CLINICAL AND STATISTICAL REVIEW

Application Type	sNDA
Application Number(s)	021986, S-021
Priority or Standard	Priority
Submit Date(s)	6/29/2018
Received Date(s)	6/29/2018
PDUFA Goal Date	12/29/2018
Division/Office	DHP/OHOP
Reviewer Name(s)	Aviva Krauss, MD (Clinical Reviewer, Clinical Team Leader and Cross-Disciplinary Team Leader) Jiaxi Zhou, MS (Statistical Reviewer) Yuan Li Shen, PhD (Statistical Team Lead) Thomas E. Gwise, PhD (Deputy Division Director, OB, DBV)
Review Completion Date	12/20/2018
Established/Proper Name	Dasatinib
(Proposed) Trade Name	Sprycel®
Applicant	Bristol-Myers Squibb Company (BMS)
Dosage Form(s)	Oral tablets (20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg)
Applicant Proposed Dosing Regimen(s)	Weight-based dosing: 10 to less than 20 kg: 40 mg 20 to less than 30 kg: 60 mg 30 to less than 45 kg: 70 mg At least 45 kg: 100 mg
Applicant Proposed Indication(s)/Population(s)	For the treatment of pediatric patients with newly diagnosed Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy
Recommendation on Regulatory Action	Regular Approval for revised indication
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of pediatric patients 1 year of age and older with newly diagnosed Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy

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Glossary

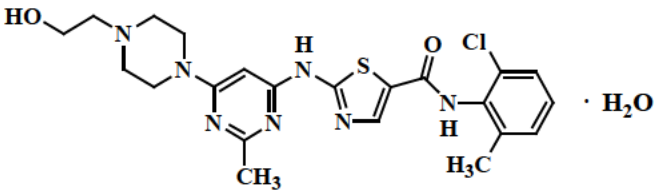
AC	advisory committee
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	adverse reaction
AST	aspartate aminotransferase
BID	twice daily
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COD	cause of death
COG	Children's Oncology Group
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response/remission
CRF	case report form
CRO	contract research organization
CRp	complete response with incomplete platelet recovery
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DBP	diastolic blood pressure
DFS	disease-free survival
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DMPH	Division of Maternal and Pediatric Health
DSMB	data safety monitoring board
ECG	electrocardiogram

eCTD	electronic common technical document
EFS	event-free survival
ETASU	elements to assure safe use
FAB	French-American-British
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HSCT	hematopoietic stem cell transplantation
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IR	Information Request
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MAED	MedDRA Adverse Events Diagnostic
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRD	minimal residual disease
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
Ph+	Philadelphia chromosome positive
Ph-	Philadelphia chromosome negative
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome

PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SDN	study document number
SEER	Surveillance, Epidemiology, and End Results
SMQ	standard MedDRA query
SOC	standard of care
SOC	system organ class
TEAE	treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
ULN	upper limit of normal
UTI	Urinary tract infection
WHO	World Health Organization

2. Executive Summary

2.1. Product Introduction

Trade Name:	Sprycel®
Established Name:	dasatinib
Chemical Name:	N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate
Molecular Formula:	C22H26ClN7O2S • H2O
Chemical Structure:	
Molecular Weight:	506.02 g/mol
Dosage Forms:	Tablet, 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg.
Therapeutic Class:	Antineoplastic
Chemical Class:	Small molecule
Pharmacologic Class:	Kinase inhibitor
Mechanism of Action:	Inhibits multiple receptor tyrosine kinases, including BCR-ABL. Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase. In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate-sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib could overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression.

Dasatinib is an approved drug for multiple adult and pediatric indications (see 3.1, U.S. Regulatory Actions and Marketing History). Supplemental NDA 021986/021 was submitted for the proposed indication of the treatment of "pediatric patients with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy" using a dose of 40, 60, 70 or 100 mg daily for patients 10 to <20 kg, 20 to <30 kg, 30 to <45 kg and >45 kg, respectively.

Also included with this submission was a request for pediatric exclusivity, which was granted by the exclusivity board on 9/27/2018. See Appendix 13.4 for a detailed review of the response to the written request.

2.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of dasatinib for the indication "pediatric patients 1-year of age or older with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy" using a dose of 40, 60, 70 or 100 mg daily for patients 10 to <20 kg, 20 to <30 kg, 30 to <45 kg and >45 kg, respectively. The recommendation is based on the finding of 3-year Event Free survival (EFS) of patients treated on Study CA180372 (NCT01460160).

The development of a pediatric formulation that will make the agent available to younger pediatric patients who cannot swallow tablets is already being undertaken by the applicant, and the goal of a post-marketing commitment associated with this approval.

Study CA180372 was a phase 2, multicenter, non-randomized, open-label, historically-controlled study comparing outcomes for pediatric patients more than 1 to less than 18 years of age with newly diagnosed Ph+ ALL treated with dasatinib added to standard chemotherapy ("cohort 1"), using the AIEOP-BFM ALL2000 backbone, to those of 2 historical control groups: those treated with the chemotherapy backbone alone, without a tyrosine kinase inhibitor (TKI; "cohort 2"), and those treated with the same backbone in combination with imatinib ("cohort 3"), another TKI that inhibits BCR/ABL. Dasatinib was given orally at a dose of 60mg/m2 once daily starting on day 15 of Induction block IA, after Philadelphia chromosome positivity was confirmed, continuously with the AIEOP-BFM ALL2000 multiagent chemotherapy backbone (see Appendix 14.3) for a total of 2 years. Subjects who had minimal residual disease (MRD) above pre-defined thresholds at the end of induction/start of consolidation and/or at the end of consolidation, and who had a genotype-matched donor (9/10 or 10/10) were to undergo hematopoietic stem cell transplantation (HSCT) following consolidation block 3 (HR3) instead of continuing the AIEOP-BFM ALL 2000 regimen. Patients who underwent HSCT could receive an additional optional course of dasatinib monotherapy at the same 60mg/m2 daily dose for up to 12 months.

The study design included hierarchical testing of the 3-year binomial EFS rate in patients

treated with dasatinib and the AIEOP-BFM ALL2000 backbone in comparison to 3-year EFS from 2 sets of historical controls: those of cohort 2 (the backbone alone), testing superiority, followed by those of cohort 3 (the backbone in combination with imatinib), testing non-inferiority and superiority (using a margin of -5%). The applicant was informed by the steering committees of both historical control studies in 2013 that they would not be able to provide patient-level data for either study to allow for a rigorous statistical comparison between the dasatinib cohorts and the other cohorts, a major deficiency of the study design. They did commit to providing trial level data for both studies, and this was included with the sNDA submission (see limitations in section 6.2). According to the statistical analysis plan for CA180372, *"the main intention of the evaluation for "superiority" and "non-inferiority" versus the historical control studies is a way to provide context for the EFS results from the single-arm study CA180372 in the absence of a control arm.* (See sections section 4.1 and 4.2, for full details regarding the pre-submission history of this development program). At the time of the final analysis, there were 106 patients treated on Study CA180372. The 3-year binomial EFS rate for these patients was 66% (95% CI:56.2, 75.0), compared with a 3-year binomial EFS rate of 49.2% (95% CI:36.1, 62.3) for cohort 2 and 59.1% (95% CI: 50.4, 67.4) for cohort 3. See section 6.1.2 Study Results, Efficacy Results – Primary Endpoint, for more details regarding the efficacy evaluation.

For the purposes of establishing efficacy in the intended population, FDA's analysis included only patients treated with tablet form of dasatinib exclusively (N=82), and for whom a diagnosis of Ph+ ALL was adjudicated and confirmed by the clinical reviewer (N= 78).

The FDA Efficacy Analysis Population (EAP) included 78 patients with a median age of 10.5 years (range 2.6-17.9 years); 46% were < 10 years old, 45% were male, and 82% were white. All patients had precursor B-cell immunophenotype, 57% had high risk disease per NCI risk stratification, 41% had a WBC of >50,000/mcl at diagnosis, and 22% had extramedullary disease, including 17% with CNS involvement. Fifteen percent of patients proceeded to allogeneic HSCT transplantation, all in first remission (CR1).

The 3-year binomial EFS rate as adjudicated by the FDA clinical reviewer was 64.1% (95% CI: 52.4%, 74.7%). The Kaplan-Meier estimate for 3-year EFS was 63.3% (95% CI: 51.4%, 73%). The lack of an adequate set of covariates in cohorts 2 and 3, in addition to their small sample sizes, precluded using a rigorous statistical approach such as a propensity score analysis to create treatment groups with adequately similar characteristics to allow for comparison between the 3-year EFS of cohort 1 and the historical control cohorts 2 and 3. However, FDA did receive a limited patient level dataset for both the AIEOP-BFM ALL study and the amended EsPhALL study to enable performance of various descriptive analyses (e.g. K-M EFS estimates and the 95% CI), and allow for a more accurate comparison of the EFS estimates between the cohorts, using the same EFS definition, than that which could be gleaned from trial level data alone. See Section 7.1, for more details regarding the use of these data and their quality.

Supporting evidence for the efficacy of dasatinib in pediatric patients with newly diagnosed Ph+ ALL came from Study CA180204 (NCT00720109) a multicenter, open-label, non-randomized phase 1/2 study evaluating dasatinib given continuously or intermittently in combination with the COG AALL0031 multiagent chemotherapy backbone to pediatric and young adult patients with newly diagnosed Ph+ ALL. The reported K-M estimated EFS rate of 68.4% (95% CI 48.3%, 88.6%) is limited by small numbers, 2 dosing regimens, and early closure of the trial to start enrollment on the pivotal study CA180372 described above but supports the contribution of dasatinib to this backbone when compared to the reported literature regarding the outcomes seen with multiagent chemotherapy alone, with or without allogeneic HSCT.

In general, a time-to-event endpoint such as EFS in a single-arm trial is difficult to interpret. Patient-level data was submitted by the cooperative groups for the historical control arms, but these data had limitations with regard to content and confirmation for the derived values, and the data for the non-TKI group included a small number of patients, precluding propensity score analyses that would enable robust statistical comparisons between the cohorts as described above. Nonetheless, it is acknowledged that the estimated median EFS for the patients treated on CA180372 was substantially greater than expected based on the outcomes reported on the AIEOP-BFM ALL2000 study and those reported in the literature for patients treated with multiagent chemotherapy with or without allogeneic HSCT. Since the majority of patients on Study CA180372 did not undergo subsequent allogeneic HSCT these results are particularly striking, as most of the patients treated with AIEOP-BFM ALL2000 did undergo HSCT and still, the results with dasatinib were more favorable, supporting the notion that dasatinib improves outcomes over chemotherapy alone and may spare patients the need to undergo allogeneic HSCT, a treatment modality with not insignificant associated short- and long-term morbidity and mortality. The plausibility of these results is supported by the demonstration of efficacy based on achievement of Major hematologic response (MaHR) in adult patients with imatinib-resistant or intolerant Ph+ ALL, as well as in adult patients with accelerated or lymphoid blast phase Ph+ CML with resistance to or intolerance to prior therapy including imatinib, and pediatric patients with Ph+ CML in chronic phase.

For the proposed indication, 3-year EFS alone in a single-arm trial would not be sufficient to support the approval of dasatinib in combination with multiagent chemotherapy in the proposed population. But when taken together with the patient-level data provided for the historical controls, and with the striking results seen, in the context of a drug with established clinical benefit in patients with more advanced (relapsed/refractory) disease (adult Ph+ ALL) and diseases with related biology (CML), the totality of the data provides substantial evidence of effectiveness.

2.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Dasatinib is a small molecule that inhibits multiple tyrosine kinases, including BCR-ABL. Approximately 2-4% of pediatric patients with newly diagnosed ALL harbor the t(9:22) translocation, known as Philadelphia-positive (Ph+) ALL. This translocation is associated with a slightly lower response rate to initial therapy, but more significantly with adverse long-term outcomes and much increased relapse risk compared to other pediatric patients with ALL. Standard of care in the pre-TKI era was multiagent chemotherapy to induce remission followed by allogeneic HSCT in patients with suitable donors, but even in with this treatment, long term outcomes were dismal, with 5-year OS reportedly as low as 54%. The applicant's proposed indication is "For the treatment of pediatric patients with newly diagnosed Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy." The benefit-risk assessment supports regular approval of dasatinib for the treatment of pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy.

The efficacy of dasatinib is based primarily on the results of a multicenter, non-randomized historically controlled phase 2 study (CA180372) where dasatinib was administered at 60 mg/m^2/day by mouth in combination with the multiagent chemotherapy backbone per Study AIEOP-BFM ALL 2000 to patients aged 1 to <18 years of age with newly diagnosed Ph+ ALL, starting by day 15 of induction IA, and for up to two years of therapy. Seventy-eight patients for whom a diagnosis of Ph+ ALL could be confirmed based on the data submitted, and who received exclusively the tablet formulation of dasatinib were considered for evaluation of efficacy. The 3-year binomial EFS in these patients was 64.1% (95% CI, 52.4%, 74.7%). Although the data submitted did not allow for robust comparison to the historical control cohorts, including cohort 2, treated with the AIEOP-BFM ALL backbone without a TKI, the data submitted allowed for a descriptive analysis of 3-year EFS in that cohort of 49.2% (95% CI 36.1%, 62.3%). This, together with the fact that there no reports in the literature of 3-5 year EFS greater than 44% for this population of patients treated with chemotherapy alone with or without allogeneic HSCT but without a TKI, all support the effectiveness of dasatinib in combination with the AEIOP-BFM ALL 2000 backbone in this population. This is further supported by the low percentage of patients who proceeded to allogeneic HSCT on Study CA180372 (15%), and by previous approval of dasatinib monotherapy in adult patients with Ph+ ALL with resistance or intolerance to prior therapy.

The safety database consists mostly of the 106 pediatric patients treated with dasatinib in combination with the AIEOP-BFM ALL 2000 backbone above, with an emphasis on patients who received exclusively the tablet formulation (b) (4) [redacted]. In general, the additive toxicity of dasatinib in the context of multiagent chemotherapy does not appear to be excessive; there were no deaths within the first 60 days of therapy, the induction death rate was 0 if

limited to Cycles IA and IB, and 2% if HR cycles 1-3 are included, which is not higher than expected with multiagent chemotherapy in the treatment of pediatric ALL. Fatal adverse reactions occurring within 30 days of the last dose of dasatinib occurred in 4% of patients in the safety population and were mostly due to infection. The most common (≥20%) ARs were mucositis, febrile neutropenia, pyrexia diarrhea, nausea, vomiting, musculoskeletal pain, abdominal pain, cough, headache, rash, fatigue, arrhythmia, hypertension, oedema, viral infection, hypotension, altered state of consciousness, hypersensitivity, dyspnea, epistaxis, peripheral neuropathy, sepsis (excluding fungal), fungal infection, pneumonia (excluding fungal), pruritis, clostridium infection (excluding sepsis), UTI, bacteremia (excluding fungal), pleural effusion, sinusitis, dehydration, renal insufficiency, visual impairment, conjunctivitis, dizziness, muscle weakness, haematochezia, anxiety, flushing and balance disorder. Many of these are already associated with dasatinib, and some of these as well as others are known toxicities associated with the various chemotherapeutic agents that comprised the chemotherapy backbone. Although they should be included in section 6 of the PI, no new safety signals were detected that warrant additional warnings and precautions in the dasatinib PI. Finally, the improved outcomes on Study CA180372 in a population who for the most part did not undergo allogeneic HSCT is an added benefit from a safety perspective, as if treatment with dasatinib can spare patients the need for allogeneic HSCT and its attendant morbidities and mortalities, this is a safety advantage of dasatinib treatment as well. However, from the data submitted, a definitive conclusion regarding the need for allogeneic HSCT after dasatinib therapy cannot be assessed at this time.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In contrast to newly diagnosed pediatric ALL overall, where the majority of patients are cured with multiagent chemotherapy alone, the subset of patients with Ph+ ALL have historically had an EFS of <44% with the same treatment approach • Due to this poor prognosis, this subset of patients have historically been treated as candidates for allogeneic HSCT in first remission	Newly diagnosed, Ph+ ALL is a recognized subset of pediatric ALL that can be accurately diagnosed at presentation. Prior to TKI therapy, the only therapies with curative intent for this disease were intensive, and themselves potentially life-threatening therapies. Even with these treatments, the outcome was dismal.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Intensive chemotherapy with or without HSCT yields expected 3-5 year OS in the 48-60% range. • With the addition of a TKI to multiagent chemotherapy, outcomes have improved, with a 4-year EFS of 70% (95% CI: 54%, 81%), in the pivotal trial upon which approval of imatinib for this indication was based, in which 30/50 patients were treated with chemotherapy alone and 20/50 patients were treated with allogeneic HSCT after induction remission.	Outcomes for patients treated with TKIs in combination with multiagent chemotherapy have improved, but outcomes are still much worse than for the overall population of pediatric patients with Ph+ ALL, and more effective regimens are needed.
Benefit	• Study CA180372 was a non-randomized, multicenter, historically controlled study of dasatinib in combination with multiagent chemotherapy per the AIEOP-BFM ALL 2000 backbone from day 15 of induction IA for up to 2 years in pediatric patients with newly diagnosed Ph+ ALL. • The 3-year binomial EFS in the FDA efficacy population (N=78) was 64.1% (95% CI, 52.4%, 74.7%).	The totality of the evidence supports approval, despite the suboptimal study design, lack of detailed patient-level historical control data, and inability to use inferential statistics.
Risk and Risk Management	• There were no deaths within the first 60 days of therapy, and the death rate was 2% through the end of HR3 • The most common (>20%) ARs were mucositis, febrile neutropenia, pyrexia diarrhea, nausea, vomiting, musculoskeletal pain, abdominal pain, cough, headache, rash, fatigue, arrhythmia, hypertension, oedema, viral infection, hypotension, altered state of consciousness, hypersensitivity, dyspnea, epistaxis, peripheral neuropathy, sepsis (excluding fungal), fungal infection, pneumonia (excluding fungal), pruritis, clostridium infection (excluding sepsis), UTI, bacteremia (excluding fungal), pleural effusion, sinusitis, dehydration, renal insufficiency, visual impairment, conjunctivitis,	The safety profile of dasatinib in combination with the AEIOP-BFM ALL 2000 backbone is consistent with the well-characterized safety profile seen with dasatinib as well as the multiple components of the backbone chemotherapy regimen. These ARs should be included in section 6 of the PI, but no boxed warnings, new warnings and precautions or REMS are warranted.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	dizziness, muscle weakness, haematochezia, anxiety, flushing and balance disorder.	

2.4. Patient Experience Data

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

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

3. Therapeutic Context

3.1. Analysis of Condition

Ph+ ALL is characterized by the presence of the Philadelphia chromosome, a reciprocal translocation between chromosomes 9 and 22 (t(9;22)(q34;q11)) resulting in the fusion of the breakpoint cluster region gene on chromosome 22 with c-abl gene sequences translocated from chromosome 9 and the expression of the BCR-ABL tyrosine kinase.

Ph+ ALL is a subtype of very high risk ALL that has been reported to account for approximately 3-4% of childhood ALL (Bernt and Hunger, 2014). Historically, fewer than one third of children with this leukemia were cured with intensive multi-agent chemotherapy, in contrast to the approximately 90% overall survival seen in the general pediatric ALL population (Pui, 2015). Because of the dismal prognosis of pediatric patients with Ph+ ALL, HSCT in first remission has been considered standard of care (SOC), especially for those children with available HLA-matched family donors (Arico, 2010).

Chemotherapeutic agents commonly included in very high risk ALL therapy include:

- corticosteroids (prednisone or dexamethasone)
- vincristine
- asparaginase
- anthracycline (daunorubicin)
- methotrexate
- mercaptopurine
- cytosine arabinoside
- etoposide
- ifosfamide
- cyclophosphamide
- intrathecal medications (methotrexate, hydrocortisone, cytosine arabinoside)

These agents are administered in cycles of therapy. When part of Children's Oncology Group (COG) very high-risk protocols, the largest cooperative group enrolling patients in the US, these cycles typically included:

- Induction (administered prior to enrollment on the trial)
- Consolidation
- Reinduction #1
- Intensification #1
- Reinduction #2
- Intensification #2
- Maintenance

When administered as part of European protocols by the various European cooperative groups

(AIEOP, BFM, MRC etc.), these cycles included:

- Induction IA, starting with a prednisone only "prophase" for the first 7 days
- Consolidation (IB) (#1)
- High Risk (Consolidation #2, consisting of HR blocks 1, 2 and 3)
- Reinduction #1
- Interim Maintenance
- Reinduction #2
- Continuation (maintenance)

In both approaches, HSCT candidates are ideally taken to transplant after their second (COG) or third (AIEOP-BFM, HR3) cycle of consolidation.

While there are many similarities between these approaches, it is noted that there are some differences in intensity between the regimens (see 6.1.1, Study design for details).

Given the dismal results seen with multiagent chemotherapy, even when followed by allogeneic HSCT, for pediatric patients with newly diagnosed Ph+ ALL, the publication of the results of the COG study of the first approved TKI targeting the activity of BCR-ABL, imatinib, Study AALL0031, were transformative. Based on the results of this trial, the international pediatric oncology community including those in the United States consider treatment with a TKI to be standard therapy for newly diagnosed patients with Ph+ ALL (Hunger S. P., 2011), and imatinib was approved for this indication (GLEEVEC prescribing information). Recent literature suggests that the use of TKIs in combination with multiagent chemotherapy in adults with Ph+ ALL abrogates the poor prognosis associated with this translocation (Igwe, 2017).

Dasatinib is a potent, broad-spectrum, competitive inhibitor of multiple oncogenic tyrosine kinases and kinase families, including BCR-ABL, SRC, c-KIT, platelet-derived growth factor receptor (PDGFR), and ephrin receptor kinases. Dasatinib is ~325-fold more potent than imatinib in inhibiting BCR-ABL in vitro. This second generation TKI was first approved for use in 2006 under the accelerated approval regulations for the treatment of adults with chronic, accelerated or blast phase chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy, as well as for the treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy. In October 2010, dasatinib was approved for the treatment of adults with newly diagnosed Ph+ CML in chronic phase. In November 2017, dasatinib was approved for the treatment of pediatric patients with Ph+ CML in chronic phase. See section 3.1, below for more details.

3.2. Analysis of Current Treatment Options

Table 1. Currently Available Therapies for the Treatment of Ph+ ALL in the Pediatric Population

Product (s) Name	Excerpted Indication	Additional information
Agents Indicated Specifically for Ph+ ALL in That Include a Pediatric Indication		
Imatinib	For the treatment of pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (ALL) in combination with chemotherapy	Year approved 2012 Basis of Approval: 4-year EFS, single arm trial with historical control data
Blinatumonab	For the treatment of adults and children with Relapsed or Refractory B-cell Precursor ALL	While the initial approval for r/r BCP ALL, including pediatric patients, was specifically in Ph- disease, the indication was expanded in 2017 to include Ph+ patients, based on the results of the ALCANTRA study.
Agents Indicated for the Treatment of ALL in Pediatric Patients (not specifically Ph+ ALL)		
Erwinaze asparaginase *Erwinia chrysanthemi*	A component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to E. coli-derived asparaginase	2011
Nelarabine	For the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens	2005
Clofarabine	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens	2004
Teniposide	In combination with other approved anticancer agents, is indicated for induction therapy in patients with refractory childhood acute lymphoblastic leukemia.	?2002
Cytosine arabinoside (IV, IT, SQ)	Useful in the treatment of acute lymphocytic leukemia	1998
Pegaspargase (Oncaspar®)	a component of a multi-agent chemotherapeutic regimen for treatment of patients with: ▪ First line ALL ALL and hypersensitivity to E. coli-derived native asparaginase [*E. coli*-derived native asparaginase is no longer available]	1994
Daunorubicin (Daunomycin) injection	In combination with other approved anticancer drugs for the remission induction in acute lymphocytic leukemia of children and adults	1979

Elspar® asparaginase	Elspar is an asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL	1978
Doxorubicin (Adriamycin)	To produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia	1974
Vincristine injection	Indicated in acute leukemia	1963
Cyclophosphamide (capsule, injection)	Cyclophosphamide, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to cyclophosphamide treatment: acute lymphoblastic (stem-cell) leukemia in children	1959
Methotrexate	Used in maintenance therapy in combination with other chemotherapeutic agents.	1959
Dexamethasone (Oral, injection)	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood	1959
Prednisone	Palliation of leukemias in adults, acute leukemia of childhood	1955
Mercaptopurine	Maintenance therapy of acute (lymphocytic, lymphoblastic) leukemia as part of a combination regimen	1953

Source: FDA Clinical Reviewer

As stated above, outcomes using any of the multiple chemotherapy agents approved for the treatment of pediatric patients with ALL without a TKI are poor, and SOC since the results of the imatinib study were published includes TKI in combination with multiagent chemotherapy. Although the role of allogeneic HSCT in first CR this context has been questioned in light of the results of the COG study AALL0031, which demonstrated that outcomes in patients who underwent allogeneic HSCT after imatinib therapy were similar to those who did not (Schultz, 2014), this has not been definitively proven (reviewed in Bleckmann and Schrappe, 2016) and remains largely a matter of institutional policy, depending on other factors such as early response to therapy and MRD results.

Particularly noteworthy is that in a literature review performed by the FDA reviewer during the submission of NDA 21588, supplement 37 for imatinib for the treatment of pediatric patients with Ph+ ALL in combination with multiagent chemotherapy. In 7 single institution reports in which at least 20 pediatric patients with Ph+ ALL were treated with multiagent chemotherapy between 1984 and 2001, the 4-5 year EFS rates range from 20 to 44%, and in pooled multi-institutional data from 326 such patients treated between 1986 and 1996, , the 5 year EFS was 28%, and in 610 patients treated between 1995 and 2005, the 5-year EFS was 44% (95% CI 41, 46%) in patients who underwent allogeneic HSCT, and 34% (95% CI 31, 38%) in those who received chemotherapy alone (See review, PDinndorf, Reference ID 3233510).

In addition to the multiple chemotherapy agents approved for pediatric ALL, and imatinib, approved for pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy as summarized in Table 1, multiple other BCR/ABL targeting TKIs are approved for other indications, as summarized in Table 2. Only nilotinib is approved for the treatment of

pediatric patients with newly diagnosed CML-CP or those with CML-CP that is resistant or intolerant to a prior TKI.

Table 2. BCR/ABL targeting TKIs Approved for Adults, Other Indications

Product (s) Name	Excerpted Indication	Additional information
Nilotinib	For the treatment of: • Adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. • Adult patients with chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib. • Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.	Boxed warning for QT prolongation, Sudden death
Erlotinib	for: • The treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen. • First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.	
Bosutinib	for the treatment of adult patients with • Newly-diagnosed chronic phase Ph+ chronic myelogenous leukemia (CML). • Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy	Accelerated approval (newly diagnosed)
Ponatinib	For the treatment of adult patients with: • chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated. • with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)	Boxed warning for arterial occlusion, venous thromboembolism, heart failure and hepatotoxicity

Source: FDA Clinical Reviewer.

4. Regulatory Background

4.1. U.S. Regulatory Actions and Marketing History

Table 3. US regulatory History for Dasatinib

Year	Action	Indication	Dose	Comment
2006	Initial Approval	1) for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib (AA) 2) for the treatment of adults with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy (RA)	70 mg po BID	Frequent dose interruptions, reductions→actual average daily dose closer to 100 mg daily
2007	Supplement, new dose	Adults with CML as above, new dose	100 mg po daily (AA)	
2009	Supplement, change in approval type	Adults with CML as above, at the new dose	100 mg po daily (RA)	
2010	New indication	Adults with newly diagnosed Ph+ CML-CP (RA)		
2017	New indication	For the treatment of pediatric patients with Philadelphia Chromosome Positive (Ph+) Chronic Myelogenous Leukemia (CML) in Chronic Phase (RA)	Weight based, flat 10 to <20, 40 mg 20 to <30, 60 mg 30 to <45, 70 mg	Tablet form only, not dissolved (see next row)

Year	Action	Indication	Dose	Comment
			≥45, 100 mg	
(b) (4)				
2018	Exclusivity determination, granted			See Appendix 13.4 for review of the exclusivity determination checklist. The exclusivity board granted exclusivity on 9/27/2018.

Source: FDA clinical reviewer. AA, Accelerated Approval; RA, Regular Approval, ALL, acute lymphoblastic leukemia; CML, chronic myeloid/myelogenous leukemia; AP, accelerated phase; BP, blast phase; Ph+, Philadelphia chromosome positive;

4.2. Summary of Presubmission/Submission Regulatory Activity

Table 4 summarizes the relevant presubmission and submission regulatory activity related to the pediatric Ph+ ALL indication, including submissions related to the written request that was ultimately issued in 2007. During the pre-NDA meeting, the challenges and limitations associated with a historically-controlled study were related to the applicant in the meeting

minutes and requested that justification for the use of historical controls be included in the current submission.

Table 4. Presubmission Regulatory Activity Related to the Pediatric Ph+ ALL Indication

Year	Action	Indications studied	Comment
2005	Orphan designation	Tx of CML and Ph+ ALL	Exempt from PREA requirements
2006	Initiation of pediatric development program in US	CML, AML, ALL	
2007	WR issued	CML, ALL, patients aged 1-<18 years; development of an age-appropriate formulation	
2009	WR Amendment #1		
2013	WR Amendment #2		
2014	WR Amendment #3		
2015	WR Amendment #4		
2018	WR Amendment #5		Included a statement that "(b) (4) m²"
2018	Pre-NDA meeting	Pediatric patients with newly diagnosed Ph+ ALL, in combination with chemotherapy	The Agency raised the issue that *"the ability of data from the historical control groups for CA180372 and the analysis results to support approval and a favorable benefit:risk profile for the proposed indication will be a review issue."*

Source: FDA clinical reviewer. ALL, acute lymphoblastic leukemia; CML, chronic myeloid/myelogenous leukemia; AP, accelerated phase; BP, blast phase; Ph+, Philadelphia chromosome positive.

As part of M2.5, Clinical Overview (page 23), the applicant submitted this rationale, based on the following arguments:

- The rarity of Ph+ ALL in the pediatric population, coupled with its unmet medical need, made randomized studies "not feasible with a study duration of <10 years." Their estimate of the required sample size to show a 10% difference in 3-year EFS with an alpha of 0.05 and 80% power was 565 patients with a study duration of 21.8 years.
- The FDA's agreement with revision of the PPSR to include Studies CA180372 and CA180204, using historical controls.

- Their interpretation of the FDA's acceptance of the use of "descriptive analysis" on study CA180372 in Amendment 5 of the WR.
- The availability of the contemporaneously-conducted amended EsPhALL study using the same chemotherapy backbone such that these results could serve as a "valid external historical control" for CA180372.
- The availability of data from the AIEOP-BFM ALL 2000 as an external control study.
- The conduct of CA180372 was in close collaboration with the two primary investigators from COG and EsPhALL, and they claim that both AIEOP-BFM ALL 2000 and emended EsPhALL were "single-arm trials of comparable disease and clinical setting using the same backbone chemotherapy, and [with] EFS as the primary outcome measure."

Clinical Reviewer Comment: There is no documentation of the teleconference referred to the by the applicant on 3/18/2014 regarding discussion of the 3rd bullet. In any case, as stated above, at the pre-NDA meeting in 2/2018, the Agency expressed concerns regarding interpretability of a historically controlled study with a TTE endpoint.

4.3. Foreign Regulatory Actions and Marketing History

Pediatric clinical development was initiated in 2009 in the EU, where it is authorized for use in the treatment of adults with newly diagnosed Ph+ CML in CP, CML in CP, AP or BP with resistance or intolerance to prior therapy including imatinib mesylate, Ph+ ALL and lymphoid BP CML with resistance or intolerance to prior therapy, and for pediatric patients with newly diagnosed Ph+ CML in CP or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib. Pediatric clinical development is in accordance with the European Pediatric Investigational Plan (PIP) for CML and Ph+ ALL (EMEA-000567-PIP01-09-M04).

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

5.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations conducted inspections for Study CA180372 at clinical sites in Indianapolis, Illinois (Site #30, Riley Hospital for Children) and Houston, TX (Site #10, Baylor College of Medicine). These sites had the highest accrual and were significantly higher than at the other sites (5 vs 1-2 patients/site), such that they had the greatest impact on the study outcomes.

The Inspection of Site #30 resulted in issuance of a Form 483 due to finding that the site failed to follow protocol-delineated SAE reporting requirement with regard to the timeline (24 hours)

for this reporting. Although one patient had 2 SAEs that were not reported within the 24 hours timeframe, both SAEs were eventually reported to the sponsor. The PI at site #30 (Dr. Sandeep Batra) responded adequately to the Form 483 on 9/28/2018. Clinical Site #10 did not have any form F483 issued and appeared to be in compliance with GCP.

5.2. Product Quality

No new CMC data were submitted with this supplement.

5.3. Clinical Microbiology

No new microbiology data were submitted with this supplement.

5.4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted with this supplement.

5.5. Clinical Pharmacology

In the Clinical Pharmacology review of the sNDA for the pediatric CML indication, the review team noted that while BSA-based dosing was used throughout the pediatric development program, the actual dose used in practice is limited by the commercially available dasatinib tablet dosing strengths (20, 50, 70, 80 and 100 mgs; see DARRTS ID 4164247, Yuhong Chen, 10/6/2017 for details). They consequently evaluated the applicant's proposal for flat dosing for specific body-weight categories (10 to less than 20 kg, 20 to less than 30 kg, etc.; so-called "weight-tiered (WT) dosing"), and found that with some adjustment to the categories, WT dosing provided similar exposures (defined as within 20% of the target exposure for the geometric mean of simulated steady-state exposure) as seen with the BSA-based dosing used in the pediatric CML protocols.

In the pediatric Ph+ ALL protocols used to support the current indication, the dosing for both tablet and PFOS formulations was the same as that used for the tablet formulation in the pediatric CML protocols, namely 60 mg/m^2/day. Per protocol, the dose was to be rounded up to the nearest 5 mg because the protocol also used investigational tablets of 5mg of dasatinib, which are not approved for clinical use (the applicant did not submit this formulation for review by the Agency).

Clinical reviewer comment: Given the PK findings above and the same considerations with regard to dosing confusion taken into account during the pediatric CML supplement review and approval, the proposal for WT dosing for the pediatric Ph+ ALL indication appears reasonable.

Also, while it is noted that the pediatric CML protocol allowed for dose escalation based on disease response, this was not the case for the Ph+ ALL protocols. Section 2.4 in the PI should clearly distinguish between these populations to mitigate the risk of confusion and application of dose escalation rules to the wrong population.

As previously stated, on Study CA180372, both the tablet and PFOS formulations could be used, at the same 60 mg/m^2 daily dose. (b) (4)

(b) (4)

Additionally, the CA180372 protocol allowed for dispersion of tablets in lemonade or preservative-free juice for patients who were unable to swallow the tablets whole, although it did specify that tablets should not be crushed, cut, or broken. The clinical pharmacology review referred to above showed that use of the intact tablet dissolved in juice resulted in exposures similar to those seen with the PFOS concentration. In response to an Agency Information request (IR), the applicant provided data that 5 patients on Study CA180372 received at least one dose of intact tablet dissolved in juice as per the protocol instructions. No PK data were available for these patients, and given the small number, no definitive efficacy or safety conclusions can be made on this subset. See Section 6.2.2 for full details of these analyses.

Reviewer comment: (b) (4) ***the 5 patients treated with intact dasatinib tablet dissolved in juice on Study CA180372 are part of the efficacy population and did perform significantly worse or better than the rest of the population enrolled. Further, it is noted that 32/106 treated patients (30%) on study were under 6 years of age, the age at which children are commonly expected to be able to swallow tablets. Although still relatively uncommon, the diagnosis of patients under 6 years of age with Ph+ ALL is not as rare as in the pediatric CML population, and the PI should include a description of the dissolution method, with its limitations and caveats, to allow prescribers to make an informed decision regarding the use of this particular TKI in patients with newly diagnosed Ph+ ALL who are unable to swallow tablets.***

5.6. Devices and Companion Diagnostic Issues

Studies CA180372 and supporting Study CA180204 both included only patients with Ph+ ALL, defined as documented presence of t(9:22) by cytogenetics or BCR-ABL fusion via RT-PCR or FISH by local laboratory test (CA180372) or from an approved COG cytogenetics laboratory

(CA180204). Some of the secondary objectives of CA180372 included MRD levels. Per protocol, this included MRD by quantitative PCR detection of clone-specific immunoglobulin and T-cell receptor (TCR) gene rearrangements (Ig/TCR) (Section 8.3.2.3) as the method of choice for determination of HSCT eligibility (See Study Design below) as well as for assessment of MRD at each MRD time point (prior to the start of IB, HR1 (the beginning of consolidation), and end of the HR blocks (end of consolidation) as well as prior to HSCT and at the end of treatment), but allowed also for MRD testing by RT-PCR for BCR-ABL or flow cytometry as part of the exploratory objectives, and to be done for HSCT eligibility determination for patients with uninformative PCR for Ig/TCR gene rearrangement at baseline (Protocol CA180372, Amendment 05, Section 3.1, page 27). The applicant proposes the following language in section 14.4 of the prescribing information as part of the current supplement:

(b) (4)

Clinical reviewer comment: (b) (4)

5.7. Consumer Study Reviews

No label comprehension, patient self-selection or other human factors studies were evaluated as part of this submission.

6. Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Table 5. Clinical Trials Relevant to the Pediatric Ph+ ALL Indication

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
Pivotal Study to Support Efficacy and Safety								
CA180372	NCT01460160	Phase 2, open label, multi-center "single arm historically-controlled study"	60 mg/m2/day po, from day 15 of induction, in combination with the AIEOP-BFM ALL backbone (see appendix)	3-year EFS (binomial) 1) Superiority over cohort 2 2) Non-inferiority compared to cohort 3 3) Superiority to cohort 3	2 years	106	Pediatric patients aged >1 to <18 years of age with newly diagnosed, Ph+ ALL	70/5
Studies to Support Efficacy and/or Safety								
CA180204	NCT00720109	Phase 2, open-label, multicenter, single-arm study	60 mg/m2/day po, from day 15 of induction, in combination with the AALL0031 backbone Cohort 1: discontinuous: the above dose during the first 2 weeks of each post-induction block Cohort 2: the above dose continuously with the same backbone	3-year EFS rate in Standard-Risk Ph+ ALL patients in cohort 2	Discontinuous: 70 weeks of a total of 129 weeks Continuous: 128 weeks	Overall: Pediatric: -35 (discontinuous dasatinib) -20 (continuous dasatinib	Children and young adults aged >1 year to <30 years with newly diagnosed ALL and BCR-ABL fusion	47/4

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
Historical Control Studies for CA180372								
AIEOP-BFM ALL 2000 "cohort 2"	NCT01117441	International Collaborative Treatment Protocol for Children and Adolescents with ALL	Same as AIEOP-BFM ALL 2000 used in CA180372	*(for the high-risk cohort): EFS, DFS	104 weeks	61 patients who did not receive a TKI and had follow-up for events	**subpopulation of a much larger study:* Pediatric patients aged 1-18 years with newly diagnosed Ph+ ALL	127
Amended EsPhALL "cohort 3"	NCT00287105	Phase 2, open-label, multicenter study	Same as AIEOP-BFM ALL 2000 used in CA180372, with the addition of imatinib at 300 mg/m2/day continuously	Primary: DFS (2-year)	104 weeks (chemo + imatinib)	155	Pediatric patients aged 1-18 years with newly diagnosed Ph+ ALL	11

Source: FDA Clinical reviewer

6.2. Review Strategy

The key materials used for the review of efficacy and safety include:

- NDA 021986/s021, including the data submitted as part of the initial sNDA as well as responses to Agency IRs
- Relevant published literature
- Relevant information in the public domain
- Very limited descriptions of summary, trial- level data for the historical control cohorts 2 and 3 on the pivotal study CA180372 were submitted as part of this sNDA by the applicant, with an explanation that their requests to obtain more detailed and/or patient-level data from these cohorts from the cooperative group steering committees were denied to due consent issues (Page 74 of the final CSR for CA180372).
    - In an attempt to obtain more robust trial-level and patient level data to allow for a comprehensive review of the results from CA180372 in an informed clinical context, the Agency requested these data from a third party.
        - Limited patient-level data (see section 6.1.2) from both studies were provided by the third party vie email on 11/26/2018. Of note, the applicant does not have access to these data.
        - These data were used as part of the efficacy review as well.

The review of efficacy was primarily based on analysis of Study CA180372, with supportive data from CA180204.

Results from both CA180372 and CA180204 were used to support the analysis of safety. Review emphasis was placed on safety data from the patients on CA180372 treated at the proposed dose and schedule of dasatinib tablet in combination with the AIEOP-BFM ALL2000 multiagent chemotherapy backbone, but pooled safety data were from all patients on CA180372 as well as patients on CA180204 were used to evaluate for potential safety signals.

All major efficacy and safety analyses were reproduced or audited. Summaries of data and statistical analyses by the clinical reviewer were performed using JMP13.0 (SAS Institute, Inc., Cary, NC). MedDRA Adverse Events Diagnostic 1.3 (MAED) (FDA, Silver Spring, MD) was used to look for safety signals. For the results of the primary efficacy analysis the methodologies used by the statistical reviewer were SAS 9.4.

7. Review of Relevant Individual Trials Used to Support Efficacy

7.1. CA180372: A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

7.1.1. Study Design

Overview and Objective

CA180372 is an open-label, multi-center, historically-controlled, Phase 2 study of dasatinib added to successive blocks of standard multi-agent chemotherapy (AIEOP-BFM ALL 2000 regimen) in children and adolescents with newly diagnosed Ph+ ALL.

The primary objective of the study was to compare the 3-year EFS of dasatinib plus chemotherapy (cohort 1) with external cohorts, in hierarchical order, as follows:
1) Superiority over chemotherapy alone of AIEOP-BFM 2000 (cohort 2)
2) Non-inferiority to continuous imatinib plus chemotherapy of the amended EsPhALL trial (cohort 3)
3) Superiority over continuous imatinib plus chemotherapy of the amended EsPhALL Trial (cohort 3)

The trial was to be considered positive if at least the first two comparisons are statistically significant (see statistical analysis plan and comments).

The key secondary objectives were:
1. To determine the safety and feasibility of dasatinib added to standard chemotherapy
2. To estimate the EFS of dasatinib plus chemotherapy (including 3- and 5-year rates)
3. To estimate complete remission (CR) rates (defined as < 5% blasts in the bone marrow and no peripheral blasts) at the end of induction

Other secondary objectives were to estimate:
1. The difference in 3-year EFS rate with the 3-year EFS rate of available historical controls such as the COG AALL0031 study
2. MRD levels (defined by PCR detection of clone-specific immunoglobulin (Ig) and T-cell Receptor (TCR) gene rearrangements)
3. BCR-ABL mutation status at baseline and time of disease progression or relapse

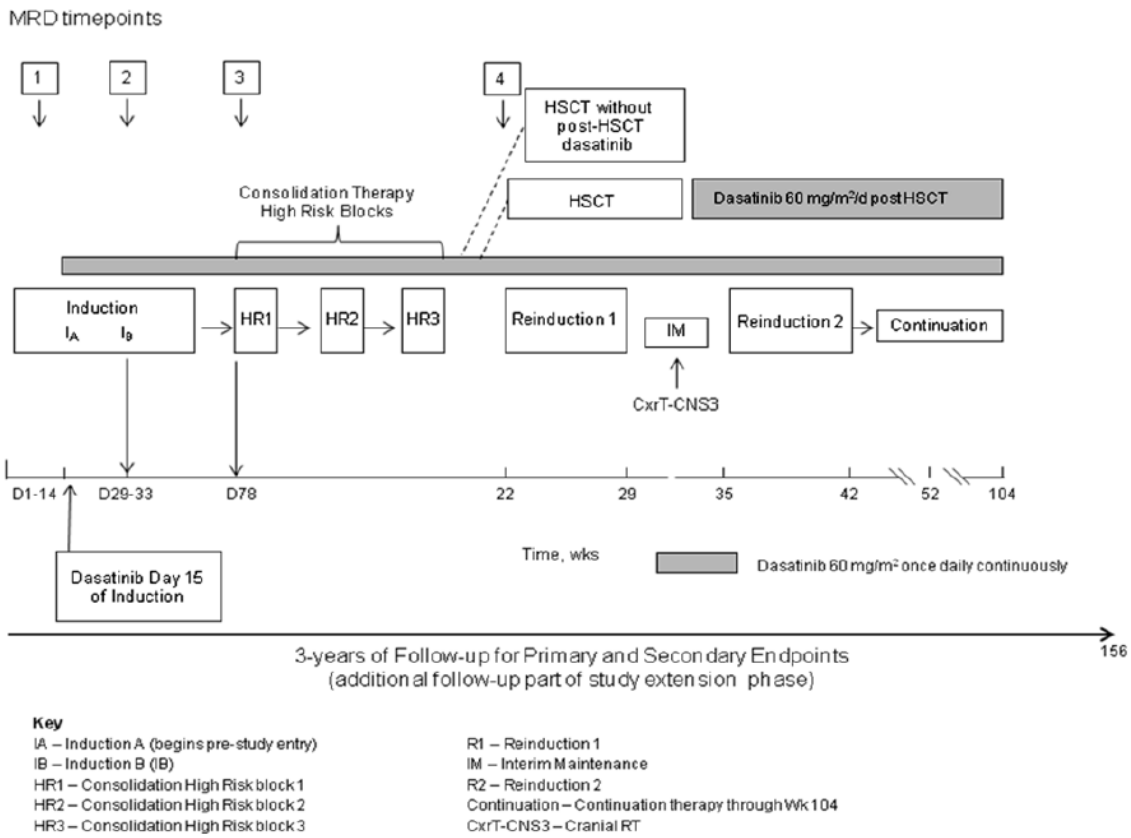
Statistical Reviewer Comment: For the purposes of this review and for labeling, we used the 3-year binomial EFS rate of dasatinib in combination with multiagent chemotherapy in the tablet only group of patients with Ph+ ALL as confirmed by the clinical reviewer based on the data submitted as the primary efficacy endpoint for efficacy evaluation.

Trial Design

The Study schema is shown in **Figure 1**. Children and adolescents (> 1 year and < 18 years old) with newly diagnosed Ph+ ALL were treated with dasatinib at 60 mg/m^2/day orally added to successive blocks of standard multi-agent chemotherapy (AIEOP-BFM ALL 2000 regimen) for a maximum duration of 2 years. Initially, at least 75 pediatric subjects were planned to be treated with dasatinib and evaluable for the primary endpoint, including at least 20 pediatric subjects evaluable for the primary endpoint in each of the following age ranges: 1 to less than 12 years and 12 to less than 18 years.

Subjects began frontline induction chemotherapy (Block IA) prior to enrollment in this study based upon the investigator's institutional standard of care. Subjects with confirmed Ph+ ALL were enrolled in the study, and at day 15 dasatinib treatment began and continued without planned interruption until the completion of therapy (102 weeks).

Figure 1. Study Schema, CA180372



Source: Applicant's CSR, CA180372, Figure 3.1-1, page 36

The components of treatment are divided into blocks as follows:

- Induction IA (4 - 5 weeks)
- Induction IB (28 days, 4 weeks)
- Recovery period (Dasatinib continues, no chemotherapy given;2 - 4 weeks)
- Consolidation blocks 1, 2, and 3 (21 days, 3 weeks each)
- Reinduction block 1, including phase IIA and IIB (63 days, 9 weeks)
- Interim maintenance (29 days, 4 weeks)
- Reinduction block 2 (63 days, 9 weeks)
- Continuation therapy (62 weeks)

These blocks included the following groups of multiagent chemotherapy:

Phase	Chemotherapy Regimen	Phase	Chemotherapy Regimen
1. Induction Block IB	Cyclophosphamide Mercaptopurine Cytarabine Methotrexate	5) 1st Reinduction Block (R1)	Dexamethasone Vincristine Doxorubicin L-Asparaginase Cyclophosphamide Cytarabine Thioguanine Methotrexate
2. High Risk Block 1 (HR1)	Dexamethasone Vincristine Methotrexate Leucovorin Cytarabine Hydrocortisone Cyclophosphamide L-Asparaginase	6) Interim Maintenance (IM)	Mercaptopurine Methotrexate
3. High Risk Block #2 (HR2)	Dexamethasone Vincristine Methotrexate Leucovorin Ifosfamide Cytarabine Hydrocortisone Daunorubicin L-Asparaginase	7) 2nd Reinduction Block (R2)	Dexamethasone Vincristine Doxorubicin L-Asparaginase Cyclophosphamide Cytarabine Thioguanine Methotrexate
4. High Risk Block #3 (HR3)	Dexamethasone Cytarabine Etoposide L-Asparaginase Methotrexate Hydrocortisone	8) Continuation Therapy	Mercaptopurine Methotrexate

Source: Applicant CSR Table 4.1.2, page 38.

For a summary of exact day and doses of each of the chemotherapy components, including hematologic parameters required for the start of each cycle, see Appendix 13.4.

Subjects who met the pre-defined MRD criteria listed below prior to the start of the first consolidation block (HR1) or after the completion of the third consolidation block (HR3) of chemotherapy and had a genotype-matched donor (9/10 or 10/10) were to undergo allogeneic HSCT after HR3 instead of continuing the AIEOP-BFM ALL 2000 regimen, although they could continue on protocol specified therapy while awaiting HSCT. Following engraftment in patients who underwent HSCT, patients had the option of treatment with dasatinib for up to 12 additional months, at the discretion of the treating investigator.

MRD criteria for HSCT referred to above were:

- End of IB/start of HR3: MRD ≥ 0.05% (5×10^{-4}) by Ig/TCR PCR
    - For patients without informative Ig/TCR PCR results: <3-log reduction in MRD as measured by RQ-PCR for BCR-ABL
        - For patients without informative PCR results, flow cytometry results for MRD using the Ig/TCR thresholds above were used.

OR

- End of IB/start of HR1 MRD between 0.005-0.05% (5×10^{-5} to 5×10^{-4}; including "positive but < quantitative range with an assay with a quantitative range of higher than 10^{-5}) by Ig/TCR PCR ***and*** MRD at end of consolidation block 3 (HR3)/start of reinduction block 1 remains positive at any detectable level (providing the assay limit is at least 0.1%).
    - For patients with uninformative Ig/TCR PCR results, positive MRD by RQ-PCR for BCR-ABL was used.
        - For patients with uninformative data from either PCR, flow cytometry was used with the same criteria as for Ig/TCR PCR.

Eligibility criteria (summarized)

1. Ph+ ALL, with documented presence of t(9;22) determined by cytogenetics or BCR-ABL fusion via RT-PCR or FISH (local laboratory)
2. Received induction chemotherapy of approximately ≤14 days per institutional SOC
3. Adequate performance status (PS), defined as Karnofsky or Lansky score of 60% or greater.
4. Adequate hepatic function (direct bilirubin ≤ 3xULN for age, AST/ALT ≤ 10xULN for age), renal function (Creatinine ≤ 1.5xULN for age/gender or CrCl or GFR ≥80 ml/min/1.73m^2), cardiac function (QTc <450 msec and LVEF ≥50% or SF≥27% by echocardiogram)
5. Age >1 year and <18 years, not pregnant, agrees to use contraception.

Patients with prior treatment with a BCR-ABL inhibitor, biopsy proven Ph+ ALL with testicular involvement, active systemic infection associated with septic shock requiring either vasopressor support or mechanical ventilation, known clinically significant disorder of platelet function or cardiovascular disease (including congenital long QT or history of ventricular arrhythmias or

heart block), trisomy 21, history of stem cell transplant or Ph+ ALL occurring as a secondary malignancy were excluded from the study. Also excluded were patients with hypersensitivity to any of the excipients in dasatinib tablets and subjects who were incarcerated or were compulsorily detained for treatment of a psychiatric or physical illness.

Study assessments

Study assessments for patients on Study CA180372 are summarized in **Table 6**.

Table 6. Study Assessments on Study CA180372

Table 5.1A: Protocol CA180372 Flow Chart/Time and Events Table																
Procedure	**Screening[a]**	**IA**	**IB**	**HR1**	**HR2**	**HR3**	**End I/HR Blocks**	**R1**	**IM**	**R2**	**C**	**HSCT Subjects[b] WITH post-HSCT Dasatinib**	**EOT[c]**	**F/U[d]**	**Notes**
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Medical History	X														
Physical Examination	X	X	X	X	X	X		X	X	X	X	X	X	X	Physical exam includes vital signs (heart rate, respiratory rate, blood pressure), height and weight, performance status, and extramedullary assessment prior to the start of each block. End of I/HR blocks perform extramedullary exam only for disease assessment.
Assessment of adverse events	X	X	X	X	X	X		X	X	X	X	X	X	X	
HSCT Summary												X			For subjects who receive a HSCT, summary data will be collected.
Chest X-Ray	X														
12-Lead ECG	X	X						X							Prior to the start of each indicated block and as clinically indicated.

Table 5.1A: Protocol CA180372 Flow Chart/Time and Events Table															
Procedure	**Screening[a]**	**IA**	**IB**	**HR1**	**HR2**	**HR3**	**End I/HR Blocks**	**R1**	**IM**	**R2**	**C**	**HSCT Subjects[b] WITH post-HSCT Dasatinib**	**EOT[c]**	**F/U[d]**	**Notes**
Echocardiogram or MUGA as per local practice	X							X		X					Prior to the start of each indicated block and as clinically indicated.
CBC & Differential	X	X	X	X	X	X		X	X	X	X	X	X		Prior to the start of each block and as indicated **NOTE: In HR1, HR2 and HR3 every 2 days after completion of chemotherapy until recovery as defined in** sections 4.3.1.3-4.3.1.5.
Serum Chemistry	X	X	X	X	X	X		X	X	X	X	X			Chemistry panel includes: BUN (or UREA), creatinine, HCO3, ALT, AST, total bilirubin, direct bilirubin (at screening and if clinically indicated), LDH, Na, K, Cl, Mg, PO4, total serum or ionized Ca and uric acid. Prior to the start of each block and as clinically indicated
Pregnancy Test	X	X	X	X	X	X		X	X	X	X	X	X		For women of childbearing potential pregnancy tests must be performed monthly. The pregnancy test at screening must be performed within 24 hours prior to the start of dasatinib.
CSF sample and analysis	X		X	X	X	X		X		X			X		Cell count including RBC and WBC and cytopathology including blast cells performed at each intrathecal dose
Mutation analysis	X													X	Mutation testing performed at baseline and if evidence of relapse during follow-up. Mutation testing at baseline will be performed off of previously banked diagnostic samples. Bone marrow is preferred specimen, peripheral blood is also acceptable.
Bone Marrow Blast %	X		X	X			X						X	X	And as clinically indicated to confirm relapse

Table 5.1A: Protocol CA180372 Flow Chart/Time and Events Table															
Procedure	**Screening[a]**	**1A**	**1B**	**HR1**	**HR2**	**HR3**	**End I/HR Blocks**	**R1**	**1M**	**R2**	**C**	**HSCT Subjects[b] WITH post-HSCT Dasatinib**	**EOT[c]**	**F/U[d]**	**Notes**
Cytogenetic or Molecular analysis for Philadelphia Chromosome status	X														To be performed via local practice
Bone Marrow MRD Assessment	X			X	X			X					X	X	X	Bone marrow MRD assessments will be assessed via: 1) PCR for Ig/TCR gene rearrangement, 2) PCR for BCR-ABL ratio, and 3) multiparameter flow cytometry. Bone marrow samples prior to each indicated treatment block should be obtained once peripheral blood counts have recovered. Subjects with HSCT and post-HSCT dasatinib should have a bone marrow MRD assessment at 3 and 12 months after transplant. Additional assessments as clinically indicated. If a bone marrow cannot be obtained, assessment could be done from peripheral blood provided the peripheral blood percentage of blasts is ≥ 40%. See Lab Manual for details.
Assessment of survival and second malignancies															X	All subjects should be contacted by phone every 3 months if not seen at the site. Assessment must be performed at the 3 and 5 year milestones following 1st dose of dasatinib. A visit window of one month after each of these milestones is acceptable. In subjects remaining event free at 3 and 5 years, assessments at 3 and 5 years should include at a minimum: CBC with diff, PE for extramedullary relapse and second malignancy. Any death or second malignancy should be reported within

Source: Applicant CSR, Study CA180372, Page 1393-1396.

Dose Modifications for Toxicity of Dasatinib

For hematologic toxicities, no interruption or modification of dasatinib was dictated per protocol unless neutropenia or thrombocytopenia resulted in a treatment delay of >14 days for the next block, dasatinib was interrupted and resumed at the same dose with the start of the next block. If the interruption and delay was ≥7 additional days, a BM assessment was to be performed. If marrow cellularity was <10%, dasatinib continued to be held until ANC recovered to >500/mcl, at which point it was resumed at the previous dose. If cellularity was >10% dasatinib could be resumed, and BM was to be repeated every 7-10 days until chemotherapy treatment continued. For anemia, no dose modification was mandated.

For non-hematologic toxicities, dose modifications followed the recommendations summarized in **Table 7**:

Table 7. Dose Modifications for Dasatinib for Non-Hematologic Toxicities on Study CA180372

Non-Hematologic	
Grade 1-2	No Dose Interruption/Reduction
Grade 2	If does not resolve despite symptomatic treatment, consider interrupting dasatinib Resume at 60 mg/m^2 after recovery to ≤ Grade 1 Consider reduction to 48 mg/m^2 for recurrent events
Grade ≥ 3	Hold therapy until ≤ grade 1 Resume at 48 mg/m^2 after recovery to ≤ Grade 1

Table 4.3.2.1: Dose Modifications for Dasatinib	
Dasatinib Related Event and Severity	**Dasatinib**
Liver Function Tests	
Direct Bilirubin > 5x institutional ULN	Hold until direct bilirubin levels have returned to baseline or < 1.5x institutional ULN. Resume at 60 mg/m^2 Reduce to 48 mg/m^2 if recurrent event
AST/ALT > 15x institutional ULN	Hold until AST/ALT levels have returned to baseline or < 2.5 x institutional ULN Resume at 60 mg/m^2 Reduce to 48 mg/m^2 if recurrent event
Bleeding	
Any bleeding or hemorrhage	Subjects who have evidence of bleeding or hemorrhage of any grade at any site may have dose adjustments or interruption at the discretion of the investigator

Source: Applicant CSR, Study CA180372, Table 4.3.2.1, page 1383-1384.

Concomitant medications:

Therapy for the treatment of Ph+ ALL other than dasatinib or the backbone above was prohibited. Medications associated with prolonged QTc were prohibited, and inhibitors of platelet function or anticoagulants were to be used with caution, as were drugs highly dependent on CYP3A4 for metabolism and with a narrow therapeutic index and strong to moderate CYP3A4 inhibitors and inducers. Avoidance of concomitant use of PPIs or H2 agonists was recommended.

Summary, AIEOP-BFM ALL 2000 and amended EsPhALL Studies

For comparison, details regarding the historical control cohorts using the AIEOP-BFM ALL regimen without a TKI (cohort 2) and the amended EsPhALL study (cohort 3) are summarized here:

AIEOP-BFM ALL 2000 (Cohort 2):

This study was a multicenter study that enrolled 4016 patients with Ph- ALL between the years 2000 and 2006, and an additional 79 patients with Ph+ ALL. Patients were categorized as MRD standard risk (MRD-SR) if MRD was $<10^{-4}$ at both days 33 (time point 1 [TP1]) and 78 (TP2), MRD intermediate risk (MRD-IR) if MRD was positive at 1 or both TPs but at a level of < than 10^{-3} at TP2. Patients with MRD $\geq 10^{-3}$ at TP2 were defined as MRD high risk (MRD-HR), independent of the sensitivity and the number of markers. Patients with Prednisone-poor response (PPR; $\geq$1000 leukemic blasts/mcl in the peripheral blood (PB) on day 8) or failure to achieve remission (i.e., with $\geq$5% leukemic blasts in the bone marrow on day 33, or persistent extramedullary disease) after induction phase IA (induction failure) or those with t(9:22) or t(4:11) were treated in the HR arm irrespective of their MRD results, such that all Ph+ ALL patients were treated on the HR

arm. Treatment on this arm randomized patients to receive 3 blocks of non–cross-resistant drugs followed by protocol III given 3 times versus 3 blocks followed by protocol II given twice in the AIEOP group, or 6 blocks followed by protocol II in the BFM group. Ph+ patients with a matched related donor (MRD) were to undergo HSCT per protocol regardless of MRD results at the various timepoints, and those with only an unrelated donor (MUD) were to undergo HSCT only if they were PPRs. Study objectives for HR patients included EFS and overall survival (OS) after initial remission as well as outcome after reintensification therapy in HR patients. CR was defined based on bone marrow blast percent of <5% in the absence of leukemia in other organs, and EFS was calculated as the time of diagnosis to first failure, including no CR by the end of HR3, relapse, death from any cause, or second malignant neoplasm.

Clinical reviewer comment: It is noted that in the publication of the study (Conter, 2010), 79 patients with Ph+ ALL were reportedly enrolled, while data for only 61 patients were provided to the FDA for analysis. Per the text accompanying the datsets, included were only patients who were treated on this study before the EsPhALL study started; the remaining 18 patients were excluded either because they received TKI, or data were incomplete on treatment received or follow-up). The lack of data submitted with regard to the other 18 patients may further bias the results and also demand caution in inferential comparison between the cohorts.

The differences in treatment betweeen the AIEOP and BFM blocks are not considered significant enough as to disallow for pooling of results from these groups the way these results are being used in this review.

Amended EsPhALL (Cohort 3):

Eligible patients were pediatric patients aged 1-17 years with newly diagnosed Ph+ ALL documented by cytogenetics, PCR or FISH for BC-ABL, who were enrolled at the time on frontline treatment protocols at a number of European and Asian centers. Initially, patients were enrolled and treatment with imatinib began at the time of start of induction B (IB), and the study was a randomized trial whereby patients were stratified as good risk or poor risk, based on early response criteria (defined below), and good risk patients were randomized to receive imatinib in combination with the AIEOP-BFM ALL backbone or chemotherapy alone, whereas poor risk patients all received imatinib in combination with chemotherapy. Good risk patients for those whose protocols included a steroid-only prophase were those who were "Prednisone good responders (PGR)," defined as a blast cell count of $\leq$1000/mcl in the peripheral blood (PB) after 7 days of prednisone and achieved a CR (defined as an M1 bone marrow) after the induction course; for protocols without a steroid only prophase, it included patients who had an M1/M2 bone marrow on day 15 or an M1 bone marrow on day 21 and achieved a CR (as above) after the induction course. Poor risk patients were those who did not achieve the above responses at the above timepoints. Based on the release of COG data showing an improvement of outcomes for a similar population of patients using a TKI,

randomization was eliminated in an amendment in 12/2009 and all patients received imatinib. The revised primary objective of the study was to evaluate in these patients the efficacy and safety of imatinib continuous exposure on top of intensive, BFM-type chemotherapy, with a secondary objective of comparison to historical controls including patients treated with chemotherapy alone (those randomized to chemotherapy alone on that study, as well as the results of the COG AALL0031 study (the study used to support approval of imatinib for the current proposed indication for dasatinib)). The primary endpoint was disease-free survival (DFS), with secondary endpoints of feasibility and safety as well as EFS, survival and others.

Study Endpoints

The primary endpoint of Study CA180372 was the 3-year event-free survival (EFS) rate, where EFS is defined as the time from the starting date of dasatinib until an event and was to be computed using binomial proportions.
Events for EFS are defined as any first one of the following:

- Lack of complete response in bone marrow (see below definition)
- Relapse at any site
- Development of second malignant neoplasm
- Death from any cause

Criteria for Response in Bone marrow (BM) were:
M1: < 5% lymphoblasts (Complete Response in BM)
M2: 5 - 25% lymphoblasts
M3: > 25% lymphoblasts

Patients who did not achieve an M1 bone marrow between the start of dasatinib and the last day of consolidation block HR3/start of first reinduction were considered to have had an event (i.e., induction failure).

Clinical reviewer comment: it is noted that according to this protocol, CR was defined solely by the presence or absence of bone marrow lymphoblasts without regard for peripheral count recovery. The latter is the standard definition of CR, and what has been used for regulatory decision making. For a detailed discussion regarding this issue in the context of this application, see clinical reviewer comment under study results below.

The primary analysis was to compare the 3-year EFS rate of dasatinib plus chemotherapy with the following historical controls:
1. 3-year EFS rate of chemotherapy alone from the AIEOP-BFM 2000 trial (cohort 2).
2. 3-year EFS rate of continuous imatinib added to chemotherapy from the amended EsPhALL trial (cohort 3).

Secondary endpoints included safety and feasibility, EFS rate (per KM estimates), MRD, CRR, and BCR-ABL mutation status.

Exploratory endpoints included disease-free survival (DFS), overall survival (OS), HSCT rate, growth and development and bone mineral content.

Statistical Analysis Plan

Sample size and power calculations

The sample size and power calculations incorporated the following assumptions:
1) a 3-year EFS rate of chemotherapy alone in AIEOP-BFM 2000 of 52%
2) a 3-year EFS rate of continuous imatinib plus chemotherapy (amended EsPhALL trial) of 78%
3) a 3-year EFS rate of continuous dasatinib plus chemotherapy will be 88% (absolute improvement of 10% over imatinib plus chemotherapy)
4) a non-inferiority margin of 5% (corresponding to approximately 1/4 of the effect size of 18% anticipated in the amended EsPhALL trial over the chemotherapy-only historical control)
5) a one-sided type I error rate of 0.05

Based on the above assumptions, a sample size of 75 subjects would yield:
• 100% power to detect a true difference of 36% in 3-year EFS of dasatinib plus chemotherapy (AIEOP-BFM 2000) over chemotherapy alone (AIEOP-BFM 2000).
• 96% power to declare non-inferiority of dasatinib/chemotherapy and imatinib/chemotherapy (EsPhALL).
• 72% power to detect a true difference of 10% in 3-year EFS between dasatinib/chemotherapy over imatinib/chemotherapy (EsPhALL).

Due to regulatory requirements, at least 20 subjects evaluable for the primary endpoint (i.e. all treated subjects) were to be enrolled in each of the following age ranges: 1 to < 12 years and 12 to <18 years.

Primary Analysis:

In the primary analysis the 3-year EFS rate from study CA180372 was to be compared with the 3-year EFS rates from two external historical controls (AIEOP-BFM 2000 and Amended EsPhALL) in hierarchical order, so that the overall experiment-wise one-sided type I error rate was preserved at 0.05.

The comparisons were to be as follows:
1. Superiority over chemotherapy alone of AIEOP-BFM 2000: 3-year EFS rate = 52%.

2. Non-inferiority to continuous imatinib plus chemotherapy of the amended EsPhALL trial: expected 3-year EFS rate = 78%. Non-inferiority margin size of 5%.
3. Superiority over continuous imatinib plus chemotherapy of the amended EsPhALL trial: expected 3-year EFS rate = 78%.

• The trial was to be considered positive if at least the first two comparisons are statistically significant.
• The difference with the 3-year EFS rate from the chemotherapy alone control arm was to be tested first. If that test is significant in favor of dasatinib, then non-inferiority relative to imatinib plus chemotherapy in the amended EsPhALL trial was to be tested. If that test is significant and non-inferiority of dasatinib is declared, then superiority testing of the difference with the 3-year EFS rate in the continuous imatinib added to chemotherapy arm from the amended EsPhALL trial was to be tested in third place.
• The comparison was to be done after the last subject treated has passed the 3-year follow-up period to ensure all subjects had the opportunity for 3-year EFS assessments (no interim analysis for primary endpoint).
• The differences in 3-year EFS rates was to be computed using binomial proportions of subjects who are free of events at 3 years over all treated subjects. Subjects lost to follow-up at any time without an event were to be considered even- free in the primary analysis. All subjects were to have the opportunity to be followed for 3 years prior to the analysis and the denominator was to include all treated subjects.
• Event rates were to be provided with exact 2-sided 90% Clopper-Pearson CI's. Differences in event rates were to be tested at the 0.05 1-sided significance level using a Pearson $\chi 2$ test.
• Non-inferiority testing against the study treatment in the amended EsPhALL trial was to be carried out using the corresponding 2-sided 90% CI for the treatment difference (3-year EFS rate in dasatinib+chemo minus 3-year EFS rate in imatinib+chemo) and comparing the lower confidence limit to the non-inferiority margin of -5%. This margin corresponds to 1/4 of the effect size of 18% anticipated in the amended EsPhALL trial over the chemotherapy-only control of the original EsPhALL trial.
• Analyses were to be conducted in the treated population. Interim analyses for DMC reports didn't include evaluation of EFS rates versus those in the historical external controls. Stopping rules were to come into effect only when poor interim EFS results were observed and the Type I error related to the primary analyses was not affected.
• In addition to the above analyses on all treated subjects, the same analyses were to be performed on subjects with uncontested Ph+ ALL at diagnosis, such that any subject that was considered during treatment not to have Ph+ ALL (e.g. CML in blast crisis), was to be excluded.

Statistical reviewer comment: The applicant provided the statistical analysis plan, and the results of their sample size and power calculation were confirmed and calculated by the FDA statistical reviewer. No record showed this primary analysis testing method was agreed upon by the FDA. Due to the limited information available for the two historical control study

datasets, AIEOP-BFM 2000 and Amended EsPhALL, patient-level comparison between the three cohorts is not feasible. The number of available important prognostic variables provided in the historical studies and/or study CA180372 is limited; due to these missing data, and the small sample sizes of the studies, an adequate analysis that considers the non-randomized nature of the comparison using historical control data, e.g. the propensity score method, is not used in this review.

Clinical reviewer comment: At the pre-sNDA meeting in February 2018 the limitations of the proposed approach, using historical controls for a TTE endpoint as described above, was reiterated by the Agency and included in the meeting minutes (see Section U.S. Regulatory Actions and Marketing History ***and*** Table 3***).***

Protocol Amendments

Date	Major protocol amendments
20-Sep-11	Amendment 1 • Changing the statistical design of the trial to allow comparison to historical external controls.
7-Dec-12	Amendment 2 • Introduce a new pediatric formulation of dasatinib (Powder of Oral Solution - PFOS) • BCR-ABL mutation status at baseline and at time of progression moved from being an exploratory objective to a secondary objective • Allow Philadelphia chromosome positivity from peripheral blood to be acceptable for study entry. • Expand the window for screening activities to 21 days. • Modify the definition of high risk group and low/standard risk group in response to Induction 1A treatment. The high-risk group will be defined by a MRD ≥ 0.01%; low/standard risk will be defined as day 29 MRD < 0.01%. This approach is consistent with the criteria used in other COG trials, and/or NCI risk group and being adopted by EsPhALL trials.
31-Jul-13	Amendment 3 • Increase of the number of treated subjects from 75 to at least 75 and up to 90. • Incorporate recommendations for subject management and supportive care during High Risk (HR) Blocks 1-3
28-Oct-13	Amendment 4 • Addition of mandatory supportive care measures during the 3 High Risk blocks

Summarized from Applicant CSR for Study CA180372, "Document history," page 1324-1325.

7.1.2. Study Results

Compliance with Good Clinical Practices

The applicant stated in M, section 4.2 of the CSR for CA180372, that the study was conducted in

accordance with GCP by qualified investigators using a single protocol to promote consistency across sites.

Financial Disclosure

A summary of financial disclosures for the studies included in the submission is provided in appendix 13.2. The applicant submitted financial disclosure information from all but 3 of the investigators and subinvestigators from (b) (6) and all but 19 investigators and subinvestigators from (b) (6) For (b) (4), 1 investigator, (b) (6) (b) (6) of (b) (6) in (b) (6) reported disclosable financial information in the category of significant payments of other sorts due to $104,000 in an individual account. The applicant attempted to obtain further information regarding the type of individual account, however (b) (6) and is no longer an Investigator at the site. (b) (6) patient was treated at this site. An additional 2 investigators had a Form 3454 of due diligence certified for them. This included 1 investigator at site (b) (6) which had (b) (6) enrolled or treated, and another at site (b) (6) b) (6), which had (b) (6) patient enrolled and treated. No financial interests or arrangements were reported for any of the remaining investigators or subinvestigators for (b) (6).

Clinical reviewer comment: Since only (b) (6) of (b) (6) patients on (b) (6) was enrolled and treated at this site, this disclosure does not appear to compromise the integrity of the trial data, nor impact the approvability of the application. For further details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 13.2 Financial Disclosure*)*

Patient Disposition

Using a data cut-off of 7/26/2017, 109 subjects were enrolled and 106 were treated with dasatinib: 71 subjects aged 1 to less than 12 years old and 35 subjects aged 12 to less than 18 years old. Patient disposition on Study CA180372 according to the applicant and according to FDA analysis is outlined in **Table 8**. In the review of disposition, any instances of physician decision where there was sufficient investigator reported information to more clearly code the reason for treatment discontinuation was adjudicated by FDA. In the FDA analysis lack of efficacy included disposition events coded as disease progression, lack of efficacy, relapse, or change in therapy not in CR.

Table 8. Patient Disposition, Study CA180372: Applicant Report and FDA Adjudication

	Applicant Analysis	FDA Adjudication			
		Treatment Group			
	All treated patients N=106 n (%)	All treated patients N=106 n (%)	Tablet only N=82[a] n (%)	PFOS administered N=24 N (%)	Tablet only, uncontested Ph+ ALL N=78 n (%)
Completed Treatment	78 (74)	78 (74)	59 (72)	19 (79)	56 (72)
Discontinued Early	28 (26)	28 (26)	23 (28)	5 (21)	22 (28)
Reason for early discontinuation					
Lack of efficacy	3 (3)	4 (4)	4 (5)		4 (5)
HSCT		6 (6)	5 (7)	1 (4)	5 (6)
AE		2 (2)	2 (2)	-	2 (3)
Decision not to give dasatinib post HSCT		4 (4)	3 (4)	1 (4)	3 (4)
AE[b]	10 (9)	7 (7)	7 (9)	-	7 (9)
Death	2 (2)	4 (4)	2 (2)	2 (8)	2 (3)
Physician Decision	-	3 (3)	1 (1)	2 (8)	1 (2)
Consent withdrawal	4 (4)	3 (3)	3 (4)	-	3 (4)
Misdiagnosis (CML)[c]	-	1 (1)	1 (1)	-	-
Other	9 (9)	-	-	-	-
HSCT Data	-				
Eligible		19 (18)	15 (18)	4 (17)	15 (19)
Planned		16 (15)	12 (15)	4 (17)	12 (15)
Done		15 (14)	12 (15)	3 (13)	12 (15)
Reason no HSCT[d]					
Not in patient's best interest		2[e]			
Death		1			
"MRD negative"		1			
No donor available		1			

Source: FDA reviewers; [a]This analysis was done prior to this reviewer's awareness that patients patient (b) (6) had been miscoded in the data sets as having received tablet only when in fact the patient received PFOS for the first 18 months of the study, so that patient is included in the "Tablet only" group here. [b]Per the applicant's analysis, 8 of these patients had dasatinib discontinued early for AE, an additional 2 had it discontinued for "study drug toxicity." Since these were considered to be synonymous per FDA, they are combined in this row of the table. [c]An additional patient was also noted to have been misdiagnosed with ALL when the actual diagnosis was CML (see text that follows table). That patient completed the 2 years of protocol-dictated therapy and thus is not included among the count of patients who discontinued early; [d]Given for only 5 patients; [e]1 due to residual neurological deficit and reason not given in the other patient.

One of the 82 "tablet only" patients with uncontested Ph+ ALL (USUBJID (b) (6)) who withdrew due to parent consent withdrawal had her dose held on day 23 for fever and rash, resumed dasatinib at the previous dose, had it held again from days 25 to 58 due to worsening rash, and then resumed on day 59. It was then held again due to neutropenia causing a delay of >14 days in the start of the next dose, and then resumed on day 79. On days 97-105 the patient

got 123% of the dose due to an error in taking 4x20mg tablets instead of 3 of these and 1x 5 mg tablets, and the parent withdrew consent on day 109, such that it appears at least possible that the reason for discontinuation in this case was actually due to toxicity, but this is not definitively the case.

One hundred and nine subjects were enrolled and 106 were treated with dasatinib: 71 subjects aged 1 to less than 12 years old and 35 subjects aged 12 to less than 18 years old. Patient disposition on Study CA180372 according to the applicant and according to FDA analysis is outlined in **Table 8**. In the review of disposition, any instances of physician decision where there was sufficient investigator reported information to more clearly code the reason for treatment discontinuation was adjudicated by FDA. In the FDA analysis lack of efficacy included disposition events coded as disease progression, lack of efficacy, relapse, or change in therapy not in CR.

Table 8 above includes data from all of the 106 patients enrolled and treated on Study CA180372. It is noted that ultimately, only 78 were included in the efficacy analysis due to the following considerations:

24 patients received at least one dose of PFOS on study, exclusively (n=8) or in combination with the tablet (n=16). See Section 4.5 above for a summary of the clinical and clinical pharmacology data using the PFOS formulation. While a PK substudy is ongoing to obtain more data regarding the PFOS formulation, CA180372 used PFOS at the same dose and schedule as that used for the tablet (60 mg/m2/day).

Clinical reviewer comment: As described previously and in the clinical pharmacology review, (b) (4) ***. As such, the efficacy population upon which approval is based is limited to the 82 patients who received only the tablet formulation of dasatinib on Study CA180372. See*** Executive Summary ***and*** Prescription Drug Labeling ***for regulatory considerations related to this approval in the pediatric population without a pediatric formulation.***

Among the 82 patients who received the tablet form of dasatinib exclusively on Study CA180372, 4 patients (b) (6) were initially identified upon FDA review as not having met the essential inclusion criteria for the trial, namely having a diagnosis of newly diagnosed Ph+ ALL. Patients (b) (6) were found to have been misdiagnosed with ALL, when they actually had CML (in blast phase, thus that the misdiagnosis is not as difficult to imagine in this clinical setting, given the similarities between the two; these data were included in the ADSL dataset under the "uncontested Philadelphia+ ALL flag" which was not yes for these 2 patients, as well as in the CSR under protocol deviations (Table S.2.3 under the CA180372 CSR). The first was taken off study after almost a year of therapy by parents' withdrawal of consent

because of the misdiagnosis, and the second completed 2 years of therapy despite this fact. The additional 2 patients ((b) (6) do not have documented M3 bone marrow examinations at screening that allow for confirmation of an ALL diagnosis: (b) (6) had 1% blasts at the start of therapy and no BM or PB blasts from any date prior, including screening. FISH did show 188/200 cells that were Ph+, but the diagnosis of ALL cannot be confirmed. For (b) (6) there are no BM results included in the data submitted prior to day 46, and the patient had no peripheral blasts, such that he was initially excluded from the efficacy population. However, based on the ZL dataset, the patient had 20% peripheral blasts at screening, and based on ADBL he had a positive RTPCR for the BCR-ABL fusion, so he was ultimately included in the efficacy population.

Finally, the applicant CSR (page 67, Section 6.1) pointed out that patient USUBJID (b) (6) (b) (6) was identified in the database as having received tablet only, but actually received PFOS for the first 18 months and tablet for the next 6 months. (The source of the error was that the site inadvertently entered "tablet, for suspension" when they should have entered "liquid" as the formulation on the CRF).

Clinical reviewer comment: It is notable that for a randomized study, the protocol deviations above would not necessarily have led to a change in the efficacy population, although they would have necessitated performance of a sensitivity analysis that included and excluded these patients on both arms, as the randomization would have served as a safeguard to protect against biased results due to the inclusion of these patients on both arms. Given the limitations of the patient level data in this submission (see Executive Summary***), and interpretation of this study mostly as a single arm study with exploratory comparison to those limited data, patients not confirmed to have Ph+ ALL based on the data submitted, or those who received the PFOS formulation, including the patient who was labeled as "tablet only" but actually received mostly PFOS, cannot be included in the labeled efficacy population.***

While disposition beyond lack of CR by the end of HR3, relapse, death from any cause or secondary malignant neoplasm were not submitted for the historical controls, data regarding subsequent HSCT was provided for these patients. Of the 61 patients treated with the AIEOP-BFM backbone chemotherapy without a TKI and with adequate follow-up on Study AIEOP-BFM ALL2000, 45 had a subsequent HSCT (74%), including 35 who had an HSCT in CR1 (57%).

Clinical reviewer comment: The fact that only 14-15% (see Table 8***) of patients on CA180372 went to HSCT post dasatinib therapy strengthens the EFS results of this study when compared to historical controls treated with chemotherapy alone, since the majority of those patients proceeded to HSCT. Even if, due to the factors described elsewhere in this review, stemming from the inherent flaws in using historical comparisons, the differences in EFS are less robust than they would be if the same outcomes were found in a randomized trial, the fact that patients receiving dasatinib could in the vast majority of cases be spared the intensive***

subsequent HSCT procedure, with its attendant short and long-term morbidity and mortality risks, that is another clinical benefit conferred by dasatinib, and should be weighed into the risk: benefit assessment.

Protocol Violations/Deviations

The applicant detected 42 "clinically relevant" protocol deviations, defined as "significant" deviations that were "pre-specified, programmable, and defined as events that may have had considerable impact on the outcome of the study or interpretation of the results of the study" (Applicant's Final CSR, CA180372, Section 43, page 56). Overall, they identified 42 such deviations in 40 subjects, 40 of which were due to the use of concomitant medications with QTC prolonging potential, and the same 2 patients described above who were misclassified as having Ph+ ALL when they actually had blast-phase CML. With regard to the patients who received concomitant medications with QTC prolonging potential, the applicant noted that none of them experienced QTc prolongation of <450 msec on study. With regard to the 2 patients who were misdiagnosed as having Ph+ ALL, the applicant concluded that "Inclusion of these 2 subjects in analysis did not impact interpretability of study results."

Clinical reviewer comment: As described above, the 2 patients who did not actually have Ph+ ALL should not be included in the primary efficacy population. With the exception of these 2 patients, these protocol deviations do not appear to significantly impact study results, or their interpretation.

Table of Demographic Characteristics

The demographic and baseline disease characteristics of the various populations treated on Study CA180372 are summarized in Table 9 and Table 11 below.

Table 9. Demographic characteristics, Study CA180372

Demographic Parameters	Treatment Group			
	All treated patients (N=106) n (%)	Tablet only (N=82)[a] n (%)	PFOS administered (N=24)[a] N (%)	Tablet only, uncontested Ph+ ALL (N= 78) n (%)
Sex				
Male	57 (54)	45 (55)	12 (50)	43(55)
Female	49 (46)	37 (45)	12 (50)	35(45)
Age				
Median (years)	9.3	10.5	4.2	10.4
Min, max (years)	1.6, 17.9	2.6, 17.9	1.6, 13.9	2.6, 17.9
Age Group				

Demographic Parameters	Treatment Group			
	All treated patients (N=106) n (%)	Tablet only (N=82)[a] n (%)	PFOS administered (N=24)[a] N (%)	Tablet only, uncontested Ph+ ALL (N= 78) n (%)
< 18 years	106 (100)	81 (100)[a]	25(100)	78 (100)
<2 years	4 (4)	-	4 (17)	-
2-<12 years	67 (63)	48	29 (79)	45 (58)
2-<6 years	28 (26)	17	9 (38)	17 (22)
12-<18 years	35 (33)	34	1 (4)	33 (42)
1-<10 years*	58 (55)	36	17 (71)	36 (46)
Race				
White	85 (80)	66 (81)	19 (79)	64 (82)
Black or African American	13(12)	9 (11)	4 (17)	7(9)
Asian	5(5)	5 (6)	0	5(6)
American Indian or Alaska Native	1(1)	0	1(4)	0
Native Hawaiian or Other Pacific Islander	1(1)	1 (1)	0	1(1)
Other	1(1)	1 (1)	0	1(1)
Ethnicity				
Hispanic or Latino	24(23)	19 (23)	5 (21)	19(24)
Not Hispanic or Latino	55(52)	40 (49)	15 (63)	36(46)
Not reported	27(26)	23 (28)	4 (17)	23(29)
Region				
United States	76 (72)	58(71)	18(75)	54(69)
Ex-US	30(28)	30(29)	6(25)	24(31)
Australia	3(3)	2(2)	1(4)	2(3)
Canada	2(2)	2(2)	0	2(3)
Great Britain	12(11)	9(11)	3(13)	9(12)
Italy	13(12)	11(13)	2(8)	11(14)
Karnofsky/Lansky Performance Score				
90-100	73 (69)	60 (73)	13 (54)	56 (72)
70-80	26 (25)	18 (22)	8 (33)	18 (23)
60	4 (4)	2 (2)	2 (2)	2 (3)
Missing	3	2 [a] (2)	1 [b] (1)	2 (3)

Source: FDA reviewers; *included as a separate category for relevance to the NIH risk stratification, see text.; [a]With the exception of the age breakdown, this analysis was done prior to this reviewer's awareness that patients patient (b) (6) had been miscoded in the data sets as having received tablet only when in fact the patient received PFOS for the first 18 months of the study, so that patient is included in the "Tablet only" group here. [a]Two patients ((b) (6) and (b) (6)) had missing performance scores [b]One patient ((b) (6)) had a missing performance score.

To facilitate any comparison between the outcomes of Study CA180372 using dasatinib in combination with the AIEOP-BFM ALL2000 backbone alone (without a TKI), or with the amended EsPhALL2010 data using the same AIEOP chemotherapy backbone in combination with imatinib rather than dasatinib, the available demographic data from these 2 studies were

analyzed by FDA and are summarized in Table 10 below.

Table 10. Demographic Characteristics, Study AIEOP-BFM ALL2000 and Amended EsPhALL2010 Study

Demographic Parameters	Treatment Group	
	AIEOP-BFM ALL2000 (no TKI) N=61 n (%)	Amended EsPhALL2010 (Imatinib + AEIOP backbone) N=155 n (%)
Sex		
Male	41(67)	99 (64)
Female	20 (33)	56 (36)
Age		
Median (years)	7.6	8.8
Min, max (years)	1.1, 17.1	1.3, 17.9
Age Group		
< 18 years	61 (100)	155 (100)
<2 years	5 (8)	8 (5)
2-<12 years	37 (51)	104 (67)
2-<6 years	19 (31)	43 (28)
12-<18 years	19 (31)	43 (28)
1-<10 years*	36 (59)	93 (60)
Race	N/A	
Ethnicity		
Region[a]		
United States	-	-
Ex-US	61 (100)	155 (100)
BFM	39 (64)	19 (12)
AIEOP	22 (36)	21 (14)
FRALLE	NOT APPLICABLE	38 (25)
MRC		22 (14)
PINDA		17 (11)
NOPHO		15 (10)
DCOG		9 (6)
COALL		5 (3)
CPH		5 (3)
Hong Kong		4 (3)
Karnofsky/Lansky Performance Score	N/A	

Source: FDA reviewers; *included as a separate category for relevance to the NIH risk stratification, see text. N/A, not available. [a]This pertains to the regional protocol used, not necessarily the region where the patients were treated.

Statistical review comment: This side-by-side table shown above is not intended for formal between-group comparison.

Other Baseline Characteristics

Disease characteristics at baseline, including those associated with outcomes such as WBC at diagnosis, NCI risk category, disease immunophenotype (e.g. B-cell precursor (BCP) or T-cell), and CNS involvement, for Study CA180372 are summarized in **Table 11** below.

Table 11 Baseline Disease Characteristics, Study CA180372

	Treatment Group			
	All treated patients (N=106) n (%)	**Tablet only (N=82)[a] n (%)**	**PFOS administered (N=24) N (%)**	**Tablet only, uncontested Ph+ ALL (N= 78) n (%)**
NCI risk group				
High	75 (71)	61 (74)	14 (58)	57 (73)
Standard	31 (29)	21(26)	10 (42)	21 (27)
ALL Subtype				
Pre-B	104 (98)	82 (100)	22 (92)	78 (100)
T-cell	2 (2)	-	2 (8)	-
WBC at diagnosis				
<50,000/mcl	59 (56)	48 (58)	11 (46)	46 (59)
≥50,000/mcl	47 (44)	34 (41)	13 (54)	32 (41)
CNS disease at baseline				
Yes	14 (13)	13 (16)	1 (4)	13 (17)
No	92 (87)	69 (84)	23 (96)	65 (83)
Extramedullary disease at baseline				
Yes	19 (18)	17 (21)	2 (8)	17 (22)
Prednisone Response (PGR vs PPR)				
Unknown	4 (4)	4 5)	-	4 (5)
Not Applicable[b]	102 (96)	78 (95)	24 (100)	74 (95)

Source: FDA reviewers; PGR, Prednisone Good Response, defined as the presence of <1000 lymphoblasts/mcl of blood after the first 7 days of prednisone therapy; PPR, Prednisone Poor Response, defined as >1000 lymphoblasts/mcl of blood after the first 7 days of prednisone therapy [a]This analysis was done prior to this reviewer's awareness that patients patient (b) (6) had been miscoded in the data sets as having received tablet only when in fact the patient received PFOS for the first 18 months of the study, so that patient is included in the "Tablet only" group here. [b]resumably because the backbone received did not include a steroid-only pre-treatment phase.

Since the study enrolled patients who had confirmed Ph+ ALL and started dasatinib treatment on day 15 of induction, while the backbone induction chemotherapy started prior to knowledge of the patient's Philadelphia chromosome status, data regarding the day 7 prednisone response (for patients treated with induction per the BFM protocols, which contains a week of steroid monotherapy prior to initiation of multiagent chemotherapy) or day 14 or 21 bone marrow response was not included in the submission. In response (11/29/2018) to an Agency IR, the applicant provided an analysis of induction regimens for patients on CA180372 from which it can be concluded that 4 patients on the study ((b) (6) ,

(b) (6) and (b) (6), all of whom received the tablet formulation exclusively, and for all of whom the diagnosis of Ph+ ALL was confirmed by FDA, received induction regimens that started with a week of prednisone only treatment, which would allow for analysis of prednisone response. However, for none of these 4 patients was the applicant able to provide data regarding response to prednisone (day 8 blast count). In that same response, they stated that since the protocol required only a BM assessment at screening, and BM assessments post initiation of dasatinib, day 7, 14 or 21 BM status, another factor that has been reportedly associated with prognosis for pediatric patients with newly diagnosed ALL (Schultz, 2007), remain an unknown disease characteristic in the population treated on CA180372.

Clinical reviewer comment: These missing data contribute to the limitations in comparing the CA180372 study results to those seen with the historical control regimens using chemotherapy alone, or imatinib in combination with chemotherapy.

Baseline disease characteristics for Studies AIEOP-BFM ALL2000 and EsPhALL2010 are summarized in Table 12 below.

Table 12. Baseline Disease Characteristics, Studies AIEOP-BFM ALL2000 and Amended EsPhALL2010

Demographic Parameters	Treatment Group	
	AIEOP-BFM ALL2000 (no TKI) N=61 n (%)	Amended EsPhALL2010 (Imatinib + AEIOP backbone) N=155 n (%)
NCI risk group*		
High	35 (57)	104 (67)
Standard	26 (43)	51 (33)
ALL Subtype		
Pre-B	59 (97)	153 (99)
T-cell	1 (2)	2 (1)
Unknown	1 (2)	-
WBC at diagnosis		
<50,000/mcl	37 (61)	73 (47)
≥50,000/mcl	24 (39)	82 (53)
CNS disease at baseline		
Positive	2 (3)	8 (5)
Negative	56 (92)	146 (94)
Unknown	3 (5)	1 (1)
Prednisone Response		
PGR	46/60 (77)[b]	94/152 (62)[b]
PPR	13/60 (22)[b]	25 /152(16)[b]
N/A[a]	1 (2)	3 (2)

Demographic Parameters	Treatment Group	
	AIEOP-BFM ALL2000 (no TKI) N=61 n (%)	Amended EsPhALL2010 (Imatinib + AEIOP backbone) N=155 n (%)
Unknown	1/60 (2)	33/152[b] (22)
Risk Stratification per EsPhALL[b]		
"Good Risk"	Not available	102 (66)
"Poor Risk"		53 (34)

*Source: FDA reviewers; *High: <1 year of age, >10 years of age, or with WBC of >50,000/mcl at diagnosis. Standard risk: 1-10 years of age and WBC ≤50,000/mcl at diagnosis. N/A, not applicable; [a]Presumably, these patients did not receive induction with prednisone alone, but this is not stated explicitly in the datasets received. [b]This includes 21 patients coded as "unknown," 8 coded as "not performed" and 4 coded as "not assessed," such that it is not known how many got prednisone pre-treatment and should be included in the denominator and how many were not. For the purposes of this table, only the 1 patient on the AIEOP-BFM ALL2000 protocol and 3 patients on the amended EsPhALL2010 protocols were excluded from the denominator for determination of prednisone response. PGR, Prednisone Good Response, defined as the presence of <1000 lymphoblasts/mcl of blood after the first 7 days of prednisone therapy; PPR, Prednisone Poor Response, defined as ≥1000 lymphoblasts/mcl of blood after the first 7 days of prednisone therapy. [b]Risk Stratification per EsPhALL took into account achievement of early response to treatment (based on prednisone response and/or BM on day 15 or 21, depending on the induction protocol used), and achievement of an M1 marrow with no extramedullary disease by the end of Induction IA. "Good Risk" patients included those who achieved an early response, defined as a PGR (see above definition), OR had an M1 or M2 marrow (≤25% BM blasts) at day 15, OR an M1 marrow (<5% blasts) at day 21, and achieved what is referred to as a "CR" by protocol, but was defined as an M1 marrow without evidence of extramedullary disease (independent of peripheral count recovery) by the end of Induction IA. Patients who did not achieve both of these things were defined as "Poor Risk."*

Statistical reviewer comment: Because of the lack of an adequate set of prognosticfactors available for the two historical control studies and study CA180372, and small sample sizes for the external datasets, a formal comparison of the 3-year EFS between study CA180372 and the external control arm cannot be performed.

Clinical reviewer comment: Overall, the available demographic factors appear generally similar between the patients treated with dasatinib on Study CA180372 and those treated on the 2 studies of historical controls used for comparison of outcomes. With regard to disease specific characteristics, the lack of availability of prednisone response for those who received prednisone-only regimens for the first week of induction, or day 7 or 14 bone marrow results, both of which are known to have prognostic significance, for the patients on CA180372, are 2 limitations of the comparison.

Since response to early induction therapy is a powerful prognostic factor in pediatric ALL in general, and in high risk ALL in particular, the missing data with regard to prednisone response, where applicable, or day 7 or 14 BM for all 3 trials, contributes to the uncertainty in comparing outcomes of the CA180372 population to those of historical controls using only the results of the 61 patients with Ph+ ALL treated on AIEOP-BFM-ALL alone. The majority of

patients (75%) receiving chemotherapy alone in AIEOP-BFM-ALL2000 had a good response to prednisone therapy during the first week of induction; this was slightly higher than the 65% PGR rate reported for 61 Ph+ patients treated in the earlier AIEOP/BFM ALL studies (ALL-BFM 86, ALL-BFM 90, AIEOP-ALL 88 and AIEOP-ALL 91, total of 4760 pts with newly diagnosed BCP or T-cell ALL between the years 1986 and 1995; Schrappe M, 1998), and lower than the 10% reported in the 998 evaluable patients with ALL treated on those trials (Reiter, 1994)***. While the latter is expected- the Ph+ population is a higher risk one with disease that is less likely to respond and more likely to relapse- the reason for the higher rate of PGR in the AIEOP-BFM-ALL2000 trial compared to that seen in the prior trials is not clear. However, if this is due to some type of selection bias in the 2000 study, the result would be a population of patients who would be expected to have a better EFS than that actually predicted in the Ph+ population using chemotherapy alone, and would risk that the results of CA180372 would be less likely to detect an improvement over this "falsely" elevated rate seen with the historical controls. As such, this makes the comparison between the CA180372 and AIEOP-BFM-ALL2000 studies more robust, at best, and in general decreases the likelihood that the EFS advantage of the addition of dasatinib to the AIEOP-BFM-ALL2000 backbone is due to differences in population biasing the results in favor of CA180372. As for the overall risk: benefit assessment, the fact that there are no published literature with a 4- or 5-year EFS that exceeds 44% (upper limit of the 95% CI of 53%) for pediatric patients with Ph+ ALL treated with chemotherapy alone (without a TKI; with or without HSCT) helps support the notion that across risk categories, the EFS seen in Study CA180372 with dasatinib added to chemotherapy is better than that expected using chemotherapy alone.***

For comparability with imatinib in combination with the same backbone (as used on the amended EsPhALL2010 study), the combination of PGR, M1-M2 BM at day 14 or M1 BM at day 21 into the "Early responder" category in the dataset provided conflates responses due to prednisone and/or chemo alone with those due to imatinib (which started on day 15 and thus may have contributed to achievement of M1 BM on day 21). Although all of these have been reported to be associated with a better prognosis (with prednisone response being more predictive than day 14 BM response in T-cell ALL and the converse being the case in BCP ALL, (Lauten, 2012)***, it is challenging to distinguish the contribution of dasatinib from that of the induction chemotherapy, and again the comparison to the results of CA180372, where none of the data regarding early responses are available makes that comparison challenging as well. The data regarding PGR and PPR were provided independently, but there is a lot of missing data (see*** Table 12 ***above) which makes interpretation challenging. Using a best and worst case scenario analysis, assuming all of the 33 "missing" patients either achieved a PGR (127/152, 84%) or PPR (58/152, for a PPR rate of 38% and a PGR rate of 62%), neither of which are likely, in the best case scenario, the PPR rates are about 10% higher on the imatinib study overestimating its addition to chemotherapy, or they are around 10% lower than those using chemotherapy alone, and the advantage of imatinib over chemotherapy alone is even more robust. In either case, the rates are not strikingly different from the AIEOP-BFM-ALL***

Study (77%, close to the middle, which is likely where the rate would lie if the missing data were available) using chemotherapy alone; this consistency again provides supportive evidence for the validity of the comparison, albeit descriptive in nature. This consistency also mitigates the concern that the early response rates on CA180372 were so much better than those seen on either of the historical control studies as to define a population with such a better expected outcome that comparison to the historical controls, even descriptively, is not possible at all.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All patients on study received dasatinib in combination with the multiagent chemotherapy backbone from protocol AIEOP-BFM-ALL (see study design above). Just over half of the patients (56%) had a delay of >14 days in the start of consolidation (HR1), and about 23% had a delay of >14 days in the start of reinduction. See Section 8.2.1 (Overall Exposure) for a detailed analysis of cycles completed by treatment group (all patients, tablet only etc.).

Efficacy Results – Primary Endpoint

The 3-year binomial EFS of Dasatinib plus chemotherapy treatment in the FDA efficacy population (n=78) is 64.1% (95% CI: 52.4%, 74.7%).

The statistical analysis results of multiple cohorts based on the methods proposed by the applicant are displayed in Table 13.

Table 13. Summary of efficacy endpoints, applicant's analysis

Endpoint	CA180372 (cohort 1) N = 106	AIEOP-BFM 2000 (cohort 2) N = 61	Amended EsPhALL (cohort 3) N = 137
3-year binomial EFS rate, n/N (%) (90% CI)	70/106 (66.0) (57.7, 73.7)	30/61 (49.2) (38.0, 60.4)	81/137 (59.1) (51.8, 66.2)
Difference CA180372 minus external cohort		16.86 (3.9, 29.8)	6.91 (-3.3, 17.2)
p-value		0.032	0.271

Source: Applicant's CSR for study CA180372, section 7.1, page 73

Per the applicant's analysis, the 3-year binomial EFS rate with dasatinib plus chemotherapy was superior, compared to chemotherapy alone in AIEOP-BFM 2000 (49.2% [90% CI:

38.0, 60.4]), and non-inferior (90% CI: -3.3, 17.2), compared to continuous imatinib plus chemotherapy in the Amended EsPhALL Trial (59.1% [90% CI: 51.8, 66.2]) in all treated subjects, but was not superior.

Statistical and clinical reviewer comment: According to the applicant, their requests to obtain patient level efficacy data for the two external historical control trials (AIEOP-BFM 2000 and Amended EsPhALL) were denied by the respective study steering committees due to lack of subject consent for data sharing with the applicant. However, the applicant was granted permission to access study-level response data. Although the applicant did not provide patient-level data for the historical controls, FDA acquired patient-level datasets of two historical studies from a third party, data not available to the applicant, and did further analyses as described below. (b) (4)

Results in three cohorts are presented in Table 14 for comparison. In the Amended EsPhALL study, the study level summery included 137 patients, which limited the analysis to patients enrolled up to December 2013. In the dataset obtained by the Agency for this study, a total of 155 patients enrolled up to December 2014 were included.

As stated above, only the patients on CA180372 who had confirmed Ph+ ALL and received the tablet formulation exclusively were considered for the efficacy population ("Tablet only group"). The 3-year binomial EFS rate in this group was 64.1% (95%CI: 52.4, 74.7). The 3-year KM estimate EFS rate in this group is 63.3% (95%CI: 51.4, 70.3). In all the studies and subgroup analyses, the 3-year binomial EFS rate is consistent with the 3-year EFS K-M estimate. The statistical reviewer was able to reproduce the study level summary results provided by the applicant.

There were 18 more patients included in the patient level dataset acquired by FDA for the amended EsPhALL study than originally provided by the applicant. The 3-year binomial EFS rate for the 155 patients in the updated dataset is 61.3%, slightly higher than the previous result of 59.1%. Median follow up time for the three studies are 3.9 years, 9.8 years and 4.9 years in CA180372, AIEOP-BFM2000, and the amended EsPhALL study, respectively.

Table 14. Summary of efficacy endpoints, FDA analysis

Endpoint	CA180372 (n =106)	CA180372 Tablet Only (N = 78)	AIEOP-BFM 2000 (n=61)	Amended EsPhALL (n=137)	Amended EsPhALL (n=155)
3-year binomial EFS rate, n/N (%) (95% CI)	70/106 (66.0) (56.2, 75.0)	50/78 (64.1) (52.4, 74.7)	30/61 (49.2) (36.1, 62.3)	81/137 (59.1) (50.4, 67.4)	95/155 (61.3) (53.1, 69.0)
3-year EFS K-M estimate, % (95% CI)	65.5 (55.5, 73.7)	63.3 (51.4, 73.0)	49.2 (36.2.60.9)	59.1 (50.4, 66.8)	60.4 (52.1, 67.7)

Source: FDA reviewers; EFS = event free survival; K-M = Kaplan-Meier; CI = confidence interval.

Statistical reviewer's comments: The lower bound of the 95% CI of 3-year EFS rate of study CA180372 appears to rule out the 3-year EFS rate estimates of study AIEOP-BFM 2000 (external historical control group). There was no substantial difference observed in the observed 3-year EFS rates between study CA180372 and amended EsPhALL. Such comparison should take the missing data regarding comparability of the important prognostic factors between two groups into consideration.

It is noted that the definition of EFS per protocol included failures of induction AND CONSOLIDATION, rather than induction alone as per the standard definition. To better understand the trajectory of patients who received dasatinib in combination with chemotherapy on CA180372, FDA performed the following analyses:

1) Of the 102 patients with documented BMs at the end of induction IA, 3 patients were not in M1.
    a. 3 of these 5 patients achieved an M1 marrow by the end of IB, which is still considered part of induction per protocol
        i. The additional 2 would be considered induction failures per the traditional definition. Since they both achieved an M1 marrow by the end of HR1, they were not considered induction failures per protocol, nor for the EFS definition.
2) The 4 remaining patients who did not have BM assessment by the end of IA all had an M1 response by the end of IB (n=1, (b) (6) not induction failure per either definition) or HR1 (n=3, (b) (6) and (b) (6)).

Clinical reviewer comment: While the novel definition of EFS introduces challenges to interpretation of these results, these are still considered relevant and supportive of clinical benefit for the above reasons. Also, FDA performed various exploratory analyses using

different definitions of EFS (from the time of diagnosis, from the time of start of treatment etc.; see full discussion under CR rates above) in attempt to allow for descriptive comparison between studies such that determination could be made regarding whether the data supported the fact that the outcomes using dasatinib on Study CA180372 were better than would be expected using the backbone chemotherapy alone, and that these outcomes were not substantially worse than those seen using imatinib in combination with the same chemotherapy backbone.

Overall, the results of the FDA analyses of 3-year EFS for the efficacy population on Study CA180372 using dasatinib in combination with AIEOP-BFM ALL2000 backbone chemotherapy regimen in a population of patients in whom long-term EFS results of >45-50% are not reported in the literature, in combination with the submission of limited patient-level data from the AIEOP-BFM ALL study, are sufficient to allow for a conclusion that dasatinib + this backbone are better than the backbone alone in the intended population. This approach is not precedent setting, as a similar approach was taken in support of the imatinib approval for the same indication in 2011; that approval was also based 4-year EFS on a single arm combination study and very limited comparison to historical controls using a much earlier cut-off for the EsPhALL study, which was used only as supportive for safety and efficacy of imatinib, rather than as a comparison. Also, in that application and review, patient-level data for those controls were not available outside of the submission of a CSR.

Data Quality and Integrity

The quality and integrity of the submitted data were sufficient for the reviewers to review the application.

Per the Applicant CSR for Study CA180372, Section 4.2, BMS personnel conducted training including completion of electronic CRFs (eCRFs) and paper CRFs. Data were submitted to BMS using eCRFs and paper CRFs. Data queries for missing or ambiguous information were computer generated by BMS or Accenture personnel and forwarded to the investigator for resolution. Further, sites were managed and monitored by BMS personnel according to internal standard operating procedures (SOPs), and on-site monitoring by the applicant was performed to evaluate the study's progress, verify accuracy and completeness of CRFs, assure that all protocol requirements, laws and regulations were met, and resolve any inconsistencies in the study record. Sites were also audited according to an internal audit plan (by the Research and Development Quality Department of BMS).

Efficacy Results – Secondary and other relevant endpoints

Kaplan-Meier estimate of 3-year EFS rates: Dasatinib in combination with multiagent chemotherapy in the 78 patients of the FDA efficacy population yielded a 3-year K-M estimate

EFS rate of 63.3% (95% CI: 51.4, 73.0).

The 3-year binomial EFS rate (64.1%) in the 78 patients was similar to the 3-year EFS K-M estimate (63.3%). In all treated and Ph+ ALL adjudicated and confirmed population (N=103), the EFS rates are consistent and close to 65%.

Kaplan-Meier estimate of 3-year OS rates: Dasatinib in combination with multiagent chemotherapy in the 78 patients in the FDA efficacy population yielded a 3-year OS rate of 92.2% (95% CI: 83.4, 96.4), and the median OS was not reached. The 3-year OS rate is 91.2% (95% CI: 83.8, 95.3) in all treated and Ph+ ALL adjudicated and confirmed population (N=103), and the median OS was not reached. These results are summarized in Table 15 below.

Table 15. Summary of 3-year EFS Rates and 3-year OS Rates by Kaplan-Meier Estimates

CA180372	All treated and Ph+ ALL confirmed (N = 103)	Tablet Only (N = 78)	At Least 1 Dose of PFOS (N = 25)	At least 1 dose of tablet (n=95)	PFOS only (n=8)
3-year binomial EFS rate, n/N (%)	67/103 (65.1)	50/78 (64.1)	17/24 (68)	62/95 (65.3)	5/8 (62.5)
95% CI	(55.0, 74.2)	(52.4, 74.7)	(46.5, 85.1)	(54.8, 74.7)	(24.5, 91.5)
3-year EFS K-M estimate, % (95% CI)	64.4 (54.3 72.9)	63.3 (51.4, 73.0)	68.0 (46.1, 82.5)	64.6(54.0, 73.4)	62.5(22.9, 86.1)
3-year OS K-M estimate, % (95% CI)	91.2 (83.8, 95.3)	92.2 (83.5, 96.4)	88.0 (67.3, 96.0)	91.5(83.8, 95.7)	87.5 (38.7, 98.1)

Source: FDA statistical reviewer

Complete Remission Rate: In the applicant's CSR, and based on the datasets they created, the CR rate with the combination of dasatinib plus chemotherapy on Study CA180372 was 88.7% at the end of Induction IB and 93.4% at the end of the Consolidation period in all treated subjects. Per the applicant's analysis, the CR rates in subjects treated with tablet only or at least 1 dose of PFOS were consistent with the all treated population.

However, the FDA clinical reviewer adjudicated complete response rates for all patients based on bone marrow blasts counts in addition to recovery of peripheral counts. The latter (CR) is an endpoint that, in contrast to reduction in marrow blast counts without regard for peripheral count recovery, has been discussed by the Agency in public workshops (**Appelbaum, 2007)**, and used for approvals of agents in the treatment of acute leukemias (inotuzumab prescribing information, blinatumomab prescribing information). **Table 16** summarizes CR and CRh* rates at the end of induction (IB) and consolidation (HR3) by FDA adjudication for the efficacy population on Study CA180372. Since the goal of the analysis was determination of the number

of patients who achieved CR by the end of consolidation, and of these for how many this had been achieved by the end of induction, rather than for determination of response duration, the rates are presented cumulatively, such that patients who achieved a CR by the end of induction who then reverted to CRh* by the end of consolidation are still counted as having achieved a CR by the end of consolidation.

Table 16. FDA Adjudicated CR and CRh* Rates Overall, and in the FDA Efficacy Population, on Study CA180372

	FDA efficacy population (N = 78)
M1 bone marrow blasts[a]	
By end of Induction (IB)	75 (96%)
By end of Consolidation (HR3)	76 (98%)
CR	
By end of Induction	62 (79%)
By end of Consolidation (HR3)	65 (83%)
CRh*	
By end of Induction	13 (17%)
By end of Consolidation (HR3)	13 (17%)[b]
CR+CRh*	75 (96%)

Source: FDA clinical reviewer. [a]For this analysis, an M1 marrow is only included as having been achieved in the absence of extramedullary disease, such that USUBJID (b) (6), who technically achieved <5% BM blasts at the end of IB bone marrow assessment is not included due to the documentation of extramedullary disease at that timepoint per the eCRF. It is noted that this patient did achieve an M1 marrow by the end of consolidation. Similarly, USUBJID (b) (6) had a BM assessment with <5% blasts at the end of IB, but had CSF positivity on the same day, which persisted through one of his repeat CSF assessments in the midst of consolidation. However, his next BM with documentation of <5% BM blasts was not done until the reinduction phase, and so this patient is also not counted towards the M1 marrow rates during induction or consolidation in this table. [b]No additional CRh*s were achieved by the end of HR3 that hadn't already been there by the end of IB, and some of the CRhs converted to CRs, such that the final number of CR+ CRh did not change between end of induction and end of consolidation.

Clinical Reviewer comment: Per the statistical analysis plan, since not enough data regarding the historical controls were submitted as to allow for rigorous statistical analyses of the results of CA180372 cohort in comparison to those controls (cohort 2 and cohort 3), neither non-inferiority nor superiority to imatinib + multiagent chemotherapy treatment could be demonstrated with associated statistical significance. As such, the other secondary endpoints such as CR rates cannot be considered as statistically relevant endpoints of this trial either. (b) (4) ***, as proposed by the applicant.***

At the same time, it is recognized that:

a) ***Standard practice in pediatric ALL, especially newly diagnosed ALL, is not to wait until complete count recovery to begin subsequent cycles of therapy, especially during the first 6 months of therapy. Most protocols are written such that once partial recovery of counts is reached, the next cycle begins, and this is how most patients are treated, even when not on clinical trials; it is standard to "push through" as treatment/dose intensity is considered a primary factor in outcome. It would be fairly standard to continue patients through at least the end of consolidation without ever having them achieve a true "CR," as long as they have decreasing blast count percentages in the bone marrow and they have some semblance of peripheral count recovery.***

b) ***It would be informative for treating pediatric hematologist/oncologists to have information regarding the rates of achievement of M1 bone marrows at the end of induction and consolidation with dasatinib therapy on Study CA180372 in order to make treatment decisions.***

c) ***CRh*, which is an endpoint used by the Agency as a clinical benefit endpoint in the context of relatively non-toxic therapies used in patients without curative intent (e.g. relapsed/refractory acute leukemias, or certain subpopulations of newly diagnosed patients, such as the elderly, in adults), is not relevant to the population studied for the proposed indication, namely pediatric patients with newly diagnosed ALL.***

   As such, the relevant endpoint for inclusion in section 14 of the PI for the current indication is rates of M1 marrows, or <5% blasts, at the end of induction and consolidation.

Disease Free Survival: The K-M estimate of 3-year Disease-free survival rate in all subjects treated with dasatinib plus chemotherapy was 65.4%. (95% CI: 55.4, 73.7). The results in the tablet-only group and subjects who used PFOS at least once group were similar to those in the all treated population.

Clinical Reviewer comment: DFS is not an endpoint used for regulatory decision making in this clinical context and is considered descriptive and exploratory only.

MRD Response, Study CA180372
The Applicant proposed inclusion of the following sentence in Section 14 of the PI, for Study CA180372:

(b) (6)

(b) (6)

Per protocol (Section 8.3.2.3), the method of reference for MRD negativity was quantitative PCR detection of the clone-specific immunoglobulin and T-cell receptor gene rearrangements (Ig/TCR), with an assay with a limit of detection of approximately 10^{-4} to 10^{-5} (0.01% - 0.001%). The protocol further specified (section 8.4.2.4) that MRD assessments at various time points were to be done by 3 methods, in central laboratories, to ensure standardization and quality control (QC). The additional to assays described were RT-PCR for BCR-ABL transcript levels, and flow-cytometry. The "primary" assay to be used as the method of reference for enrollment, as well as to compute MRD levels for each subject at each time point, was specified as the Ig/TCR method. It is noted that the day 29 BM MRD results were used for risk stratification on Study CA180372 (amendment 2), determining for which patients allogeneic HSCT would be recommended. While stipulations were made with regard to the use of MRD for these treatment purposes, namely that if Ig/TCR results were not informative, RQ-PCR would be used, and if both of these were uninformative, flow cytometry would be used, for the purposes of response rate computations, in order to allow for an "all treated" analysis, Section 8.4.2.4 of the protocol specified that patients with missing data (e.g. no valid Ig/TCR assessment) would be considered non-responders. "MRD negative" was declared as long as the MRD level was undetectable with an assay lower limit of at least 10^{-3} (0.1%).

However, in response to an IR by the CDRH flow cytometry reviewer, the limit of detection of the flow cytometry assay used for this study was actually 0.01% (see consult memo, J Cleary, 11/27/2018).

Analysis of the MRD results in the 78 patients in the FDA efficacy population revealed that:

1) Only 32/78 had MRD assessed by flow cytometry at some point during induction.
    a. Of these patients, 13/32 had undetectable MRD on this assay (<0.01%) and were in CR
    b. An additional 10 patients had undetectable MRD on this assay and were in CRh
    c. An additional 3 patients had undetectable MRD on this assay and were in CRi (excluding CRh)
2) Fifteen patients had MRD assessed by flow cytometry at some point during consolidation, which included 5 additional patients in addition to 10 patients for whom MRD data by flow cytometry was also available during induction (1 above).
    a. Of these patients, 11/15 had undetectable MRD on this assay and were in CR
    b. An additional patient had undetectable MRD on this assay and was in CRh
    c. An additional patient had undetectable MRD on this assay and had no counts available for determination of CR status.

Reviewer comment: (b) (4)

(b) (4)

Dose/Dose Response

Since most of the patients on Study CA180372 received 60 mg/m2/day of dasatinib, no detailed analysis of dose-response was undertaken by the FDA for this Study. SEE clinical pharmacology review for an evaluation of exposure-response.

Durability of Response

Durability of response is part of the primary endpoint, EFS, and is discussed above.

Persistence of Effect

Since dasatinib treatment is continued for up to 2 years, and median follow-up was 3.9 years at the data cut-off, the primary efficacy result is evidence of persistence of effect beyond

discontinuation of treatment.

Additional Analyses Conducted on the Individual Trial

To test the robustness of CA180372 study efficacy results and to verify that the results are somewhat comparable to the two historical studies, the FDA reviewer conducted additional sensitivity analyses as follows:

1. In both historical studies, EFS was calculated as the time ***from diagnosis*** to a qualifying event, as defined above. In CA180372, EFS was calculated as the time ***from treatment start date*** to the qualifying event. We therefore performed an EFS analysis using the date of diagnosis as the start date for CA180372 as well.
   Using this definition, the 3-year KM estimate EFS rates are the same as in the primary analysis in all treated subjects, and 63.3% (95%CI: 51.4, 73.0) for the FDA efficacy population (n=78).
2. While the binomial 3-year EFS rates was used for the primary efficacy endpoint, sensitivity analyses were done using Kaplan-Meier estimates for EFS.
3. Subgroup analyses were performed looking at patients who did or did not undergo allogeneic HSCT, presenting 3-year EFS rate with 95% CIs for subjects who underwent HSCT, and subjects who did not undergo HSCT. These were done first for all patients who underwent HSCT regardless of whether or not it was in CR1, as well as for those who underwent HSCT in CR1 vs everyone else.
4. In addition, a sensitivity analysis was done where patients who underwent HSCT were censored at the time of transplantation.

The results of 2 -4 above are summarized in Table 17 below.

Table 17. Sensitivity Analyses for EFS for Study CA180372, Cohorts 1, 2 and 3

	CA180372		AIEOP-BFM2000	Amended EsPhALL	
	Cohort 1- all confirmed Ph+ ALL (N=103)	Cohort 1, FDA efficacy population (N=78)	Cohort 2 (N=61)	Cohort 3, Original submission (N=137)	Cohort 3, Updated data (N=155)
3-year binomial EFS rate, n/N, %, 95%CI	67/103, 65.1	50/78, 64.1	30/61, 49.2	81/137, 59.1	95/155, 61.3
	55.0, 74.2	52.4, 74.7	36.1, 62.3	50.4, 67.4	53.1, 69.0
without HSCT	58/88, 65.9	43/66, 65.2	6/16, 37.5	42/66. 63.6	52/78, 66.7
	55.0, 75.7	52.4, 76.5	15.2, 64.6	50.9, 75.1	55.1, 76.9
HSCT	9/15, 60.0	7/12, 58.3	24/45, 53.3	39/71, 54.9	43/77, 55.8
	32.3, 83.7	27.7, 84.8	37.9, 68.3	42.7, 66.8	44.1, 67.2

	CA180372		AIEOP-BFM2000	Amended EsPhALL	
	Cohort 1- all confirmed Ph+ ALL (N=103)	Cohort 1, FDA efficacy population (N=78)	Cohort 2 (N=61)	Cohort 3, Original submission (N=137)	Cohort 3, Updated data (N=155)
3-year EFS K-M estimate, % (95%CI)	64.4 (54.3, 72.9)	63.3 (51.4, 73.0)	49.2 (36.2.60.9)	59.1 (50.4, 66.8)	60.4 (52.1, 67.7)
without HSCT	65.3 (54.3, 74.3)	64.3 (51.4, 74.7)	37.5 (15.4, 59.8)	63.6 (50.7, 73.9)	65.9 (54.0, 75.4)
with HSCT	60.0 (31.8, 79.7)	58.3 (27.0, 80.1)	53.3 (37.9, 66.6)	54.9 (42.7, 65.6)	55.0 (43.1, 65.4)
3-year EFS, censored at HSCT	65.7 (54.7, 74.6)	64.7 (51.7, 74.9)	31.2 (18.7, 44.5)	54.9 (45.6, 63.3)	47.5 (38.5, 56.0)

Source: FDA statistical reviewer.

Clinical reviewer comment: While recognizing the limitations of the post-hoc subgroup analyses, as well as the additional limitations of looking at such small subgroups, especially when the numbers of patients in 1 subgroup (those who did not proceed to HSCT, N=66) on CA180372, are so large compared to the other subgroup (those who did proceed to HSCT, N=12), these data provide additional supportive evidence of efficacy of dasatinib. In cohort 2, patients treated with multiagent chemotherapy without a TKI, a slight majority of patients, 45/61 (74%) eventually proceeded with HSCT (36 in CR1 and 9 at relapse), while only 16/61 (26%) did not. Patients who went to transplant on that study had improved 3-year EFS (53%) compared to those who did not (38%), but strikingly the outcomes for the majority of patients treated with dasatinib on CA180372 (65, 83%) who did not procced with transplant were improved even over the outcomes of those who did proceed to HSCT in cohort 2. Since the numbers in the subgroups are so small, no definitive conclusions can be made with regard to the need for HSCT after dasatinib treatment, but overall these data further support the contribution of dasatinib to the efficacy results in this population of patients treated with dasatinib in combination with multiagent chemotherapy on Study CA180372.

Results for patients who received dasatinib tablet dissolved in juice

Due to the fact that the proposed indication includes a population of patients (<6 years of age) who would not be expected to swallow intact tablets, and there are still insufficient data upon which to support approval of the PFOS formulation, FDA did an exploratory analysis looking at the 5 patients who received the tablet dissolved in juice on Study CA180372. In this analysis, the outcome for these 5 patients was as follows:

One patient ((b) (6) had an EFS of 9 months due to pneumonia 42 days post HSCT Two patients had EFS of 58.8 months (b) (6)) and 39.8 months (b) (6)), and both of these patients were censored at last assessment. Two additional patients had EFS of 34.7 months ((b) (6)) and 26.5 months ((b) (6))- both relapsed at those

points.

Reviewer comment: The small numbers preclude any assessment of efficacy in these patients, and there are no PK data with which to correlate response. However, given that their outcomes seem to reflect overall the general outcome in the efficacy population on the trial, together with the fact that no pediatric formulation is available, and approximately 1/3 of enrolled patients were under 6 years of age, it would be helpful for physicians to have a summary of these data in the PI, without any recommendation to dissolve the tablet, and including the precaution regarding lower exposure in patients receiving dissolved tablet as well as lingering uncertainty regarding its effect on safety and efficacy in this population.

7.2 Study CA180204: Intensified Tyrosine Kinase Inhibitor Therapy (dasatinib: IND# 73969, NSC# 732517) in Philadelphia Chromosome Positive Acute Lymphoblastic leukemia (ALL)

7.2.1 Study Design

Overview and Objectives

Study CA180204 was an open-label, multicenter, single-arm Phase 2 study in children and young adults aged >1 year to ≤30 years with newly diagnosed ALL and BCR-ABL fusion who had enrolled on one of the COG ALL trials or Dana Farber Childhood ALL Consortium (DFCI) trial and should not have received day 15 of induction on those trials. Patients received dasatinib in combination with a multiagent chemotherapy backbone.

The primary objective was to determine the feasibility and toxicity of an intensified chemotherapeutic regimen that incorporates dasatinib for the treatment of the above patient population, and to determine whether intensification of TKI through addition of dasatinib from days 15-28 of induction and substitution of dasatinib for imatinib post-induction in the context of an AALL0031 multiagent chemotherapy backbone and a good early response to therapy would lead to a 3-year EFS of at least 60% in these subjects.

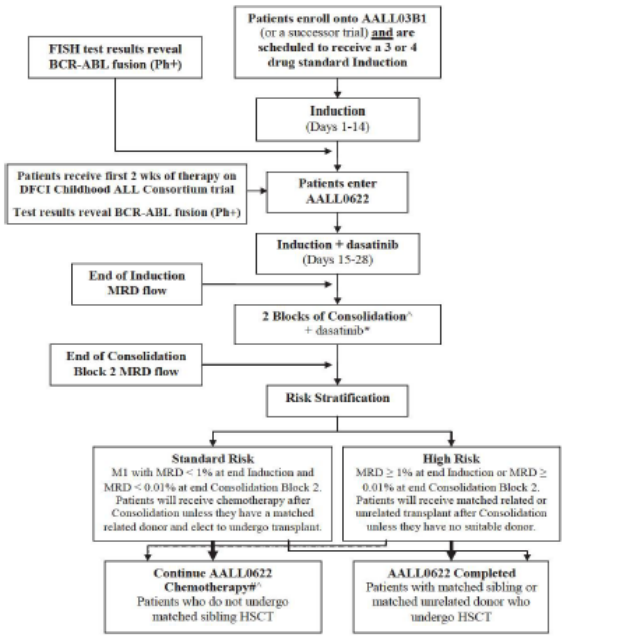
Secondary objective included determination of whether the addition of dasatinib on days 15-28 of induction would decrease levels of MRD at the end of induction compared to patients treated on Study AALL0031, whether early intensified TKI therapy (i.e., addition of dasatinib on days 15 through 28 of Induction) would lower end Consolidation MRD levels as compared to subjects on COG AALL0031 that received imatinib in Consolidation Blocks 1 and 2 (Cohorts 3-5), 3-year EFS rate for the whole cohort of Standard- and High-Risk subjects treated with dasatinib, the long-term effects of dasatinib on growth and development and bone metabolism, assessment of BCR-ABL mutation status at time of diagnosis and progression/relapse, and OS.

Trial Design

The trial schema for CA180204 is depicted in Figure 2 below.

Patient in the safety phase (cohort 1, discontinuous dasatinib) received dasatinib at 60 mg/m2 daily during the first 2 weeks of each 3- to 4-week post-Induction treatment block. If this dose was well tolerated, the subjects in Cohort 2 (continuous dasatinib) received dasatinib treatment at 60 mg/m2/dose daily for the entire treatment block.

Figure 2. Study Design, Study CA180204



*Dasatinib was given in first 14 days of each chemotherapy block for Cohort 1 and was given continuously during each chemotherapy block for Cohort 2.

#Remainder of CA180204 (AALL0622) chemotherapy followed AALL0031-Cohort 5 backbone chemotherapy, but with dasatinib substituted for imatinib. See Section 4.0 of the protocol for treatment details.

^Consolidation Block 1: Testicular irradiation for subjects with clinically evident or biopsy-proven testicular disease at end of Induction.

Source: Applicant's CSR, CA180204. Figure 3.1-1, page 25.

Study monitoring and assessments were similar to those done on Study CA180372, tailored to the different blocks on Study CA180204 given the different backbone regimen. The primary efficacy endpoint was 3-year EFS in Standard-Risk Ph+ ALL subjects in Cohort 2 (continuous dasatinib). Endpoint definitions for EFS was the time from entry on study until any of the following events: induction failure (disease progression during Induction A, defined a M3 BM at end of IA), relapse at any site, secondary malignancy, or death.

7.2.2 Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that this study was conducted in accordance with GCP as defined by the ICH, and in accordance with the ethical principles underlying EU Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

Financial Disclosure

A summary of financial disclosures for Study (b) (6) was provided. Four investigators disclosed financial information due to equity interest of <$50,000 in two investigators ((b) (6)), one who was a (b) (6) (b) (6) of the applicant who had owned stock and/or options in their company ((b) (6) (b) (6)), and one who reported significant payment os <$25,000 (b) (6)). For an additional 15 investigators, a form certifying due diligence in obtaining their financial information without being able to do so was submitted.

Reviewer comment: The large number of investigators for whom due diligence was certified might have an impact on reliability of the study results. However, since this study was used only as supportive evidence of efficacy and safety for this application and did not form the basis for approval, these disclosures do not impact interpretability for this application.

Patient Disposition

Sixty-three patients were enrolled on CA180204 and 62 patients were treated, including 40 patients receiving discontinuous dasatinib and 22 receiving continuous dasatinib. Of these patients, only 55 were under the age of 18, including 35 patients who received discontinuous dasatinib and 20 patients who received continuous dasatinib. Almost half of the patients on study did not complete study therapy (45%); for a majority of these patients this was due to initiation of bone marrow transplantation procedures.

The applicant notes that while the expected number of patients on cohort 2, and thus the expected primary efficacy population sample size, was 73, the study was closed early in order to open the successor study CA180372 (the pivotal trial for the proposed indication, described in 6.1 above) such that the actual number in the primary efficacy cohort was less than 1/3 of what was expected (Applicant's CSR Study CA180204, page 3).

Reviewer comment: Given the small number of pediatric patients treated on CA180204, and the even smaller number of patients treated at the proposed dose and schedule, this trial cannot be used as anything more than supportive of the proposed indication. This is particularly relevant given the time to event endpoint used in this single arm trial. Further, the early closure of this study specifically to open the pivotal study also supports the fact that none of the safety or efficacy information from Study CA180204 should be included in the PI.

Efficacy Results-Primary Endpoint

The primary endpoint was in all subjects, but FDA included only the pediatric patients in the efficacy population. Of the 19 patients treated with at least one dose of continuous dasatinib, the 3-year EFS by KM estimate was 68.4% (95% CI 48.3, 88.6).

Clinical reviewer comment: the wide confidence interval due to the small number of patients renders the results unable to support an efficacy determination with dasatinib using this COG multiagent chemotherapy backbone, since the lower limit is essentially the same as the point-estimate for the AIEOP-BFM ALL 2000 regimen described in section 6.1 above. All of the caveats and limitations regarding the use of historical controls apply here, with the additional fact that the chemotherapy backbone differed, and the overlapping CIs support the fact that these results cannot be used as anything other than supportive for the proposed indication.

8. Integrated Review of Effectiveness

8.1. Assessment of Efficacy Across Trials

Given the multiple limitations of the data submitted with regard to Study CA180204, including small numbers and early closure of the trial due to enrollment on the pivotal study submitted for the current indication, the application and review primarily relies on the results of Study CA180372 to support the efficacy of dasatinib added to standard multiagent chemotherapy in pediatric patients with newly diagnosed Ph+ ALL.

8.2. Additional Efficacy Considerations

8.2.1. Considerations on Benefit in the Postmarket Setting

While patient populations enrolled on clinical trials tend to be more homogeneous than the "real-world" population due to the generally strict eligibility criteria on these trials (Beaver, 2017; Kim, 2017), there are no clear signals noted in this review that would suggest differences in disease response that could be predicted when dasatinib is used in the real-world setting.

8.3. Integrated Assessment of Effectiveness

The efficacy of dasatinib in combination with multiagent chemotherapy in pediatric patients $\geq$ 1 year of age with newly diagnosed Ph+ ALL has been established, primary based on results from the open-label, multi-center, historically-controlled, Phase 2 study of dasatinib added to

successive blocks of standard multi-agent chemotherapy (AIEOP-BFM ALL 2000 regimen) in which the 78 patients with FDA-confirmed Ph+ ALL who received exclusively the tablet formulation of dasatinib in combination with the aforementioned chemotherapy backbone had a binomial 3-year EFS of 64.1% (95% CI, 52.4%, 74.7%). This a population with no 4-5 year EFS of greater than 44% reported in the literature even in patients who undergo allogeneic HSCT, and is further placed in context by the limited data provided for the 61 pediatric patients with Ph+ ALL treated with the multiagent chemotherapy backbone alone on Study AIEFOP-BFM ALL 2000, who had a 3-year EFS of 39% (95% CI, 36%, 62%). Given the similar biology of Ph+ ALL across pediatric age groups, efficacy could be extrapolated to patients under 1 year of age, but since no safety data in this age group were submitted for any indication, the indication should be limited to patients 1 year of age or older.

The limited data provided for Study CA180204, a non-randomized, multicohort, phase 2 study where 35 pediatric patients with newly diagnosed Ph+ ALL were treated with discontinuous dasatinib in combination with a different chemotherapy backbone, and 20 pediatric patients were treated with continuous dasatinib using that backbone, are not sufficient to support approval of dasatinib using the chemotherapy backbone used in this study.

9. Review of Safety

9.1. Safety Review Approach

The key material used for the review of safety included data submitted to sNDA 021986 s-021, relevant published literature, and relevant information in the public domain. The review of safety included data from the pivotal Study CA180372, as well as supportive safety data from CA180204 in pediatric patients with Ph+ ALL treated with dasatinib using the COG rather than the BFM backbone, and relevant data from Studies CA180018, CA180226, and CA180038. Since the latter studies included a more heterogeneous group of patients (patients with various solid tumors and/or relapsed/refractory leukemias, or CML), at various dasatinib doses, and have been extensively reviewed prior to approval of the CML indication (See review in DARRTS by Rachel Ershler, 10/16/2017, as well as the (b) (6) ; (b) (4))), they are referred to in this review only with regard to data relevant to the review of the current submission for the current proposed indication. Since the proposed dose and schedule of dasatinib for the current application is unique to study CA180372, the data from the various studies were not pooled. The number of patients from each trial used to support safety of the proposed dose and schedule in the pediatric Ph+ ALL indication is included in Table 5 above. In an attempt to determine whether the safety and efficacy findings with regard to the PFOS formulation discussed by the clinical and clinical pharmacology teams during review of

NDA 021986-s020 and (b) (4) were consistent to this supplement, the safety data from the 81 patients who received dasatinib as a tablet exclusively on Study CA180372 were reviewed separate from and together with the data from patients who received at least one dose of PFOS on Study CA180372, and an analysis of those who received PFOS exclusively was also undertaken. Since they were treated with dasatinib at the proposed dose and schedule as per Study CA180372, the patients excluded from the primary efficacy analyses due to lack of confirmation of the Ph+ ALL population were included in the safety population and analyses.

9.2. Review of the Safety Database

9.2.1. Overall Exposure

Of the 106 pediatric patients treated with dasatinib in combination with chemotherapy, patients received a median of 23.6 months of treatment (range 2.43 to 27.07 months).

Clinical reviewer comment: the fact that the range of treatment exceeds the 24 months dictated per protocol is likely due to the small number of patients (see below) who underwent HSCT and received dasatinib post-HSCT, which was optional per protocol.

A summary of exposure by subgroup, namely, in patients who received tablet only vs those who received PFOS, is included in Table 18.

Table 18. Exposure to Dasatinib and Backbone Chemotherapy on Study CA180372

	Treatment Group		
	All treated patients (N=106) n (%)	**Tablet only (N=81) n (%)**	**PFOS administered (N=25) N (%)**
Dasatinib			
Median Exposure, months	23.6	23.6	23.4
Range	2.43, 27.1	2.43, 27.1	3.9, 24.9
Median Dose Intensity (%), overall	99%	99%	100%
Range	52-111%	52-111%	82-110%
<90%	29 (27)	27 (33)	2 (8)
<80%	14 (13)	14 (17)	-
Median Dose Intensity (%), end of Consolidation	99% Range: 47-114%	99% Range: 47-114%	99% Range: 77-109%
Backbone Chemotherapy Blocks			
Delay in Start of Consolidation, Y*	101 (98)	78 (96)	23 (92)
Median Duration of Delay (days)	15	17	11
Duration of Delay, range	3-62	3-62	3-29
Delay of >14 days?	52 (49)	45 (56)	7 (28)
Median Duration of Delays >14 days	21	21	21

	Treatment Group		
	All treated patients (N=106) n (%)	Tablet only (N=81) n (%)	PFOS administered (N=25) N (%)
Range	15-62 days	15-62	15-29
Delay in Start of Reinduction, Y	47 (44)	36 (44)	11 (44)
Median Duration of Delay (days)	15	15	12
Duration of Delay, range	1-212 days	1-212	1-50
Delay of >14 days?	24 (23)	19 (23)	5 (20)
Median Duration of Delays >14 days	28	27	29
Range	15-212	15-212	19-50

Source: FDA clinical reviewer; *Block HR1.

Clinical reviewer comment: Although the numbers are small and thus interpretation limited, the fact that the range for dose intensity is overall higher in patients who received the PFOS formulation and that dose delays are shorter (and for the most part less than the 14 days that are considered clinically significant in this treatment context, especially with regard to the start of consolidation) are consistent with the PK findings of lower exposure and clinical findings of lower toxicity in patients with pediatric CML who received this formulation (see review of (b) (4)).

The fact that over 50% of patients in the tablet only group experienced delays in consolidation of >14 days duration and about 1/5 of patients experienced delays of this length during reinduction would present a safety concern with regard to the tolerability of dasatinib added to the AIEOP-BFM ALL 2000 regimen. The fact that the EFS findings were still much improved over that expected with the chemotherapy backbone alone adds support to the contribution of dasatinib to the effectiveness of this regimen, consistent with the data supporting the imatinib approval in the same population as discussed above, and the standard of care inclusion of TKIs in the upfront treatment of this disease.

9.2.2. Relevant characteristics of the safety population:

The Demographics of the safety population are the same as those described in the various efficacy populations, see Table 9 above.

9.2.3. Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions expected to be observed in the population treated with dasatinib on the proposed regimen. Further, the safety profile of dasatinib has been fairly well characterized in the previous submissions that supported the indications approved to date. Being a cooperative group study, Study CA180372 enrolled a population that was fairly representative of patients

with newly diagnosed Ph+ ALL on clinical trials; it is however no exception to the rule that non-white and Hispanic patients are underrepresented compared to the overall population of pediatric patients with ALL in the US (Siegel, 2017).

9.3. Adequacy of Applicant's Clinical Safety Assessments

9.3.1. Issues Regarding Data Integrity and Submission Quality

No major issues involving data integrity or submission quality were identified.

9.3.2. Categorization of Adverse Events

Adverse events were reported down to the verbatim term and were coded using MedDRA version 20.0. CTCAE version 4.0 was used for toxicity grading. Treatment-emergent adverse events (TEAE) excluded events starting and ending before the start of study drug. FDA administered custom queries for selected adverse events of special interest (see Appendix 14.6 for FDA's grouped terms).

9.3.3. Routine Clinical Tests

Routine clinical tests included vital signs, CBC, chemistry, electrocardiograms and echocardiograms or MUGA scans. The frequency of the monitoring was considered adequate.

9.4. Safety Results

9.4.1. Deaths

There were 15 deaths in the 106 patients treated with dasatinib on Study CA180372 (14%), including 11 (14%) of the 81 patients who received only the tablet formulation, and 4 of the 25 patients (16%) who received at least one dose of PFOS. FDA adjudicated causes of death by arm and time of death as related to treatment, as depicted in Table 19 below. Notably, there were no deaths that occurred within the first 60 days of dasatinib treatment.

Table 19. Causes of Death, Study CA180372

	All treated patients (N=106) n (%)	Tablet only (N=81) n (%)	PFOS administered (N=25) n (%)
Overall	15 (14)	11 (14)	4 (16)
COD			
PD	2 (2)	1 (1)	1 (4)
AE	13 (12)	10 (12)	3 (12)
Within 60 days of initiation of therapy	-		

	All treated patients (N=106) n (%)	Tablet only (N=81) n (%)	PFOS administered (N=25) n (%)
On treatment/within 30 days of last dose	5 (5)	3 (4)	2 (8)
COD			
AE	5 (5)	3 (4)	2 (8)
Infection	4 (4)	3 (4)	1 (4)
Unknown (in CR)	1 (0.1)	-	1 (4)
>30 days from last dose	10 (9)	8 (10)	2 (8)
COD			
PD	2 (2)	1 (1)	1 (4)
AE, non-TRM	5 (5)	4 (5)	1 (4)
AE, TRM	3 (3)	3 (4)	-

Source: FDA reviewer; COD, cause of death; PD, progressive disease; AE, adverse event; TRM, transplant related mortality (not in the setting of PD).

The three deaths in the tablet only population adjudicated by FDA to be at least possibly related to dasatinib included:

(b) (6), an 11-year-old female diagnosed with Ph+ ALL on 12/1/2012 who started dasatinib on (b) (6). She presented on day 153 of therapy with lower extremity pain, rash and hypotension with accompanying pancytopenia. She received aggressive fluid resuscitation and treatment with IV antibiotics and antifungal treatment, and urine and blood cultures grew Keblsiella pneumonia and Citrobacter youngae. Her clinical condition deteriorated and despite intubation and vasopressor therapy, she full coded without response to resuscitation errors, and died on day 154 (b) (6), 5 days after receiving her last dose of dasatinib. There is no record of relapse at the time of death, and her last BM assessment on day 87 of therapy showed <5% blasts (3%), down from 90% blasts at screening. Per the applicant CSR, she was in CR at the end of IB on 3/20/2013.

(b) (6) is a 12-year-old female who initiated dasatinib therapy on (b) (6). On day 151 ((b) (6)), she was hospitalized for bacteremia, with a positive blood culture for yeast, and she received broad spectrum antibiotics, antifungals and steroids. Her clinical status deteriorated on day 155 when she developed septic shock requiring fluid resuscitation and vasopressor therapy and was transferred to the pediatric intensive care unit, and on the same day dasatinib therapy was discontinued. She was diagnosed with neutropenic colitis the next day, and her EKG results showed prolonged QTc with a chest x-ray showing bilateral pulmonary edema. Although her condition initially improved, she was transferred back to the PICU on (b) (6) (day 162) and died on day 168 ((b) (6). She had no reported blasts present at the time of death, and her last BM assessment on 10/8/2012 showed <5% blasts (1%), down from 93% blasts at screening. Per the applicant CSR, she was in CR at the end of IB ON 10/31/2012.

(b) (6) was a 12-year-old male who began dasatinib therapy on 8/22/2012. He developed diarrhea on day 652 (6/4/2014), after discontinuing dasatinib therapy on 5/12/2014. with subsequent abdominal pain, nausea, vomiting and jaundice, and was hospitalized with grade 4 enteritis. CT of the abdomen showed diffuse small bowel wall thickening/edema, and blood culture was positive for aerominos sobria. He developed hypotension requiring treatment with broad spectrum antibiotics, vasopressors, hydrocortisone and blood products, but his clinical status continued to deteriorate, and he died on (b) (6) of sepsis. He had no reported blasts present, and his end of treatment BM on 5/18/2014 was still <M1, with 1.5% blasts.

Technically, there were no deaths during induction, defined as IA or IB. There were 3 patients, all of whom died within 15 days of the last dose of dasatinib, 2 of whom received exclusively tablet (b) (6) and (b) (6) and one of whom received at least one dose of PFOS ((b) (6)) who died technically after the end of HR3, but very soon after this date (1, 5 and 15 days later). Since for the first-line treatment of pediatric ALL using treatment regimens such as the AIEOP-BFM ALL2000 backbone, induction failures are not declared until the end of consolidation (HR3), and patients with <5% blasts, and sometimes even those with borderline blast counts that have decreased from diagnosis, continue treatment regardless of peripheral count recovery (most commonly lack thereof), one could make an argument that deaths through consolidation are also "deaths in induction." Even if this broad definition of induction deaths is used, the 3% rate of deaths during induction (3/106; 2/81 patients who received the tablet formulation exclusively (2%)), is still lower than the 5% (3/61) rate seen in the historical controls treated with chemotherapy alone (AIEOP-BFM-ALL). Based on the data submitted for the amended EsPhALL2010 Study, there were no deaths during induction on that study.

Notably, all but 1 of the deaths that occurred >30 days after the last dose of dasatinib occurred at a range of 133 to 959 days after the last dose, with 7/10 occurring >550 days after the last dose. The one that occurred at <133 days was due to pneumonia in a patient who was post-HSCT.

Clinical reviewer comment: Overall, the death rate and early death rates on CA180372 do not raise any red flags with regard to the safety of the dasatinib-AIEOP-BFM ALL backbone combination.

9.4.2. Serious Adverse Events

SAEs occurred in 101 (95%) of all treated patients on CA180372, including 79 (98%) of those who received tablet only and all 8 (100%) of those treated exclusively with the PFOS formulation. The most common SAEs are listed in below.

Table 20.Common (≥10%, or >5% Grade>3) Serious Adverse Events on Study CA180372

	All treated patients N=106 n (%)		Tablet only N=81 n (%)		At least 1 dose of PFOS N=17 N (%)		PFOS only N=8 n (%)	
Preferred Term[a]	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4
Febrile neutropenia	81 (76)	80 (75)	60 (74)	60 (74)	15 (88)	14 (82)	6 (75)	6 (75)
Pyrexia	52 (49)	15 (14)	38 (47)	9 (11)	10 (59)	4 (24)	4 (50)	2 (25)
Mucositis	47 (44)	33 (31)	29 (36)	25 (31)	5 (29)	5 (29)	3 (38)	3 (38)
Diarrhea	34 (32)	24 (23)	26 (32)	19 (24)	5 (29)	2 (12)	3 (38)	3 (38)
Sepsis	31 (29)	n/a[b]	24 (30)	n/a[b]	4 (24)	n/a[b]	3 (38)	n/a[b]
Hypotension	22 (21)	22 (21)	15 (19)	15 (19)	4 (24)	4 (24)	3 (38)	3 (38)
Bacteremia (excluding fungal)	17 (16)	17 (16)	13 (16)	13 (16)	3 (18)	3 (18)	1 (13)	1 (13)
Hypersensitivity	14 (13)	12 (11)	13 (16)	12 (15)	1 (6)	-	-	
Pneumonia (excluding fungal)	19 (18)	19 (18)	13 (16)	13 (16)	6 (35)	6 (35)		
Clostridial infection (excluding sepsis)	13 (12)	10 (9)	12 (15)	9 (11)	-		1 (13)	1 (13)
Renal insufficiency	14 (13)	5 (5)	12 (15)	4 (5)	2 (12)	1 (6)	-	
Abdominal pain	12	5 (5)	11 (14)	4 (5)	-		1 (13)	1 (13)
Musculoskeletal pain	11 (10)	5 (5)	10 (12)	4 (5)			1 (13)	1 (13)
Viral infection	9 (8)	7 (7)	8 (10)	6 (7)			1 (13)	1 (13)
Vomiting	16 (15)	9 (8)	13 (16)	8 (10)	1 (6)	-	2 (25)	1 (13)
Dehydration	11 (10)	9 (8)	8 (10)	7 (9)	1 (6)	-	2 (25)	2 (25)
Pleural effusion	9 (8)	7 (7)	8 (10)	6 (7)	1 (6)	1 (6)	-	
Arrhythmia	6 (6)	5 (5)	5 (6)	5 (6)	1 (6)	-		
Dyspnea	5 (5)	5 (5)	5 (6)	5 (6)	-			
Fungal infection	6 (6)	5 (5)	5 (6)	4 (5)	1 (6)	1 (6)	-	
Rash	9 (8)	6 (6)	7 (9)	5 (6)	2 (12)	1 (6)		
UTI	4 (4)	4 (4)	4 (5)	4 (5)	-			

Source: FDA clinical reviewer; [a]includes grouped terms, see Appendix 14.4; [b]Per CTCAE, sepsis is by definition grade 4.

Reviewer comment: The numbers are too small in the PFOS subgroups as to make any definitive conclusions, but given the higher incidence of serious vomiting and dehydration in the PFOS group compared to the other groups, one wonders If one of the contributing factors toward lower exposures in these patients is due to palatability in the inability to keep the PFOS down, in addition to other factors that may contribute to the exposure differences, as

(b) (4) ***The lack of incidence of hypersensitivity in the PFOS group is consistent with the lower exposures in this population. Similarly, the finding of the AESI pleural effusion in 10% of tablet treated patients compared to its absence in the PFOS population is consistent with these findings as well.***

9.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Of the 106 patients treated with dasatinib on CA180372, 87 (82%) had a TEAE resulting in dose reduction, interruption or permanent discontinuation or interruption of treatment, including 69 (85%) of those receiving exclusively the tablet form. Notably, there were no TEAE leading to permanent discontinuation or dose reduction in the patients who received at least one dose of PFOS, or PFOS exclusively. The most common TEAEs associated with each of these modifications are listed in Table 21, in decreasing order of incidence in the population of patients who received exclusively the tablet form of dasatinib. For interruptions, only those that led to interruption in >2 patients in this population are included in the table. The most common TEAE leading to discontinuation of treatment were infections (fungal sepsis in one patient, CMV in one patient and pneumonia in one patient). The most common TEAE requiring treatment interruption was neutropenia. Unlike with regard to description of rates of TEAE elsewhere in this review, where laboratory abnormalities are included in a separate table based on the ADLB dataset rather than reported laboratory terms, these are included here since in these instances they are listed as the reason for dose modification.

Table 21. TEAE Resulting in Dose Reduction, Interruption or Permanent Discontinuation on Study CA180372

Preferred Term[a]	All treated patients N=106 n (%)	Tablet only N=81 n (%)	At least 1 dose of PFOS N=17 N (%)	PFOS only N=8 n (%)
TEAE resulting in permanent discontinuation	**8 (8)**	**8 (10)**		
Fungal sepsis	See tablet only	1 (1); fatal	-	
GVHD (liver)		1 (1); post HSCT		
Thrombocytopenia		1 (1) each		
CMV infection				
Pneumonia				
Nausea				
Enteritis				
Drug Hypersensitivity				
TEAE resulting in dose interruption	**84 (79)**	**66 (81)**	**11 (65)**	**7 (88)**
Neutropenia	27 (25)	25 (31)	1 (6)	1 (13)
Hepatotoxicity[b]	22 (21)	18 (22)	2 (12)	2 (25)
Febrile neutropenia	23 (22)	17 (21)	3 (18)	3 (38)
Sepsis	18 (17)	15 (19)	2 (12)	1 (13)

Preferred Term[a]	All treated patients N=106 n (%)	Tablet only N=81 n (%)	At least 1 dose of PFOS N=17 N (%)	PFOS only N=8 n (%)
Pyrexia	20 (19)	12 (15)	6 (35)	2 (25)
Diarrhea	14 (13)	11 (14)	3 (18)	
Thrombocytopenia	11 (10)	11 (14)	-	
Vomiting	11 (10)	9 (11)	2 (12)	-
Pleural effusion	7 (7)	7 (9)	-	
Anemia	8 (8)	7 (9)	1 (6)	
Mucositis	8 (8)	7 (9)	-	1 (13)
Hypotension	10 (9)	7 (9)	3 (18)	-
Leukopenia	6 (6)	5 (6)	1 (6)	-
Musculoskeletal pain	5 (5)	5 (6)	-	
Oedema	5 (5)	5 (6)		
Bacteremia (excluding fungal)	6 (6)	4 (5)	2 (12)	-
Clostridial infection	5 (5)	4 (5)	1 (6)	-
Dyspnea	4 (4)	4 (5)	-	
Headache	4 (4)	4 (5)		
Pneumonia	8 (8)	4 (5)	4 (24)	-
Renal insufficiency	5 (5)	4 (5)	1 (6)	-
Viral infection	5 (5)	4 (5)	-	1 (13)
Fungal infection	4 (4)	3 (4)	1 (6)	
Hypoalbuminemia	3 (3)	3 (4)		-
Hyponatremia	3 (3)	3 (4)		
Lower GI haemorrhage	4 (4)	3 (4)	-	1 (13)
Pneumonitis	3 (3)	3 (4)		-
Rash	3 (3)	3 (4)		
TEAE resulting in dose reduction	**13 (12)**	**13 (16)**	-	
Cytopenia	See tablet only	4 (5)		
Neutropenia		4 (5)		
Anemia		1 (5)- also had neutropenia		
Transaminase elevation		2 (3)-1 also had transaminase elevation		
Decreased appetite		2 (3)		
Cough and oropharyngeal pain		1 (1) each		
Arthralgia and headache				
Pleural effusion				
Wheezing				
Weight decreased				
Hypokalemia				

Source: FDA clinical reviewer; [a]includes grouped terms, see Appendix 14.4, with the exception of hepatotoxicity, which is listed for these analyses only and includes the terms: ALT increased, AST increased, blood alkaline phosphatase increased, blood bilirubin increased, GGT increased, hyperbilirubinemia, LFT increased, and

transaminases increased.

Reviewer comment: Again, though limited conclusions can be drawn due to small numbers, the fact that only patients who received exclusively the tablet formulation of dasatinib had TEAE that led to permanent discontinuation or dose reduction of the agent supports the clinical and PK findings for the PFOS formulation revealed in the clinical pharmacology review for this as well as the CML indication, and (b) (4)

In response to an IR sent with the revised PI, received on 12/6/2018, the applicant presented an analysis of the number of patients for whom a treatment block was delayed by >14 days (what would be considered "prolonged" in clinical practice, and per the protocol) for cytopenias. The applicant submitted a listing of the 22 patients who had a dose delay, all but 2 of whom received only the tablet formulation. The delays ranged from 18 to 62 days and occurred during various phases of the protocol. Six of these patients underwent bone marrow assessments at some point during the delay, including 1 patient who had 3 block delays ((b) (6)), who had a 28-day delay of initiation of HR1, a 21-day delay of initiation of HR3, and a 20-day delay of initiation of continuation- and none of them had excessive bone marrow blasts at the time of delay. The outcome of this group of patients with regard to 3-year EFS was not any different than that seen for the efficacy population.

Reviewer comment: these findings support inclusion of the dose modifications on Study CA180372 in the prescribing information for this indication.

9.4.4. Significant Adverse Events

See Section 8.5.1 for an analysis of AESI associated with dasatinib.

9.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment Emergent Adverse Events (TEAEs) of all grades, and grade ≥3, that occurred within 30 days of the last dose of dasatinib on Study CA180372 are depicted in **Table 22**. Since the dasatinib was given in combination with multiagent chemotherapy, and there are not adequate safety data from the historical controls to allow for discrimination between adverse reactions (ARs) clearly related to dasatinib treatment versus those due to the other agents included in the regimen, all ARs within 30 days of the last dasatinib dose were included in this FDA analysis. An analysis of specifically those AESI known known to be associated with dasatinib monotherapy was performed in an attempt to better characterize the incidence of these toxicities when dasatinib is combined with multiagent chemotherapy; this analysis depicted in **Table 22** as well as in sections 9.4.9 and 9.5.1 below.

For all of these analyses, non-laboratory adverse events were analyzed separately from laboratory events. The latter were analyzed based on the laboratory datasets rather than the

reported AE terms, as underreporting of these events on clinical trials, especially cooperative group trials in pediatric oncology, is a well-recognized phenomenon (Miller, 2015; Miller 2018).

Table 22.Common (≥ 10%) Non-laboratory Treatment Emergent Adverse Events, Study CA180372

	All treated patients N=106 n (%)		Tablet only N=81 n (%)		At least 1 dose of PFOS N=17 N (%)		PFOS only N=8 n (%)	
Preferred Term[a]	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4
Mucositis	96 (91)	66 (62)	75 (93)	49 (60)	14 (82)	11 (65)	7 (88)	6 (75)
Febrile neutropenia	94 (89)	93 (88)	70 (86)	70 (86)	17 (100)	16 (94)	7 (88)	7 (88)
Pyrexia	92 (87)	21 (20)	69 (85)	14 (17)	15 (88)	5 (29)	8 (100)	2 (25)
Diarrhea	76 (72)	34 (32)	68 (84)	25 (31)	13 (76)	5 (29)	5 (63)	4 (50)
Nausea	82 (77)	11 (10)	68 (84)	9 (11)	8 (47)	1 (6)	6 (75)	1 (13)
Vomiting	85 (80)	17 (16)	67 (83)	14 (17)	11 (65)	1 (6)	7 (88)	2 (25)
Musculoskeletal pain	82 (77)	25 (24)	66 (81)	20 (25)	12 (71)	3 (18)	4 (50)	2 (25)
Abdominal pain	79 (75)	18 (17)	63 (78)	14 (17)	11 (64)	2 (12)	5 (63)	2 (25)
Cough	78 (74)	2 (2)	63 (78)	1 (1)	10 (59)	1 (6)	5 (63)	-
Headache	73 (69)	14 (13)	62 (77)	12 (15)	9 (53)	1 (6)	2 (25)	1 (13)
Rash	73 (69)	7 (7)	55 (68)	6 (7)	11 (65)	1 (6)	7 (88)	-
Fatigue	61 (58)	2 (2)	48 (59)	2 (3)	9 (53)	-	4 (50)	-
Arrhythmia	49 (46)	11 (10)	38 (47)	10 (12)	6 (35)	1 (6)	5 (63)	-
Hypertension	48 (45)	10 (9)	38 (47)	8 (10)	6 (35)	1 (6)	4 (50)	1 (13)
Oedema	44 (42)	5 (5)	38 (47)	5 (6)	4 (24)	-	2 (25)	-
Viral infection	46 (43)	13 (12)	33 (41)	10 (12)	5 (29)	1 (6)	3 (38)	2 (25)
Hypotension	41 (39)	29 (27)	32 (40)	21 (26)	6 (35)	5 (29)	3 (38)	3 (38)
Altered state of consciousness	30 (28)	5 (5)	24 (30)	3 (4)	2 (12)	2 (12)	3 (38)	-
Hypersensitivity	35 (33)	21 (20)	29 (36)	16 (20)	4 (24)	3 (18)	2 (25)	2 (25)
Dyspnea	32 (30)	9 (8)	28 (35)	8 (10)	3 (18)	1 (6)	1 (13)	-
Epistaxis	28 (26)	5 (5)	25 (31)	5 (6)	1 (6)	-	2 (25)	-
Peripheral Neuropathy	30 (28)	6 (6)	25 (31)	6 (7)	5 (29)	-	1 (13)	-
Sepsis (excluding fungal)	33 (31)	n/a[b]	25 (31)	n/a[b]	5 (29)	n/a[b]	3 (38)	n/a[b]
Fungal infection	27 (25)	10 (9)	24 (30)	9 (11)	2 (12)	1 (6)	1 (13)	-
Pneumonia (excluding fungal)	30 (28)	27 (25)	23 (28)	20 (25)	6 (35)	6 (35)	1 (13)	1 (13)
Pruritis	30 (28)	-	23 (28)	-	4 (24)	-	3 (38)	-
Clostridial infection (excluding sepsis)	25 (24)	14 (13)	20 (25)	11 (14)	2 (12)	1 (6)	3 (38)	2 (25)
UTI	21 (20)	13 (12)	19 (24)	11 (14)	3 (18)	2 (12)	-	

	All treated patients N=106 n (%)		Tablet only N=81 n (%)		At least 1 dose of PFOS N=17 N (%)		PFOS only N=8 n (%)	
Preferred Term[a]	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4
Bacteremia (excluding fungal)	22 (21)	20 (19)	18 (22)	16 (20)	3 (18)	3 (18)	1 (13)	1 (13)
Pleural effusion	21 (20)	8 (8)	17 (21)	7 (9)	3 (18)	1 (6)	1 (13)	-
Sinusitis	18 (17)	9 (8)	17 (21)	8 (10)	1 (6)	1 (6)	-	
Dehydration	20 (19)	9 (8)	16 (20)	7 (9)	1 (6)	-	3 (38)	2 (25)
Renal insufficiency	20 (19)	6 (6)	16 (20)	5 (6)	4 (24)	1 (6)	-	-
Visual impairment	17 (16)	-	16 (20)	-			1 (13)	-
Conjunctivitis	16 (15)	1 (1)	15 (19)	1 (1)	1 (6)	-		
Dizziness	15 (14)	-	15 (19)	-				
Muscle weakness	22 (21)	6 (6)	15 (19)	3 (4)	5 (29)	2 (12)	2 (25)	1 (13)
Haematochezia	14 (13)	1 (1)	12 (15)	1 (1)	1 (6)	-	1 (13)	-
Anxiety	15 (14)	3 (3)	11 (15)	2 (3)	2 (12)	1 (6)	2 (25)	-
Flushing	10 (9)	-	9 (11)	-	1 (6)	-		
Balance disorder	13 (12)	1 (1)	8 (10)	1 (1)	2 (12)	-	3 (38)	-

Source: FDA clinical reviewer; [a]includes grouped terms, see Appendix 14.4; [b]Per CTCAE, sepsis is by definition grade 4.

While the only grouped or preferred terms associated with bleeding that occurred at rates warranting inclusion in Table 22 were epistaxis and hematochezia, it is notable that using the broad SMQ for haemorrhage terms, excluding laboratory terms, the incidence rates in each of the above groups were 57 (70%) in the tablet only group, 8 (47%) in the group that received at least one dose of PFOS in combination with tablet, and 7 (88%) in the group of patients who received exclusively PFOS. These included 47 different hemorrhage terms.

Reviewer comment: The PI for dasatinib already includes a warning and precaution for mylosuppression, including thrombocytopenia, and bleeding events. All patients on CA180372 received dasatinib in combination with multiagent chemotherapy. Aside from including the incidence of hemorraghic events overall in section 6 the PI, this does not appear to require a listing of all of the bleeding events that occurred in this section.

9.4.6. Laboratory Findings

Laboratory abnormalities for the patients who received only the tablet form of dasatinib as well as for those who received at least one dose of PFOS are summarized in Table 23 below.

Table 23: Laboratory Abnormalities, Study 372

	Tablet only N=82				PFOS used N=24			
	All grades		Grades 3-4		All grades		Grades 3-4	
Non-hematologic Parameters								
ALT elevated	79	(96)	39	(48)	24	(100)	15	(63)
Hypocalcemia	68	(83)	15	(18)	20	(83)	3	(13)
Hypokalemia	59	(72)	33	(40)	15	(63)	9	(38)
Hyponatremia	46	(56)	8	(19)	15	(63)	3	(13)
Hypermagnesemia	44	(54)	1	(1)	16	(67)	1	(4)
Hypomagnesemia	40	(49)	1	(1)	11	(46)	-	
Hypophosphatemia	36	(44)	9	(11)	14	(58)	4	(17)
Hyperbilirubinemia	27	(33)	9	(11)	3	(13)	-	
Creatinine elevated	24	(29)	2	(2)	2	(8)	-	
AST elevated	74	(90)	22	(27)	22	(92)	7	(29)
Hyperkalemia	11	(13)	-		6	(25)	2	(8)
Uric acid elevated	6	(7)	-		3	(13)	1	(4)
Hematologic Parameters								
Neutropenia	81	(99)	79	(96)	24	(100)	24	(100)
Anemia	82	(100)	67*	(82)	24	(100)	21	(88)
Leukopenia	81	(99)	77	(94)	24	(100)	23	(96)
Thrombocytopenia	79	(96)	72	(88)	22	(92)	21	(88)
Lymphopenia	77	(93)	60	(73)	24	(100)	17	(71)

Source: FDA clinical reviewer, based on the ADLB dataset; *all were grade 3.

Of note, when AST and ALT are looked at as one category, all patients experienced hypertransaminasemia of any grade and 57 (54%) experienced grade 3-4 hypertransaminasemia. Of the 82 patients who received only the tablet form of dasatinib, 41 (50%) experienced grade 3-4 hypertransaminasemia, compared to 66% (16/24) in the PFOS group. Seventy patients (85%) who received tablet only and 19/24 in the PFOS group (79%) had elevated LDH per the ADLB dataset, although this is not graded per CTCAE.

For phosphorus, there is no grading for hyperphosphatemia in CTCAE v4, which is the version used for these analyses. It is noted that when analyzed by FDA there were 449 events that were graded as "0" but upon review by FDA noted to be high, and technically grade 1 per CTCAE v5 (as this version grades hyperphosphatemia by lab value only (grade 1) versus abnormal lab value requiring various degrees of intervention to life threatening- e.g. requiring dialysis- as grade 4). As such hyperphosphatemia is not included in Table 23 above, but this involved 41 patients (50% of all patients), including 32/82 from the tablet only group (39%) and 9/24 (38%) from the group that received at least 1 dose of PFOS, who experienced grade 1 hyperphosphatemia per CTCAE v5.

While there were 27 patients overall, including 23 (28%) from the tablet only group, who experienced at least 1 episode of leukocytosis above the ULN, none of these were grade 3 or

greater, as per CTCAE v5, this is reserved for patients with WBC of greater than 100,000/mm3 (grade 3) or life-threatening consequences (grade 4); patients with elevated leukocyte counts below this threshold are not graded per CTCAE v4.

Clinical reviewer comment: The rates of laboratory abnormalities in pediatric patients with Ph+ ALL on Study CA180372 were considerably higher than those seen in the trials used to support approval in the adult CML and ALL as well as pediatric CML indications. However, it is notable that CA180372 uses dasatinib in combination with intensive chemotherapy whereas the trials supporting the other indications were all using dasatinib monotherapy. Also noted are differences between the adult studies themselves, where in the trial supporting the use of dasatinib in newly diagnosed CML-CP, only 13-29% of patients experienced notable hematologic toxicities, compared to 47-63% of patients with CML-AP and 52-85% of those with CML in myeloid or lymphoid blast phase (SPRYCEL prescribing information)***. It is also noted that these latter adult populations are closer to the pediatric Ph+ ALL population in that they are patients with acute leukemias that often are associated with hematologic and non-hematologic and/or organ toxicities due to the underlying disease. Overall, no new signals were identified based on these analysis, but instead of the applicant's proposed description in labeling that the laboratory abnormalities in patients with Ph+ ALL are similar to those seen in the other SPRYCEL populations, section 6 should include a table with the most common laboratory abnormalities seen in patients on CA180372.***

9.4.7. Vital Signs

Per the applicant's CSR, no formal analyses of vital signs were performed on Study CA180372. In the review of dasatinib monotherapy for the pediatric CML indication (supplement 20), no trends of clinical relevance were noted.

9.4.8. Electrocardiograms (ECGs)

On Study CA180372, ECGs were done at screening, prior to the start of IA, IB and R1, and as clinically indicated. Only results regarding QT prolongation were analyzed as part of this review.

9.4.9. QT

Although QT prolongation is a listed warning and precaution in the current dasatinib PI, there were no reports of QT prolongation on Study CA180372 per the ADAE dataset. Per the ADEC dataset, only one patient on study had a QTc of >450 msec; this was at baseline ((b) (6) (b) (6) QTc of 478). A repeat EKG on this patient was normal after HR3 (404 msec) per the data listing included in the CFR (Appendix 7.2, page 13634).

Reviewer comment: the administration of dasatinib in combination with multiagent chemotherapy does not appear to worsen the risk of QTc prolongation already associated

with dasatinib therapy.

9.4.10. Immunogenicity

Not applicable.

9.5. Analysis of Submission-Specific Safety Issues

9.5.1. Adverse Events of Special Interest (AESI) for dasatinib

Given the initial approval of dasatinib in 2006, its various approved indication and its widespread use in these different clinical contexts, the dasatinib clinical development program has included detection and characterization of various AESI that are associated with dasatinib in particular, or with TKIs, including but not limited to those targeting BCR/ABL, in general. Analyses focusing on these AESI on Studies CA180372 are summarized here.

Commercially available tyrosine kinase inhibitors include Sprycel® (dasatinib), Gleevec® (imatinib), Tasigna® (nilotinib), Tarceva® (erlotinib), Bosulif® (bosutinib), and Iclusig® (ponatinib). The most common overlapping toxicities include myelosuppression, fluid retention/edema, hepatic toxicity and embryo-fetal toxicity. Table 24 below summarizes the main toxicities listed in the Warnings and Precautions section of each label:

Table 24.Warnings and Precautions Associated with Dasatinib and Other TKIs

	Dasatinib	Imatinib	Nilotinib	Erlotinib	Bosutinib	Ponatinib
Myelosuppression	X	X	X		X	X
Hemorrhage/Bleeding						
Hemorrhage in patients taking warfarin				X		
Bleeding related events	X	X				X
Thromboembolic Events						
Arterial Occlusion						X*
Venous thromboembolism						X*
Microangiopathic hemolytic anemia with thrombocytopenia				X		
Cardiac Events						
Cardiac dysfunction	X					
QT prolongation	X		X			
Cardiac arrhythmias						X
Congestive heart failure, LV dysfunction		X				X*
Pulmonary arterial hypertension	X					
Cardiac and vascular		X				

	Dasatinib	Imatinib	Nilotinib	Erlotinib	Bosutinib	Ponatinib
events						
Sudden deaths (ventricular repolarization abnormality)			X			
Neurologic						
Neuropathy						X
Reversible posterior leukoencephalopathy syndrome (RPLS)						X
Driving and using machinery		X				
Metabolic						
Renal failure				X		
Hypothyroidism		X				
Tumor lysis syndrome (TLS)	X					X
Growth retardation		X				
Electrolyte abnormalities			X			
Gastrointestinal (GI)						
GI toxicity					X	
GI perforation		X	X			X
Other						
Fluid retention/edema	X	X			X	X
Hepatotoxicity		X	X	X	X	X*
Cerebrovascular accident				X		
Hypertension						X
Pancreatitis and elevated serum lipase			X			
Interstitial lung disease				X		
Dermatologic toxicities	X	X	X			
Compromised wound healing						X
Ocular disorder						X
Embryo-fetal toxicity	X	X	X	X	X	X

Source: Adapted from FDA clinical reviewer for the CML indication. *Boxed warning.

There were no new signals with regard to these AESIs in the data submitted in support of the current sNDA. A summary of these findings are included here.

Fluid retention events: Oedema was one of the common AEs reported on study CA180372 and is included in Table 22. Pleural effusion also occurred in 21 of patients and is included there as well. With regard to fluid retention events specifically to pericardial effusion, pulmonary edema, cardiac failure or cardiomegaly, 12 patients overall (11%) experienced at least 1 PT in this category, including 10 in the tablet only group (12%), and 1 each in those who had either gotten 1 dose of PFOS or PFOS exclusively. The PTs specifically were:

-7 patients experienced a pericardial effusion, including 1 with associated pulmonary edema and another with associated cardiomegaly
-3 additional patients experienced pulmonary edema, one with associated cardiac failure
-1 additional patient experienced cardiomegaly without the other associated PTs
The 2 patients who were not in the tablet only group had isolated pericardial effusion and isolated pulmonary edema. There were no grade 4 or 5 events in any of these categories, and the 5 grade 3 events occurred in 4 patients, 3 in the tablet only group and 1 in the PFOS group, and included the case of cardiac failure and pulmonary edema, and two additional cases of pulmonary edema, as well as one case of grade 3 pericardial effusion in the PFOS group.

Pulmonary hypertension: There were no reported cases of pulmonary hypertension in patients treated on Study CA180372.

Bleeding-related events: See section 8.4.5 for an analysis of hemorrhagic events on Study CA180372.

Cardiac and respiratory disorders: With the exception of the cardiac and pulmonary events described above under fluid retention, other cardiac AEs are described above in Table 22.

Pediatric bone growth and development: Negative effects on growth and development have previously been reported in nonclinical studies of dasatinib as well as clinical studies of imatinib in children. On Study CA180372, the only PT related to pediatric bone growth and development was osteopenia, reported in 4 patients overall (4%), including one patient who received PFOS. Of the 3 patients receiving tablet only, 1 of them had osteopenia reported only during the HSCT phase, although this patient ((b) (6)) did get continue to get dasatinib after undergoing HSCT on 3/21/2013, and the osteopenia was reported one year prior to his dasatinib discontinuation date of 5/28/2014. All 4 cases were grade 1 in severity. The other three had the osteopenia reported during IB and continuation.

Reviewer comment: Overall, the AESIs for dasatinib and imatinib were reported in patients treated on CA180372 as well. It is extremely challenging, especially in a non-randomized study, to tease out which of these were truly due to the effect of dasatinib, given the various other chemotherapeutic agents given as part of the AIEOP-BFM ALL 2000 backbone. For example, the osteopenia which occurred in 4% of patients is also a very well-established side effect of steroid therapy that is an integral part of the treatment of pediatric ALL, and cardiac and respiratory disorders are known ARs seen with anthracyclines that are given as part of this regimen. Similarly, bleeding events are also associated with the thrombocytopenia seen with intensive chemotherapy administration in general. All of these events are already in the W&P of the PI, and there does not appear to be a need to add any additional information to that portion of the PI, especially given the fact that physicians administering this multiagent chemotherapy are familiar with these ARs, and doing so would risk attributing them solely to

dasatinib, which is not substantiated by the safety data presented in the application.

9.6. Safety Analyses by Demographic Subgroups

Due to the very small numbers of patients in each subgroup, an analysis of pediatric age groups within each of the subgroups analyzed above is not reliable. To detect any potential signals in patients in various age subgroups, all patients treated on CA180372 were pooled, regardless of the formulation of dasatinib they received. Non-laboratory ARs where the risk difference between patients 12 years of age or older and any other age group is >15%, with the exception of in comparison to the under 2 age group, since the numbers wre so small, are summarized in Table X below.

Preferred term[a]	<2 years N=4	2-<7 years N=32	7-<12 years 35	12-<18 years 35
Rash	2 (50)	23 (72)	27 (77)	21 (60)
Pneumonia (excluding fungal)	-	14 (44)	8 (23)	8 (23)
Sinusitis	-	9 (28)	5 (14)	4 (11)
Viral infection (excluding sepsis, pneumonia)	2 (50)	15 (47)	14 (40)	11 (31)
Clostridium infection, no sepsis	2 (50)	9 (28)	8 (23)	6 (17)
Hypersensitivity	2 (50)	9 (28)	14 (40)	10 (29)
Oedema	-	9 (28)	13 (37)	22 (63)
Fatigue	2 (50)	14 (44)	20 (57)	25 (71)
Abdominal pain	2 (50)	21 (65)	24 (69)	32 (91)
Musculoskeletal pain	-	21 (65)	30 (86)	31 (89)
Dizziness/vertigo	-	2 (6)	3 (9)	10 (29)
Hypotension	1 (25)	9 (28)	14 (40)	17 (49)

Preferred term[a]	<2 years N=4	2-<7 years N=32	7-<12 years 35	12-<18 years 35
Renal insufficiency	-	9 (28)	5 (14)	11 (31)
Hypertension	-	13 (41)	15 (43)	20 (57)
headache	-	18 (56)	30 (86)	25 (71)
Conjunctivitis	-	5 (16)	3 (9)	9 (26)

Source: FDA clinical reviewer; [a]includes grouped terms, see Appendix 13.4.

Reviewer comment: No red flags were detected in any particular pediatric age subcategory that alters the safety profile for any age group in particular. Overall, the AEs were equally distributed throughout the pediatric age spectrum, and if anything AR rates tended to be higher in the older subjects; this might be due to the fact that they were more likely to get tablets and younger patients were more likely to have received PFOS such that this might be due to differences in exposure that are formulation-based rather than true differences in rates by age subgroup. In any cas,; any differences are difficult to interpret due to the small numbers in each group.

9.7. Specific Safety Studies/Clinical Trials

No specific additional safety studies were submitted in support of this application. The safety of dasatinib in combination with another multiagent chemotherapy backbone regimen, as used on Study Ca180204 (see section 6.2.1 above for study design details) was reviewed as part of this application, and common TEAE that occurred in the patients <18 years old treated on this study are summarized in Table 25 below.

Table 25. Common (>10%) TEAE on Study CA180204

	Discontinuous dasatinib N=35		Continuous dasatinib N=20	
Preferred term[a]	N	%	N	%
Neutropenia	26	74 %	13	65 %
Febrile neutropenia	26	74 %	12	60 %
Mucositis	12	34 %	8	40 %
Hypersensitivity	2	6 %	8	40 %
Diarrhea	6	17 %	7	35 %
Vomiting	3	9 %	7	35 %
Nausea	5	14 %	5	25 %
Sepsis (except fungal)	17	49 %	5	25 %

Preferred term[a]	Discontinuous dasatinib N=35 N	%	Continuous dasatinib N=20 N	%
Hypotension	6	17 %	5	25 %
Hypertension	1	3 %	5	25 %
Dehydration	4	11 %	4	20 %
Peripheral neuropathy	8	23 %	4	20 %
Pneumonia (except fungal)	6	17 %	4	20 %
Musculoskeletal pain	4	11 %	4	20 %
Headache	3	9 %	4	20 %
UTI	4	11 %	3	15 %
Abdominal pain	4	11 %	2	10 %
Anxiety	1	3 %	2	10 %
Clostridial infection (excluding sepsis)	1	3 %	2	10 %

Source: FDA clinical reviewer; [a]includes grouped terms, see Appendix 14.4;

Reviewer comment: as stated above, the small number of patients treated with continuous dasatinib on Study CA180372, the different backbone and different AE profile of that small group of patients precludes inclusion of the safety profile of this regimen in the PI at this time.

9.8. Additional Safety Explorations

9.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

9.8.2. Human Reproduction and Pregnancy

No pregnancies were reported on the CA180372 or CA180204. Exposure to dasatinib during pregnancy has not been permitted in the clinical development program.

9.8.3. Pediatrics and Assessment of Effects on Growth

Since the whole sNDA pertains to the pediatric population, as the indication and studies submitted to support it are in pediatric patients, this is discussed throughout this review. Notably, the current approved dasatinib prescribing information does include a warning and precaution for ARs associated with bone growth and development, including delayed epiphyseal, osteopenia, growth retardation, and gynecomastia, detected during review of the approval for the pediatric CML indication. Four cases of grade 1 osteopenia were reported on CA180372. See section 8.5.1 above for more details regarding this analysis.

9.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

One patient on Study CA180372 experienced a dasatinib overdose: USUBJID (b) (6) a 21-month-old patient who received exclusively the PFOS formulation. The overdose happened in November 2014, and no action was taken with the study drug. It was associated with a garde 1-2 URTI within 4 days of the overdose, also without any adverse sequelae. The patient continued treatment with dasatinib through May 2015.

There is no evidence of any dependence potential with dasatinib use.

No formal studies of rebound or withdrawal have been conducted with dasatinib. No particular events have been reported in the pediatric dasatinib studies in patients who had a transient or permanent withdrawal of dasatinib therapy.

9.9. Safety in the Postmarket Setting

9.9.1. Safety Concerns Identified Through Postmarket Experience

On 11/30/2018, the review team was made aware of findings by the Division of Pharmacovigilance (DPV2) regarding reports of encephalopathy and nephrotic syndrome (NS) in pediatric patients receiving dasatinib. Of the 5 cases of encephalopathy, there was 1 case that was not in the context of an alternative etiology, and in that case the encephalopathy recurred upon rechallenge. In the safety data submitted in support of the current proposed indication from Study CA180372, 30% of patients in the tablet only group had a term that was part of the grouped terms "altered state of consciousness," including encephalopathy. Of all of these, 5% were grade 3 or greater.

Reviewer comment: As stated above, the fact that on Study CA180372, dasatinib was given in combination with multiagent chemotherapy, the components of which each have multiple known adverse reactions, make attribution to dasatinib very challenging, especially when these signals are not seen in the pooled monotherapy population across age groups and disease states. While the finding of altered state of consciousness should be included in the AR table in section 6 of the PI for the new indication, a new W&P regarding this AR with dasatinib is not warranted at this time.

With regard to nephrotic syndrome, per DPV review, there were 6 cases of NS in a FAERS search of NS limited to age <17 years (see OPV review for full details). In response to an IR to the applicant regarding any other cases in their pooled safety database, they submitted the same 6 cases. There were no cases of NS reported in studies CA180372 or CA180204. The dasatinib prescribing information already includes the finding of NS in the PMR section.

Reviewer comment: The PI already includes nephrotic syndrome as an AR in the PMR section, and there were no cases in the pediatric ALL trials submitted in support of this sNDA, nor in the entirety of the AE data submitted as part of the ISS. Section 8.4 already states that the safety profile in pediatrics is similar to that seen in adults with the exception of effects on growth and development. Nephrotic Syndrome is thus covered, and there is no need for a revision to the PI with regard to this AR at this time.

9.9.2. Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this Application.

9.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

9.10. Integrated Assessment of Safety

The primary data in support of the safety for the proposed indication came from Study CA180372, in which 106 pediatric patients with newly diagnosed Ph+ ALL (104 with this confirmed diagnosis) were treated with dasatinib, including 81 who received exclusively tablet formulation and 25 who received at least one dose of PFOS, in combination with the multiagent chemotherapy backbone as per AIEFOP-BFM ALL2000. The median dose intensity for dasatinib was 99% in the tablet only group, and the majority of patients (83%) achieved a dose intensity of >80%. The median dasatinib exposure was 23.6 months, such that majority of patients received all 24 months of dasatinib therapy as dictated per protocol.

The study population was monitored for deaths, SAEs, common AEs of various toxicity grades, and common laboratory tests. On Study CA180372, there were 15 deaths overall (14%) including 11 (14%) in the tablet only population, none of which occurred during the first 60 days of therapy. Of the 5 deaths (5%) that occurred in all 106 treated patients, including 3(4%) in the tablet only group, that occurred within 30 days of the last dose of dasatinib, the most common cause of death was infection. There were no deaths during the actual induction cycles IA and IB, and there were 2 deaths (2% of the tablet only population) during consolidation therapy. Infection was also the most common reason for permanent discontinuation of dasatinib treatment on the study.

Common TEAEs ($\geq$20%) on Study CA180372 were mucositis, febrile neutropenia, pyrexia diarrhea, nausea, vomiting, musculoskeletal pain, abdominal pain, cough, headache, rash

fatigue, arrhythmia, hypertension, oedema, viral infection, hypotension, altered state of consciousness, hypersensitivity, dyspnea, epistaxis, peripheral neuropathy, sepsis (excluding fungal), fungal infection, pneumonia (excluding fungal), pruritis, clostridium infection (excluding sepsis), UTI, bacteremia (excluding fungal), pleural effusion, sinusitis, dehydration, renal insufficiency, visual impairment, conjunctivitis, dizziness, muscle weakness, haematochezia anxiety, flushing and balance disorder. The most common (≥10%) TEAE grade ≥3 in the tablet only population were mucositis, febrile neutropenia, pyrexia, diarrhea, nausea, vomiting, musculoskeletal pain, abdominal pain, headache, arrhythmia, hypertension, viral infection, hypotension, hypersensitivity, dyspnea, sepsis (excluding fungal), fungal infection, pneumonia (excluding fungal), clostridium infection (excluding sepsis), UTI, bacteremia (excluding fungal), and sinusitis. Due to the single arm study design and the administration of dasatinib in the context of multiple chemotherapeutic agents with known toxicity profiles that include many of the ARs listed here, the contribution of dasatinib to these ARs cannot be definitively determined nor excluded. However, although these common ARs should be included in section 6 of the PI for this study, no new warnings and precautions are warranted at this time.

While supportive safety data from Study CA180204 was submitted and reviewed with this sNDA, the differences in backbone chemotherapy regimen, small number of patients (N=20) who received continuous dasatinib, and different toxicity profile precluded inclusion of this data in the PI at this time.

10. Advisory Committee Meeting and Other External Consultations

This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

See also sections 6.1, 6.2 and 8.7 for a more detailed description of the analyses and thinking behind the labeling recommendations.

In summary:

(b) (4)

(b) (4)

See final agreed upon prescribing information at the time of approval for final labeling recommendations.

11.2. Nonprescription Drug Labeling

Not applicable.

12. Risk Evaluation and Mitigation Strategies (REMS)

It was concluded that a REMS is not needed to ensure that the benefits of dasatinib in combination with multiagent chemotherapy outweigh its risks in the intended population. Healthcare providers who will prescribe and administer dasatinib are likely to be able to monitor for and manage the dasatinib-related adverse reactions without additional risk mitigation measures beyond labeling, which includes a Medication Guide.

13. Postmarketing Requirements and Commitments

(b) (4) [redacted] Therefore, a PMC is warranted to ensure due diligence to continued development of the PFOS formulation.

PMC-1
Generate additional PK data for dasatinib powder for oral suspension (PFOS) in pediatric patients with CML or Ph+ ALL at a dosage of 90 mg/m2/day. Submit a final report and datasets for the PK substudy of CA180226.

14. Appendices

14.1. References

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14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): (b) (6) **and** (b) (6)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: (b) (4), (b) (6)) and (b) (4), (b) (6))		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 ((b) (6)) and 4 ((b) (6)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 (b) (4), (b) (6) and 1 ((b) (4), (b) (6)) Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study (b) ((b) (4), (b) (6)		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) (b) (b) (4), (b) (6) and (b) (4) ((b) (4), (b) (6))		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

14.3. Details of the AIEOP-BFM ALL Chemotherapy Backbone Used in Combination with Dasatinib on CA180372

Table 4.3A: Treatment Plan Summary

Phase	Drug/Administration Route	Dose	Day
Induction Therapy Phase IA (Until Day 29 - 33)	All patients will receive first induction according to institutional standard of care.		
	Dasatinib/po	60 mg/m^2 once daily	Start day 15 from beginning of IA or no later than when the day 15 induction chemotherapy is administered Continuously
Induction Therapy Phase IB Starts no sooner than day 33	Dasatinib/po	60 mg/m^2 once daily	Continuously
	CPM/iv (1h)	1000 mg/m^2	1, 28
	6-MP/po	60 mg/m^2/d	1-28

Table 4.3A: Treatment Plan Summary

Phase	Drug/Administration Route	Dose	Day
(Phase lasts 28 days)	ARA-C/iv or sc	75 mg/m^2/d	3-6, 10-13, 17-20, 24-27
	MTX/it	Dose by age (Table 4.3.1.2)	3, 17
Recovery period (Dasatinib continues, No chemotherapy given) (2 - 4 weeks)			
Eligible for hematopoietic Stem Cell Transplant if MRD at end of IB/start of consolidation block 1 ≥ 0.05% (see section 4.3.1.11 for subjects know to have uninformative PCR for Ig/TCR gene rearrangement assessment)			
Consolidation Block 1 (HR-1) Starts when ANC ≥ 500/µl (≥ 0.5 x 10^9/L) and platelets ≥ 50,000/µl (≥ 50 x 10^9/L) (Day 78 of therapy). HR-1 lasts 21 days.	Dasatinib/po	60 mg/m^2 once daily	Continuously
	DEXA/po or iv	20 mg/m^2/d	1-5
	MTX/it ARA-C/it HC/it	Dose by age (Table 4.3.1.3)	1
	HD-MTX/iv (24h)	5 g/m^2	1
	CF-Rescue/iv or po	Levo Form: 7.5 mg/m^2 (not available in U.S.) Racemic form: 15 mg/m^2	42, 48, 54 h after start of HD-MTX
	VCR/iv	1.5 mg/m^2/d (max 2 mg)	2, 6
	CPM/iv (1h)	200 mg/m^2 (q12h x 5)	2-4
	HD-ARA-C/iv (3h)	2 g/m^2 (q12h x 2)	5
	ASP/iv (1-2h) or im	Dose based on preparation (Section 4.3.1.3)	6
	G-CSF/sc or iv	5 ug/kg/day or pegfilgrastim 100 µg/kg s.c given once	Start anytime between day 7-11 until WBC > 3000 mm^3
Consolidation Block 2 (HR-2) Starts when ANC ≥ 500/µl (≥ 0.5 x 10^9/L) and platelets ≥ 50,000/µl (≥ 50	Dasatinib/po	60 mg/m^2 once daily	Continuously
	DEXA/po or iv	20 mg/m^2/d	1-5
	MTX/it ARA-C/it HC/it	Dose by age (Table 4.3.1.4)	1
	HD-MTX/iv (24h)	5 g/m^2	1

Table 4.3A: Treatment Plan Summary

Phase	Drug/Administration Route	Dose	Day
x 10^9/L) HR-2 lasts 21 days.	CF-Rescue/iv or po	Levo Form: 7.5 mg/m^2 (not available in U.S.) Racemic form: 15 mg/m^2	42, 48, 54 h after start of HD-MTX
	VCR/iv	1.5mg/m^2 (max 2 mg)	2, 6
	IFO/iv (1h)	800 mg/m^2 (q12h x 5)	2-4
	DNR/iv (24h)	30 mg/m^2	5
	ASP/iv (1-2h) or im	Dose based on preparation (Section 4.3.1.5)	6
	G-CSF/sc or iv	5 ug/kg/day or pegfilgrastim 100 µg/kg s.c given once	Start anytime between day 7-11 until WBC > 3000 mm^3
Consolidation Block 3 (HR-3) Starts when ANC ≥ 500/µl (≥ 0.5 x 10^9/L) and platelets ≥ 50,000/µl (≥ 50 x 10^9/L) HR-3 last 21 days.	Dasatinib/po	60 mg/m^2 once daily	Continuously
	DEXA/po or iv	20 mg/m^2/d	1-5
	HD-ARA-C/iv (3h)	2 g/m^2 x 4 (q12h x 4)	1, 2
	Etop/iv (1h)	100 mg/m^2 (q12h x 5)	3-5
	MTX/it ARA-C/it HC/it	Dose by age (Table 4.3.1.5)	5
	ASP/iv (1-2h) or im	Dose based on preparation (Section 4.3.1.5)	6
	G-CSF/sc iv	5 ug/kg/day or pegfilgrastim 100 µg/kg s.c given once	Start anytime between day 7-11 until WBC > 3000mm^3
Eligible for hematopoietic Stem Cell Transplant if MRD at end of IB/start of consolidation block 1 (HR1) 0.005-0.05% by Ig/TCR PCR and MRD at end of consolidation block 3 (HR3)/start of reinduction block 1 remains positive at any detectable level (providing the assay limit is at least 0.1%). (see section 4.3.1.11 for subjects known to have uninformative PCR for Ig/TCR gene rearrangement assessment)			

Table 4.3A: Treatment Plan Summary

Phase	Drug/Administration Route	Dose	Day
1st Reinduction (Protocol II) Protocol IIa (days 1-35) Protocol IIb (days ~36-63) 1st Reinduction starts after completion of HR-3 and lasts 63 days. Starts when ANC (≥ 500/μl; 0.5 x 10^9/L) and platelet counts (≥ 50,000/μl; 50 x 10^9/L)	Dasatinib/po	60 mg/m^2 once daily	Continuously
	DEXA/po	10 mg/m^2/d	1-7, 15-21
	MTX/it	Dose by age (Table 4.3.1.6)	1, 38, 45
	VCR/iv	1.5 mg/m^2 (max 2 mg)	8, 15, 22, 29
	DOX/ADR/iv (1h)	25 mg/m^2	8, 15, 22, 29
	ASP/iv (1-2h) or im	Dose based on preparation (Section 4.3.1.6)	Schedule base on preparation
	CPM/iv (1h)	1000 mg/m^2	36
	ARA-C/sc or iv	75 mg/m^2/d	38-41, 45-48
	6-TG/po	60 mg/m^2/d	36-49
Interim Maintenance This phase starts after completion of the 1st Reinduction and lasts 29 days. Starts when ANC (≥ 750/μl; 0.75 x 10^9/L) and platelet counts (≥ 75,000/μl; 75 x 10^9/L)	Dasatinib/po	60 mg/m^2 once daily	Continuously
	6-MP/po	50 mg/m^2/d	1-28
	MTX/po	20 mg/m^2	1, 8, 15, 22
	Cranial irradiation	18Gy	CNS3 Only
2nd Reinduction Protocol IIa (days 1-35) Protocol IIb (days ~36-63) This phase starts immediately after Interim Maintenance and lasts 63 days. Starts when ANC (≥ 500/μl; 0.5 x 10^9/L) and platelet counts (≥ 50,000/μl; 50 x 10^9/L)	Dasatinib/po	60 mg/m^2 once daily	Continuously
	DEXA/po	10 mg/m^2/d	1-7, 15-21
	MTX/it (Omit in CNS3 given cranial irradiation)	Dose by age (Table 4.3.1.8)	1, 38, 45
	VCR/iv	1.5 mg/m^2 (max 2 mg)	8, 15, 22, 29
	DOX/ADR/iv (1h)	25 mg/m^2	8, 15, 22, 29
	ASP/iv (1-2h) or im	Dose based on preparation (Section 4.3.1.8)	Schedule base on preparation

Table 4.3A: Treatment Plan Summary

Phase	Drug/Administration Route	Dose	Day
	CPM/iv (1h)	1000 mg/m^2	36
	ARA-C/sc or iv	75 mg/m^2/d	38-41, 45-48
	6-TG/po	60 mg/m^2/d	36-49
Continuation Therapy Starts after completion of the 2nd reinduction and continues for approximately 62 weeks (until a total of 2 years treatment is complete).	6-MP/po	50 mg/m^2/d	Daily
	MTX/po	20 mg/m^2 weekly	Weekly
	MTX/it (Omit in CNS3 given cranial irradiation)	Dose by age (Table 4.3.1.8)	Every 6 weeks x 6 doses
Starts when ANC ($\geq$ 750/µl; 0.75 x 10^9/L) and platelet counts ($\geq$ 75,000/µl; 75 x 10^9/L)	Dasatinib/po	60 mg/m^2 once daily	Continuously

CPM = cyclophosphamide, ARA-C = cytosine arabinoside, 6-MP = 6-mercaptopurine, MTX = methotrexate, DEXA = dexamethasone, VCR = vincristine, HD-ARA-C = high dose cytosine arabinoside, HD-MTX = high dose methotrexate, CF = citrovorum factor (folinic acid, calcium folinate, or leucovorin), ASP = asparaginase, G-CSF = granulocyte-colony stimulating factor, DNR = daunorubicin, IFO = ifosfamide, Etop= etoposide, DOX = doxorubicin, ADR = adriamycin, 6-TG = 6-thioguanine, HC = hydrocortisone, po = oral, iv = intravenous, sc = subcutaneous, it = intrathecal, im = intramuscular

Source: Applicant CSR, Study CA180372 Apendix 1.1, page 1361-1365

14.4 Grouped Terms Used for the Safety Review

Abdominal pain	abdominal pain, abdominal discomfort
	abdominal pain upper, abdominal pain lower
Altered state of consciousness	memory impairment, depressed level of consciousness, lethargy, confusional state, encephalopathy, delirium, somnolence, irritability, hallucination
Anemia	anemia, rbc decreased, hemoglobin decreased

Arrhythmia	arrhythmia supraventricular, bradycardia,bundle branch block right, cardiac arrest, sinus bradycardia, sinus tachycardia, tachycardia
Bacteremia (excluding fungal)	bacteraemia, escherichia bacteraemia, pseudomonal bacteraemia, enterobacter bacteraemia, klebsiella bacteraemia
Balance disorder	ataxia, gait disturbance
Mucositis	anorectal discomfort, gastritis, gingival pain,gingival ulceration, laryngeal inflammation, mucosal inflammation, oesophageal ulcer, oral mucosal erythema,oropharyngeal pain, pharyngeal inflammation,proctalgia, stomatitis tongue ulceration, aphthous ulcer, gingival erythema,gingival swelling, gingivitis, mouth ulceration, mucosal ulceration, oesophagitis, oral pain, pharyngeal erythema, pharyngitis, proctitis, throat irritation
Cardiac Failure	cardiac failure , left ventricular dysfunction
Clostridial infection (excluding sepsis)	clostridial infection, clostridium difficile colitis, gastroenteritis clostridial, clostridium difficile infection,
Conjunctivitis	conjunctivitis allergic, conjunctivitis, conjunctivitis viral
Cough	cough, productive cough
Diarrhea	diarrhoea, colitis, diarrhea haemoorhagic, enterocolitis, enteritis, gastroenteritis , enterocolitis haemorrhagic, neutropenic colitis
Dyspnea	dyspnea, respiratory failure, bronchospasm, respiratory distress, wheezing
Fatigue	fatigue , asthenia
Fungal infection	abscess fungal, candida infection, fungaemia, fungal infection, fungal sepsis, fungal tracheitis, oral candidiasis, oral fungal infection, pneumonia fungal, pulmonary mycosis, skin candida, splenic infection fungal, systemic candida, systemic mycosis, tinea infection, urinary tract infection fungal, vulvovaginal candidiasis
Headache	headache, sinus headache
Hyperglycemia	blood glucose increased, hyperglycaemia

Hypersensitivity	anaphylactic reaction,drug hypersensitivity, hypersensitivity urticaria, infusion related reaction
Hypertension	hypertension blood pressure increased
Hypoalbuminaemia	hypoalbuminemia blood albumin decreased
Hypocalcaemia	hypocalcemia blood calcium decreased
Hypogammaglobulinaemia	hypogammaglobulinemia blood immunoglobulin g decreased
Hypotension	hypotension blood pressure decreased
Hyperbilirubinaemia	hyperbilrubinemia blood bilirubin increased
Hypertransaminasemia	alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, liver function test increased
Leukopenia	leukopenia , wbc count decreased
Lymphopenia	lymphopenia lymphocyte count decreased
Musculoskeletal pain	arthralgia, bone pain, musculoskeletal chest pain, myalgia, non-cardiac chest pain, pain in jaw, back pain, facial pain, musculoskeletal pain, neck pain, pain in extremity, spinal pain
Neutropenia	neutropenia, neutrophil count decreased
Oedema	eyelid oedema, face oedema, fluid overload, generalized oedema, gravitational oedema, localized oedema, oedema, oedema genitral, oedema peripheral, periorbital oedema, peripheral swelling, scrotal oedema, swelling face, testicular swelling
Pancreatitis	pancreatitis acute, pancreatitis
Peripheral neuropathy	hyperaesthesia, neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, dysaesthesia, hypoaesthesia, paraesthesia peripheral sensory neuropathy
Pneumonia (excludes fungal)	lung infiltration, lung infection, pneumonia bacterial, pneumonia viral, pneumonia pneumonia klebsiella
Pruritis	eye pruritus, pruritus generalised, pruritis, ear pruritus, vulvovaginal pruritus
Rash	dermatitis, dermatitis acneiform ,dermatitis allergic, dermatitis contact dermatitis diaper, drug eruption, eczema, exfoliative rash, rash

	rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, seborrhoeic dermatitis, skin exfoliation
Renal insufficiency	acute kidney injury, blood creatinine increased, renal failure, renal impairment
Sepsis (excluding fungal)	bacterial sepsis, device related sepsis, escherichia sepsis, sepsis, septic shock, staphylococcal sepsis, streptococcal sepsis, bacterial sepsis, device related sepsis, escherichia sepsis, sepsis, septic shock, staphylococcal sepsis, streptococcal sepsis
Speech disorder	dysarthria, dysphagia, dysphonia
Thrombocytopenia	thrombocytopenia, platelet count decreased
Thrombosis	thrombosis, embolism
Sinusitis	sinus disorder, sinusitis
Urinary tract infection (UTI)	culture urine positive, cystitis, escherichia urinary tract infection, urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal
Dizziness	dizziness, vertigo
Viral infection	corona virus infection, cytomegalovirus infection, herpes simplex, herpes zoster, influenza, oral herpes, parainfluenzae virus infection, respiratory syncytial virus infection, rhinovirus infection, viral upper respiratory tract infection
Visual impairment	Diplopia, Vision blurred, Visual acuity reduced

14.5 Exclusivity Determination review

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/s/

AVIVA C KRAUSS
12/20/2018
signing as Clinical Reviewer and Clinical Team Leader

JIAXI ZHOU
12/20/2018

THOMAS E GWISE on behalf of YUAN L SHEN
12/20/2018

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