	**12 (21.818)**	**1198 (87,3)**	**215 (15.7)**
Diarrhoea	45 (81.818)	7 (12.727)	1103 (80.4)	145 (10.6)
Abdominal pain	36 (65.454)	2 (3.636)	489 (35.6)	35 (2.8)
Vomiting	31 (56.363)	4 (7.272)	463 (33.7)	38 (2.8)
Nausea	28 (50.909)	2 (3.636)	579 (41.5)	16 (1.2)
Gastrointestinal haemorrhage	1 (1.818)	0	24 (1.7)	7 (0.5)
General disorders and administration site conditions	**30 (54.545)**	**4 (7.272)**	**733 (53.4)**	**78 (5.7)**
Fatigue	19 (34.545)	2 (3.636)	439 (32.0)	36 (2.6)
Pyrexia	18 (32.727)	2 (3.636)	321 (23.4)	21 (1.5)
Oedema	5 (9.090)	0	229 (16.7)	7 (0.5)
Pain	3 (5.454)	0	60 (4.4)	5 (0.4)
Chest pain	1 (1.818)	0	84 (6.1)	11 (0.8)
Infections and infestations	**7 (12.727)**	**1 (1.818)**	**544 (40.0)**	**68 (5.0)**
Respiratory tract infection	5 (9.090)	1 (1.818)	197 (14.3)	3 (0.2)
Nasopharyngitis	2 (3.636)	0	208 (15.1)	1 (0.1)0
Pneumonia	1 (1.818)	0	105 (7.7)	57 (4.1)
Investigations	**28 (50.909)**	**9 (16.363)**	**646 (47.1)**	**355(25.9)**
Alanine aminotransferase increased	16 (29.090)	7 (12.727)	384 (28.0)	200 (14.6)
Aspartate aminotransferase increased	10 (18.181)	2 (3.636)	309 (22.5)	92 (6.7)
Blood creatine phosphokinase increased	10 (18.181)	1 (1.818)	73 (5.3)	20 (1.5)
Blood creatinine increased	7 (12.727)	0	140 (10.2)	9 (0.7)
Blood bilirubin increased	5 (9.090)	1 (1.818)	71 (5.2)	15 (1.1)
Amylase increased	3 (5.454)	1 (1.818)	117 (8.5)	30 (2.2)
Lipase increased	3 (5.454)	2 (3.636)	214 (15.6)	139 (10.1)
Metabolism and nutrition disorders	**19 (34.545)**	**2 (3.636)**	**172 (12.6)**	**7 (0.5)**
Decreased appetite	13 (23.636)	1 (1.818)	172 (12.5)	7 (0.5)
Hypophosphataemia	4 (7.272)	0	85 (6.2)	30 (2.2)
Dehydration	3 (5.454)	1 (1.818)	35 (2.5)	(9 (0.7)
Hyperkalaemia	2 (3.636)	0	50 (3.6)	16 (1.2)
Musculoskeletal and connective tissue disorders	**7 (12.727)**	**0**	**400 (29.2)**	**26 (1.9)**
Back pain	3 (5.454)	0	173 (12.6)	26 (1.9)

Derived System Organ Class[a] Preferred Term	Bosutinib Paediatric Population (BCHILD) Total (N=55)		Bosutinib Adult Population Total (N=1372)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any Adverse Event	**54 (98.181)**	**35 (63.636)**	**1349 (98.6)**	**943 (68.3)**
Myalgia	3 (5.454)	0	106 (7.7)	7 (0.5)
Arthralgia	2 (3.636)	0	251 (18.3)	11 (0.8)
Nervous system disorders	**18 (32.727)**	**2 (3.636)**	**371 (27.0)**	**19 (1.4)**
Headache	18 (32.727)	1 (1.818)	278 (20.3)	17 (1.2)
Dizziness	3 (5.454)	1 (1.818)	146 (10.6)	2 (0.1)
Respiratory, thoracic and mediastinal disorders	**10 (18.181)**	**0**	**407 (29.7)**	**86 (6.3)**
Cough**	9 (16.363)	0	226 (16.5)	1 (0.1)
Dyspnoea	1 (1.818)	0	178 (13.0)	25 (2.6)
Pulmonary hypertension	1 (1.818)	0	20 (1.5)	5 (0.4)
Skin and subcutaneous tissue disorders	**25 (45.454)**	**6 (10.909)**	**563 (41.0)**	**87 (6.3)**
Rash	20 (36.363)	4 (7.272)	450 (32.8)	68 (5.0)
Urticaria	4 (7.272)	2 (3.636)	38 (2.8)	6 (0.4)
Pruritus	3 (5.454)	1 (1.818)	139 (10.1)	7 (0.5)
Vascular disorders	**2 (3.636)**	**0**	**132 (9.6)**	**46 (3.3)**
Hypertension*	2 (3.636)	0	**132 (9.6)**	**46 (3.3)**

2.6.8.3. Serious adverse event/deaths/other significant events

Table 30. 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=24)	Phase 2 R/I (400mg /m²) (N=3)	Total (N=55)
Number (%) of Participants with Serious Adverse Eventsa: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Participants with any event	4 (66.7)	3 (27.3)	2 (18.2)	5 (20.8)	0	14 (25.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	2 (8.3)	0	2 (3.6)
Febrile neutropenia	0	0	0	1 (4.2)	0	1 (1.8)
Thrombocytopenia [1]	0	0	0	1 (4.2)	0	1 (1.8)
GASTROINTESTINAL DISORDERS	1 (16.7)	1 (9.1)	1 (9.1)	1 (4.2)	0	4 (7.3)
Vomiting	1 (16.7)	1 (9.1)	1 (9.1)	0	0 3 (5.5)	
Diarrhoea	0	0	0	1 (4.2)	0	1 (1.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (16.7)	1 (9.1)	0	0	0	2 (3.6)
Pyrexia	1 (16.7)	1 (9.1)	0	0	0	2 (3.6)

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=24)	Phase 2 R/I (400mg /m²) (N=3)	Total (N=55)
Number (%) of Participants with Serious Adverse Eventsa: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
INFECTIONS AND INFESTATIONS	3 (50.0)	1 (9.1)	0	3 (12.5)	0	7 (12.7)
Skin infection	0	0	0	2 (8.3)	0	2 (3.6)
Appendicitis	0	0	0	1 (4.2)	0	1 (1.8)
Device related infection	1 (16.7)	0	0	0	0	1 (1.8)
Lower respiratory tract infection viral	1 (16.7)	0	0	0	0	1 (1.8)
Pneumonia	1 (16.7)	0	0	0	0	1 (1.8)
Tonsillitis	0	1 (9.1)	0	0	0	1 (1.8)
Upper respiratory tract infection						
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1 (9.1)	0	0	1 (1.8)
Head injury	0	0	1 (9.1)	0	0	1 (1.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (16.7)	0	0	1 (4.2)	0	2 (3.6)
Osteonecrosis	0	0	0	1 (4.2)	0	1 (1.8)
Pain in extremity	1 (16.7)	0	0	0	0	1 (1.8)
NERVOUS SYSTEM DISORDERS	0	1 (9.1)	0	0	0	1 (1.8)
Headache	0	1 (9.1)	0	0	0	1 (1.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (16.7)	0	0	0	0	1 (1.8)
Pulmonary hypertension	1 (16.7)	0	0	0	0	1 (1.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (9.1)	1 (9.1)	1 (4.2)	0	3 (5.5)
Rash maculo-papular	0	1 (9.1)	1 (9.1)	0	0	2 (3.6)
Urticaria	0	0	0	1 (4.2)	0	1 (1.8)

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 v26.0 coding dictionary applied.
(Data cutoff date : 27FEB2023)

Deaths

No Grade 5 TEAEs were reported and no fatal SAEs were reported.

No deaths were reported during study treatment or within 28 days after the last dose of study treatment. However, one participant in the Phase 1 300 mg/m2 cohort died due to "other" causes (Meningitis1) 15 months after last dose of study treatment, which appears not related to the drug.

2.6.8.4. Laboratory findings

The most frequent shifts from Grade ≤2 at baseline to Grade 3 or 4 postbaseline (≥10% of participants) for haematology laboratory results was platelet count decreased (18.2%)T while anaemia and leukocytopenia were also frequent.

The most frequent (≥50% of participants, all grades) chemistry laboratory abnormalities reported on treatment were creatinine increased (89.1%), ALT increased (67.3%), and AST 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 (14.5%). 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.

98.2% of participants had at least an abnormal on-treatment eGFR value, of which none had Grade 3b, 4, or 5, but it needs clarification whether more severe eGFR reductions occurred in the population of children below the age of 6 year or any other trends regarding more pronounced toxicity in younger children.

2.6.8.5. Safety in special populations

Data were examined for the effects of age, gender, and race on bosutinib in participants of the BCHILD study. Overall, it is reported that the safety profile of bosutinib in paediatric participants is generally consistent with that established in adults.

2.6.8.6. Immunological events

This issue has been general sufficiently characterised in the adult population.

2.6.8.7. Safety related to drug-drug interactions and other interactions

Drug- drug interactions of bosutinib were sufficiently characterised during previous studies in adults and healthy volunteers.

2.6.8.8. Discontinuation due to adverse events

Table 31. Disposition Events Summary - End of Treatment (Safety Analysis Set) (Protocol ITCC-054/AAML1921 (B187-WI202099)) Interim Study Report

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=24)**	**Phase 2 R/I (400mg/m²) (N=3)**	**Total (N=55)**
Number (%) of Participants with Serious Adverse Eventsa: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n/(%)**	**n (%)**
Disposition phase: Treatment						
Participants Entered:	6 (100.0)	11 (100.0)	11 (100.0)	24 (100.0)	3 (100.0)	55 (100.0)
Discontinued	5 (83.3)	7 (63.6)	6 (54.5)	5 (23.8)	1 (33.3)	22 (44.9)
Reason for discontinuation						
Patient/guardian withdraws assent/consent to undergo further treatment	0	0	0	0	0	0
Unsatisfactory response or disease progression	2 (33.3)	3 (27.3)	3 (27.3)	2 (9.5)	0	10 (20.4)
Death	0	0	0	0	1 (33.3)	1 (1.5)
Lost to Follow-Up	1	0	0	0	0	1 (1.8)0
Study terminated by Sponsor for significant safety or efficacy concerns	0	0	0	0	0	0
Global Deterioration Of Health Status requiring discontinuation	0	0	0	0	0	0
Unacceptable toxicity or more than 2 dose reductions	**1 (16.7)**	**4 (36.4)**	**2 (18.2)**	**3(14.3)**	**1(33.3)**	**11(20.0)**

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/m ²) (N=24)	Phase 2 R/I (400mg/ m²) (N=3)	Total (N=55)
Number (%) of Participants with Serious Adverse Eventsa: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n/(%)**	**n (%)**
Need for treatment interruption >4 weeks	0	0	0	0		0
Need for anticancer therapy not specified in the protocol	0	0	0	0		0
Non-compliance	0	0	1 (9.1)	0		0
Pregnancy	0	0	0	0		0
Significant protocol violation	0	0	0	0		0
Other	2 (33.3)	0	0	0		2 (4.1)
Ongoing	1 (16.7)	4 (36.4)	5 (45.5)	16(76.2)	2 (66.7)	27 (55.1)

(Data cutoff date : 31MAY2023)

Table 32. Summary of Adverse Events Leading to 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 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=24)	Phase 2 R/I (400mg/ m²) (N=3)	Total (N=55)
Number (%) of Participants with Serious Adverse Eventsa: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Participants with events	**1 (16.7)**	**4 (36.4)**	**2 (18.2)**	**3 (12.5)**	**1 (33.3)**	**11(20. 0)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	1(4.2)	0	1 (1.8)
Neutropenia [1]	0	0	0	1 (4.2)	0	1 (1.8)
GASTROINTESTINAL DISORDERS	0	1 (9.1)	1 (9.1)	0	1 (33.3)	3 (5.5)
Diarrhoea	0	1 (9.1)	1 (9.1)	0	1 (33.3)	3 (5.5)

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=24)	Phase 2 R/I (400mg/ m²) (N=3)	Total (N=55)
Number (%) of Participants with Serious Adverse Eventsa: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Abdominal pain	0	0	1 (9.1)	0	1 (33.3)	2 (3.6)
Nausea	0	0	1 (9.1)	0	0	1 (1.8)
Vomiting	0	0	0	0	1 (33.3)	1 (1.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	1 (9.1)	1 (4.2)	0	2 (3.6)
Fatigue	0	0	1 (9.1)	1 (4.2)	0	2 (3.6)
INVESTIGATIONS	0	3 (27.3)	0	1 (4.2)	0 4 (7.3)	4 (7.2))
Alanine aminotransferase increased	0	2 (18.2)	0	1 (4.2)	0	3 (5.5)
Aspartate aminotransferase increased	0	2 (18.2)	0	0	0	2 (3.6)
PSYCHIATRIC DISORDERS	1 (16.7)	0	0	0	0	1 (1.8)
Delirium	1 (16.7)	0	0	0	0	1 (1.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (9.1)	1 (9.1)	1 (4.2)	0	3 (5.5)
Rash maculo-papular	0	1 (9.1)	1 (9.1)	0	0	2 (3.6)
Urticaria	0	1 (9.1)	0	1 (4.2)	0	1 (1.8)
Erythema nodosum	1 (16.7)	0	0	0	0	1 (1.8)

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 v26.0 coding dictionary applied. (Data cutoff date : 27FEB2023)

2.6.8.9. Post marketing experience

Bosutinib is marketed in over 50 countries for adults with Ph+ CML. Postmarketing experience with bosutinib is mainly in adult patients with Ph+ CML as described in the latest PSUR (reporting period from 04 March 2020 to 03 March 2021).

The following additional adverse reactions have been identified during post-approval use of bosutinib.

- Blood and Lymphatic System Disorders: Thrombotic microangiopathy
- Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Stevens-Johnson syndrome is already included in the SmPC as a known AE.

In Europe, bosutinib has not yet been approved for paediatric patients with CML, but it has recently received approval in the US for the treatment of paediatric patients 1 year and older with CP Ph+ CML, newly-diagnosed or resistance or intolerance to prior therapy (September 2023).

2.6.9. Discussion on clinical safety

Safety assessment in the applied paediatric indication is based on data from the BCHILD trial as described above.

Considering the long-term treatment needed in these patients, exposure may be seen as relatively short even after receiving the update. However, since the Bosutinib's safety in adults general is well defined and the available experience in adults reflects now more than 10 years of post-marketing experience, the exposure appears sufficient to assess safety in the paediatric target population.

Almost all patients developed adverse events during treatment and most of these AEs were suspected to be related to bosutinib by the investigators.

The most frequently reported all-causality TEAEs (≥50% of participants, all grades) reflecting the known gastrointestinal toxicity of bosutinib as Diarrhoea (81.8%), Vomiting (56.4%), Abdominal pain (54.5%), and Nausea (50.9%). Other frequently reported TEAEs (≥20% of participants, all grades) as Thrombocytopenia (34.5%), Pyrexia (32.7%), Headache (32.7%), ALT increased (29.1%), Rash maculopapular (27.3%), Fatigue (27.3%), Decreased appetite (23.6%), Abdominal pain upper (20.0%), Constipation (20.0%), and Pain in extremity (20.0%).

The most frequently reported drug-related AEs as illustrated by the AESIs were GI events, rash, myelosuppression, and liver events, and were reported in 87.3%, 45.5%, 43.6%, 34.5% of participants in the study, respectively.

The comparison of SOCs and PTs of the TEAEs shows that only minor differences were reported between the frequencies in the paediatric and the significantly larger adult population. Although differences may also reflect chance findings, it appears that gastrointestinal TEAEs are more frequent in children (abdominal pain, vomiting and nausea). This TEAEs may explain also the higher degree of exsiccosis-associated TEAEs like pyrexia, dehydration and headaches as well as decreased appetite. However, it is reassuring that hepatotoxicity in the paediatric population is similar to that in adults. In summary, it seems reasoned to use the adult TEAE frequencies for SmPC 4.8 Table also for the paediatric population.

The renal function appears to be more affected in the paediatric population and may affect pre-renal factors due to exsiccosis resulting from the gastrointestinal toxicity associated with diarrhoea and

vomiting also. The impact of dehydration due to fluid loss by gastrointestinal adverse events is also indicated by the most frequent vital signs changes of potential clinical concern: 14.8% of participants experienced DBP <55 mmHg on at least 2 separate consecutive study visits. However, according to the provided clarification these events were only of short duration and fully resolved and do not indicate in principle a significantly increased risk as initially presumed.

Regarding haematology labour testing the most frequent shifts from Grade ≤2 at baseline to Grade 3 or 4 post baseline (≥10% of participants) results was platelet count decreased (18.2%). The most frequent (≥50% of participants, all grades) chemistry laboratory abnormalities reported on treatment were creatinine increased (89.1%), ALT increased (67.3%), and AST 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 post baseline (≥10% of participants) in chemistry laboratory test values were ALT increased (14.5%) and the most frequent shifts from Grade ≤ 2 at baseline to Grade 3 or 4 at post baseline (≥10% of participants) occurred in ALT increased (14.3%). Although no potential Hy's law cases were identified during this paediatric study, such case were reported in adults and insofar the risk of severe drug induced hepatotoxicity (DILI) remains a risk also to be considered in the paediatric population.

Moreover, 98.2% of participants had at least an abnormal on-treatment eGFR value, of which none had Grade 3b, 4, or 5.

The known gastrointestinal toxicity of bosutinib appears to have contributed also to the noted high rate of TEAEs leading to permanent treatment discontinuation (20%), since the most frequently reported TEAEs leading to permanent treatment discontinuation were ALT increased and Diarrhoea (each 3 participants, 5.5%).

The most frequently reported SAE was vomiting (5.5%) while other SAEs were heterogeneous and observed only in in single patients. All SAEs occurred also in the adult population and thus, did not raise specific paediatric concerns. No fatal drug related SAE was reported.

30.9% of all participants had at least 1 dose reduction, including 16.7%, 36.4%, and 36.4% in the Phase 1 300, 350, and 400 mg/m^2 cohorts, respectively, 29.2% of participants in the Phase 2 300 mg/m^2 cohort, and 33.3% of participants in the Phase 2 400 mg/m^2 cohort. There were no Grade 5 AE.

2.6.10. Conclusions on the clinical safety

Overall, the safety profile of bosutinib in the paediatric population appears is similar to that reported for the adult population and no new safety signals were detected. Thus, safety of bosutinib in children is comparable to that well known for adults and does not raise major concerns based on the data assessed.

2.7. Risk Management Plan

2.7.1. Safety concerns

None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

None

2.7.4. Conclusion

The CHMP considered that the risk management plan version 07.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

the results from the previous readability testing are still adequate to cover the requirement of the user consultation for the proposed Bosulif PIL with this application.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The procedure is to add the paediatric population in the indication(s) as per the revised indication below:

Bosulif is indicated for the treatment of:

- Adult and paediatric patients aged 6 years and older with newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- Adult and paediatric patients aged 6 years and older with CP Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
- Adult patients with accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

3.1.2. Available therapies and unmet medical need

CML in childhood is relatively rare, accounting for fewer than 3% of all paediatric leukaemia, with an approximate annual incidence of 1 per million children. 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.

The natural history of CML in children is not significantly different from that of adults with CML, although published studies are small.

In children as in adults, a TKI is considered to be the preferred first-line therapy for CML. Favourable results from Phase 1 and 2 studies with imatinib in paediatric patient populations support its use as a first-line therapy for paediatric CML, with 96% of children achieving CHR and 69% achieving complete cytogenetic response (CCyR) after 1 year. With the recent approval of dasatinib, some paediatric oncologists favour this drug due to its good tolerability profile, the rapid deep response, and the availability of an oral solution.

For children whose disease fails or progresses or who are intolerant of imatinib, there are presently 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-alpha or hydroxyurea.

In practice, most people now switch to second-line therapy if the response criteria as defined by European Leukemia Net are not met.

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 human leukocyte antigen (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 a challenge. 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.

Available CML-TKIs

The other second-generation inhibitor, 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.

Side effects of imatinib in children occur with the same or lower frequency and tend to be less severe than in adults. Frequent side effects include myelosuppression, nausea, fluid retention, muscle cramps, bone pain, skin rash, diarrhoea, lethargy, and weight gain. Dasatinib seems to be better tolerated in children than in adults.

Nevertheless, it is agreed that an unmet need remains for treatment options in paediatric patients with newly diagnosed (ND) and resistance or intolerance (R/I) CML which are available in population-appropriate administrations, and which demonstrate clinically meaningful response and survival outcomes, with tolerable short- and long-term toxicities specifically relevant to paediatric patients.

3.1.3. Main clinical studies

The BCHILD study is an ongoing, Phase 1/2, multicenter, international, single-arm, open-label study with two Phases. Phase 1 was designed to identify a recommended dose of bosutinib administered orally QD in paediatric participants (ages 1 to <18 years) with ND CML or R/I CML who have received at least 1 prior TKI therapy in phase 2.

Of the 49 treated participants, 21 were ND (Phase 2 300 mg/m2 cohort). From the 26 participants with R/I Ph+ CML, 16, 9, and 3 had been treated with 1, 2, and 3 prior TKIs, respectively.

The study population appears representative for the applied indication.

3.2. Favourable effects

Resistant and intolerant CML cohort (R/I) [Phase1, at least 1 TKI]

In this R/I cohort, CCyR (MCyR) was achieved/maintained at any time by 82.1% (85.7%), respectively. Molecular responses achieved at any time in evaluable participants were as high as 66.7% (Major molecular responses (MMR) in the 300 mg/m^2 cohort) and 50% in the total R/I population and median time until response reflects a comparable efficacy like in adults. Most participants who achieved a response were able to maintain it for long-term as indicated by KM estimates of 72.0% at Month 24 for the R/I population.

Newly diagnosed CML cohort (Phase2)

At the cut-off data, MMR in the Phase 2 cohort was achieved only in 28.6% of the ND populations. However, 76.2% of those with newly diagnosed CML reached major cytogenetic response (MCyR) and nearly all of these subjects reached complete cytogenetic response (CCcR) response. As indicated by a median duration of~3 months of treatment to reach MCyR as well as for complete haematological response (CHR) the efficacy of bosutinib also in the first line population is not challenged and again similar to that known already from the adult population.

3.3. Uncertainties and limitations about favourable effects

Considering that development of MMR needs longer treatment duration than reaching CHR or MCyR/CCyR and the wide range of follow-up among study participants, full interpretation of the molecular response is currently premature and hampered due to the shorter duration of therapy in the phase 2 population.

Treatment start was initially applied for an age of 1 year and above which was neither sufficiently justified by the data nor appeared the posology for the youngest children below an age of 6 years sufficiently justified by the available Pop-PK analysis. Since an approach of PK bridging was agreed, the model is critical to support dosing recommendations.

The Applicant developed a separate paediatric pharmacokinetic model instead of formally testing an age covariate in a combined paediatric and adult model, which would be common practice in model development. The provided ETA plot showed that the clearance in the paediatric population is approximately 65% higher, but it is unclear whether this 65% higher clearance is apparent in the entire paediatric age range or just a subset.

It seems that the doses administered were not always able to achieve a sufficiently high exposure (Cmin) to achieve MMR, although the targeted AUC range was grossly obtained, but Cmax values were often higher than in adults.

Since the model also has limitations with respect to the ontogeny function of the main metabolizing enzyme CYP3A4, which substantially increases uncertainty about the clearance in children below the age of 6 years, proposed doses for paediatric patients below 6 years are considered too uncertain to be approved. Therefore, sensitivity analyses were requested for the different ontogeny functions with respect to their influence on doses. These analyses were not performed by the MAH. Instead, the indication was restricted to children of 6 years and older.

3.4. Unfavourable effects

As known from the adult population, Bosutinib treatment is associated with significant safety risks in terms of a high degree of drug related gastrointestinal toxicity, hepatotoxicity, myelosuppression and cutaneous toxicity in terms of rash. As known from the previous procedures, the therapeutic range is narrow, considering the safety profile associated the dose needed to suppress the BCR/ABL mutated cell clones in the bone marrow.

Gastrointestinal AESIs (87.3') reflects the most important gastrointestinal risk associated with bosutinib treatment in the paediatric population. Overall, 5.5% of participants permanently discontinued treatment due to GI AESIs. The median time to onset for diarrhea (all Grades) was 2.0 days (range: 1, 746 days) and the median duration of any grade event was 2.0 days (range: 1, 373 days). Among participants who experienced diarrhea, the median number of episodes of diarrhea per participant during treatment with bosutinib was 58 episodes (range: 1, 198 episodes). Of the participants, 64.4% had all Diarrhoea events resolved.

The most frequently reported liver AESIs (occurring in >10% of participants, all Grades) were ALT increased (29.1%), AST increased (18.2%), and Blood alkaline phosphatase increased (10.9%). Overall, 7.3% of participants permanently discontinued treatment due to liver AESIs. Although no potential Hy's law cases were identified during this study, such case were reported in adults and insofar the risk of severe drug induced hepatotoxicity (DILI) remains a risk also to considered in the paediatric population.

Myelosuppression AESIs are the consequence of the suppression of the pathological cell clone in the bone marrow and occurred in 43.6% of participants. The most frequently reported myelosuppression

AESIs (occurring in >10% of participants, all Grades) were Platelet count decreased (34.5%), Anaemia (18.2%), and Neutrophil count decreased (10.9%).

Rash AESIs are well known class effects for all TKIs used in CML and occurred in 45.5% of the investigated population. Although they are in general manageable with dose interruptions and reductions, it needs to be considered in the small population some children in the trial discontinued treatment due to these adverse events.

Overall, the most observed AEs in the paediatric population are similar to the observed safety profile of bosutinib in the adult population and no additional safety signals were detected.

3.5. Uncertainties and limitations about unfavourable effects

There is preclinical and clinical evidence that long-term exposure to imatinib results in growth impairment and dysregulation of bone metabolism, 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. The optimal approach to management of this side effect has not yet been established. Bosutinib's impact on growth and bone metabolism is currently not sufficiently characterised. Data from the pivotal study are not mature to allow meaningful analysis yet. The very limited number of participants (especially in participants with ND Ph+ CML enrolled more recently) who have data available for more than Cycle 12–13, is not adequate to assess reliably long-term outcomes regarding growth. Further data are expected by the company which has committed to provide more mature data in the post approval setting through the result for study ITCC-054/AAML1921 and to monitor the issue in future PSURs. However, at this point in time based on the results from rat juvenile toxicity studies, growth effects are not expected in humans.

3.6. Effects Table

Table 33. Effects Table for Bosutinib in the Paediatric Population

Effect	Short Description	Unit	Paediatric I/R CML population	Paediatric newly diagnosed CML	Uncertainties/ Strength of evidence	References
Favourable Effects						
MCyR [95% CI]	Major Cytogenetic Response	n/N (%)	24/28 (85.7) [67.3, 96.0]	26/30 (86.7) [69.3, 96.2]	Mature. efficacy is supported by consistent results from CHR. CCyR, and MMR	Interim study report (ISR)
Unfavourable Effects						
Safety Para-meter	**Phase 1 300mg/ m²) n (%)**	**Phase 1 (350mg/ m²) n (%)**	**Phase 1 (400mg/m²) n (%)**	**Phase 2 CP1L (300mg/ m²) n (%)**	**Total Safety Pop N=55 n (%)**	**Total Grade ¾ N=55**
Permanently Discontinued due to AE	1/6 (16.7)	4/11 (36.4)	2/11 (18.2)	3/ (14.3)	11/55 (20.0)	N/A

Diarrhoea	6/6 (100.0)	10/11 (90.0)	9/11 (81.8)	17/24 (70.8)	43/55 (78.2)	7/55 (12.5)
Vomiting	5/6 (83.3)	9/11 (81.8)	6/11 (54.5)	9/24 (37.5)	29/55 (52.7	4 (7.3)
Thrombocyto -penia	0/6 (0.0)	2/11 (18.2)	6/11 (54.5)	11/24 (45.9)	18/55 ((32.7)	10 (18.2)
ALT	1/6 (16.7)	4/11 (36.4)	5/11 (45.5)	6/24 (25.0)	16/55 (29.1)	8/55 (14.5)

Notes: According CHILD trial, Cut-off date: 21.SEPT 2022 for Efficacy and 27.FEBR 2023 for Safety

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Resistant and intolerant CML cohort (R/I) [Phase 1, at least 1 TKI]

Considering that reaching MMR and particularly deep MMR is strongly correlated with overall survival and normalisation of life expectancy in adults, thus, the importance of the demonstrated durable and sustained efficacy benefit is not challenged in the paediatric population which reached very similar outcomes. It is also agreed that bosutinib has shown clinical meaningful and relevant efficacy in the heterogeneous population. Efficacy appears to be similar to that well known characterised in the adult CML population.

Bosutinib is therefore acceptable as treatment option for the R/I-CML paediatric population and also for first line treatment CML children.

Newly diagnosed CML cohort (Phase 2)

Considering the limited duration of therapy at the cut-off data MMR in the Phase 2 cohort was achieved only in 28.6% of the ND populations. However, relevant endpoints (MCyR And CCyR) have been reached by most of the ND CML patients treated (76.2%). As indicated by a median duration of~3 months of treatment to reach MCyR as well as for complete haematological response (CHR) the efficacy of bosutinib also in the first line population is not challenged and again similar to that known already from the adult population. Despite full interpretation of the molecular response data was initially not sufficiently possible due to the shorter duration of therapy in the phase 2 population, however, considering the experience available from the adult CML population this does not substantiate any concern regarding efficacy in the paediatric subpopulation. Updated results received during the procedure have also provided further confirmation of this assumption.

In summary, clinically relevant and meaningful results demonstrate an efficacy benefit from bosutinib treatment in resistant/refractory and newly diagnosed paediatric CML patients comparable to that known in the adult population.

The QD dosing regimen of bosutinib provides specific benefits for paediatric patients by negating the need for fasting and frequent dosing, thereby minimizing compliance difficulties.

Also, the safety profile of bosutinib in the paediatric population appears to be rather similar to that observed in an adult population. There were no new safety findings observed in the paediatric population. The impact of bosutinib on growth and bone metabolism will be further characterized in the future submission of data for study ITCC-054/AAML1921 and future monitoring in the PSURs as committed by the applicant.

Treatment start was initially applied for an age of 1 year and above which was neither justified by the data nor appeared the posology for the youngest children below an age of 6 years sufficiently justified by the available Pop-PK analysis. Considering the existing concerns regarding the recommended posology and also with respect to safety, the initial proposal to allow treatment of children as young as one year of age appeared not acceptable. On basis of the MAH's new proposal to restrict the indication to children above the age of 6 years in whom the database is larger and more reassuring, the benefit risk balance in this patient group can be considered positive.

3.7.2. Balance of benefits and risks

Efficacy data currently available indicate a similar benefit in terms of efficacy endpoint outcomes like MCyR, CCyR and MMR (including MMR4) comparable to that known from treatment of the adult population in resistant/refractory as well as newly diagnosed paediatric patients with Ph+ CML.

The safety profile of bosutinib appears generally similar in the paediatric population to that observed in the adult population T

Thus, from a clinical pharmacology point of view this application for a new indication in paediatric CML patients together with a new "patient-centric" capsule formulation is approvable.

In summary, the benefit/risk balance for the applied restricted extension of indication is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall benefit/risk balance of Bosulif is positive, in the treatment of paediatric patients of 6 years and older with resistant/intolerant or newly diagnosed CML, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Bosulif 50 and 100 mg hard capsules is favourable in the following indication(s):

Bosulif is indicated for the treatment of:

- Adult and paediatric patients aged 6 years and older with newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- Adult and paediatric patients aged 6 years and older with CP Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
- Adult patients with accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and

dasatinib are not considered appropriate treatment options.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Bosulif subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0336/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Grouped variations recommendation

In conclusion, CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication (C.I.6.a) to include treatment of paediatric patients greater than or equal to 6 year of age with newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic

myelogenous leukaemia (Ph+ CML) for BOSULIF, based on interim results from study ITCC-054/AAML1921 (BCHILD); this is a phase 1/2, multicenter, international, single-arm, open-label study of bosutinib in pediatric patients with newly diagnosed chronic phase or resistant/intolerant Ph+ chronic myeloid leukemia. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 7.3 of the RMP was endorsed. In addition, the MAH took the opportunity to introduce minor editorial changes to the Product Information.