Cross-Discipline Team Leader Review

Date	December 17, 2018
From	Aviva C. Krauss, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	BLA 021986 S-021 / SDN 1659 eCTD 0161
Applicant	Bristol-Myers Squibb Company (BMS)
Date of Submission	June 29, 2018
PDUFA Goal Date	December 29, 2018
Proprietary Name	Dasatinib
Established or Proper Name	SPRYCEL
Dosage Form(s)	Oral tablets (20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 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
Applicant Proposed Dosing Regimen(s)	Weight-based dosing: 10 to less than 20 kg: 40 mg/day 20 to less than 30 kg: 60 mg/day 30 to less than 45 kg: 70 mg/day At least 45 kg: 100 mg/day
Recommendation on Regulatory Action	*Regular Approval*
Recommended Indication(s)/Population(s)	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
Recommended Dosing Regimen(s)	Weight-based dosing: 10 to less than 20 kg: 40 mg/day 20 to less than 30 kg: 60 mg/day 30 to less than 45 kg: 70 mg/day At least 45 kg: 100 mg/day In combination with multiagent chemotherapy, for two years

Material Reviewed/Consulted	NDA submission, responses to IRs
Clinical Review	Aviva C Krauss, MD
Statistical Review	Jiaxi Zhou, MS./ Yuan Li Shen, Ph.D.
Clinical Pharmacology Review	Liang Li, PhD/ Ruby Leong PharmD
CDRH Consult Memo	Aaron J. Schetter, PhD MPH, (ASO-PCR) AND Jacqueline M. Cleary B.S.MT (ASCP) (flow cytometry)
Clinical Inspection Summary	Anthony Orencia, MD
Patient Labeling Reviews	Ruth Lidoshore, PharmD (DMPP), Rachael Conklin, MS, RN (OPDP), Rhiannon Leutner, PharmD, MPH, MBA (DMEPA), Hina Mehta, Pharm D (DMEPA)

1. Benefit-Risk Assessment

The efficacy and safety results from clinical trial CA180372 demonstrate substantial evidence of efficacy and safety of Sprycel (dasatinib) 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. The recommended dosing is weight-based, as follows:
10 to less than 20 kg: 40 mg/day
20 to less than 30 kg: 60 mg/day
30 to less than 45 kg: 70 mg/day
At least 45 kg: 100 mg/day

All review teams recommend approval.

Recommended Regulatory Action: Regular Approval

Refer to the benefit-risk framework on the next page.

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

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/m2/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% that is 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 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) 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 the advent of 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.
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,	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
	sinusitis, dehydration, renal insufficiency, visual impairment, conjunctivitis, dizziness, muscle weakness, haematochezia, anxiety, flushing and balance disorder.	

2. Background

On 29 June 2018, Bristol-Myers Squibb Company (BMS; Applicant) submitted an efficacy supplement (NDA 021986 S-21) for Sprycel (dasatinib) with a proposed indication "for the treatment of pediatric patients with newly diagnosed Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy." The proposed dosing is weight-based as follows:

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

Dasatinib is a small molecule kinase inhibitor that inhibits multiple receptor tyrosine kinases, including BCR-ABL.

Dasatinib received initial US approval in 2006. The current approved indications for dasatinib are for the treatment of :

- newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase
- adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib
- adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy
- pediatric patients with Ph+ CML in chronic phase

The primary basis for the application is the clinical trial CA180372 (NCT01460160) entitled "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". Supportive trials include CA180204 (NCT00720109), a phase 2 trial in patients with newly diagnosed Ph+ ALL aged 1-30 years of age were treated with different doses of dasatinib in combination with a different chemotherapy backbone, as well as data submitted from the cooperative groups for the AIEOP-BFM ALL 2000 study, which treated pediatric patients with newly diagnosed Ph+ ALL with the same chemothepay backbone used on CA180372, without a TKI, as well as the amended EsPhALL Study, in which a similar population of patients was treated with the same chemotherapy backbone in addition to imatinib. Only limited trial-level data from the latter 2 studies were submitted by the Applicant with the sNDA; limited patient-level data was received by the Agency directly from a third source in response to an Agency request; these data were not available to the Applicant.

The first pediatric approval for dasatinib was in 2017, when it was approved under supplement 20 for the treatment of pediatric patients with Ph+ CML in chronic phase (CML-CP). Of note, at the time of that submission, another (b) (4)

(b) (4) ; (b) (4)

A Pre-sNDA submission meeting for the current indication occurred on 8 February 2018.

3. Product Quality

Refer to previous reviews. There are no major labeling changes proposed for the CMC sections with this efficacy supplement. The Applicant requested a Categorical Exclusion from Environmental Assessment under 21 CFR 25.31(b).

4. Nonclinical Pharmacology/Toxicology

Refer to previous reviews. There are no major labeling changes proposed for the Pharmacology-Toxicology sections with this efficacy supplement.

5. Clinical Pharmacology

The Office of Clinical Pharmacology recommends approval from a clinical pharmacology perspective. Although Study CA180372 used BSA based dosing for dasatinib, already in their review of the sNDA for the pediatric CML indication, they concluded that the weight-tiered dosing proposed in the PI 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 protocols. Labeling was revised to conform with current labeling practices for clinical pharmacology sections, and to include information regarding exposures in patients who receive tablets dissolved in (b) (4) or preservative-free juice, which is lower than those seen in patients swallowing intact tablets.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The efficacy of dasatinib in pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL was studied in Study CA180372. This 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 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 allogeneic 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.

A total of 106 patients were treated, of which 104 had Ph+ ALL that could be confirmed by the FDA clinical reviewer based on the data submitted. The efficacy results were based on 78 patients who received the tablet formulation of dasatinib exclusively, (b) (4) discussed above.

Of the 78 patients in the FDA efficacy population, the patients' age ranged from 2.6 to 17.9 years (median, 10.4 years), 46% were under 10 years of age and 22% were under 6 years of age. Fourty-five percent of them were male and 82% of them were white. Seventy-three percent of patients had high-risk disease per the NCI risk stratification, regardless of their Ph+ status, 41% had a WBC at baseline of ≥50,000/mcl, and 22% had extramedullary disease at baseline, including 17% who were CNS positive. Twelve patients (15%) proceeded to subsequent allogeneic HSCT, all in first complete remission (CR1).

Efficacy was established on the basis of 3-year binomial Event-Free Survival, defined as the time from the starting date of dasatinib until any of the following events:

- Lack of complete response in the bone marrow
  -This was defined as achievement of <5% BM blasts by the end of the 3rd consolidation block (HR3) , regardless of peripheral count recovery
- Relapse at any site
- Development of second malignant neoplasm
- Death from any cause.

The efficacy results are summarized in the table and text below, along with multiple sensitivity and subgroup analyses. The primary analysis results are bolded.

Table 1. Efficacy Results in Pediatric Patients with Ph+ ALL Treated with Dasatinib and Multiagent Chemotherapy on CA180372

	All treated and confirmed Ph+ ALL (N = 103)	**Tablet Only (N = 78)**
3-year binomial EFS rate, n/N (%)	67/103 (65.1)	**50/78 (64.1)**
95% CI	(55.0, 74.2)	**(52.4, 74.7)**

	All treated and confirmed Ph+ ALL (N = 103)	Tablet Only (N = 78)
3-year EFS K-M estimate, % (95% CI)	64.4 (54.3, 72.9)	63.3 (51.4, 73.0)

Source: FDA statistical reviewer analysis.

The 3-year Kaplan-Meier estimate for overall survival (OS) was an exploratory endpoint, and the results were 92.2% (95% CI 83.5%, 96.4%) for the FDA efficacy population. When patients who underwent allogeneic HSCT were censored at the time of transplant, the EFS outcomes did not change significantly. Additionally, in the subgroup of patients who did not undergo HSCT, the majority of patients on Study CA180372 (66; 85%), the outcomes were similar (3-year EFS of 65.2%), and it was slightly lower in the 12 patients who did undergo HSCT (3-year EFS 58%), although the numbers are very small, limiting interpretation of this subgroup analysis.

Although as described above, the data from the historical control cohorts 2 and 3 were limited, and the nature of the data combined with the small numbers made undertaking a propensity score analysis or other statistical method to increase comparability between the groups challenging, the review team did undertake descriptive analyses of the data submitted for these historical cohorts. Overall, the 3-year binomial EFS for cohort 2, the 61 patients treated with the AIEOP-BFM ALL 2000 regimen alone without a TKI was 49.1% (95% CI: 36.1%, 62.3%). This was consistent with the literature, as multiple single center reports as well as meta-analyses of pediatric patients with Ph+ ALL treated with multiagent chemotherapy alone (with or without HSCT) without a TKI, do not report 4-5 year EFS of greater than 44%; three- to five-year OS for these patients has been reported to be in the 48-60% range. It is noted that the majority of patients in cohort 2 (74%) eventually underwent allogeneic HSCT. Cohort 3, patients treated with the AEIOP-BFM ALL 2000 backbone in combination with imatinib, had a 3-year binomial EFS of 59.1% (95%CI, 50.4%, 67.4%), with the same limitations and caveats above described for cohort 2; notably, 59/155 patients in cohort 3 (38%) proceeded to allogeneic HSCT, per protocol.

The results of Study CA180204 were used for supportive efficacy and safety data only, as only 20 pediatric patients with Ph+ ALL were treated with continuous dasatinib in combination with the multiagent chemotherapy backbone, and the study was terminated to begin enrollment on the pivotal trial above, such that interpretation is limited.

Conclusions on the Substantial Evidence of Effectiveness:
In general, a time-to-event endpoint such as 3-year EFS in a single-arm trial is difficult to interpret. Patient-level data for the historical cohorts were limited, precluding propensity score analyses that would enable robust statistical comparisons between the cohorts as described above. Nonetheless, 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; 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 significant 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. Finally, the descriptive results from cohort 3 allay concerns that dasatinib performs less well than imatinib, an agent already approved for this population, with the same backbone regimen in the same population.

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. 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.

It is noted that similar reasoning supported the approval of imatinib for the same indication on the basis of a single arm trial that used increasing exposures of imatinib in addition to a standard multiagent chemotherapy backbone, based on 4-year EFS (see review of NDA 21588, supplement 37); the current approval is thus not setting a new precedent in this disease context.

Device Considerations: 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.

When reviewed by the CDRH review team (see consult memos), the flow cytometry assay was assessed to be analytically valid, with a limit of detection of 0.01%, but the Ig/TCR assay had data missing with regard to precision, and due to inconsistencies with the flow cytometry

results, concern was raised that some of the MRD negative results by Ig/TCR might be false negatives.

Only 41% of patients had MRD assessed by flow cytometry at some point during induction, and only 5 additional patinets had this done at some point during consolidation. Further, most of these patients had not achieved CR with complete recovery of peripheral counts. Overall, the amount of missing data precluded the inclusion of flow cytometry data in the PI, and the issues raised by the CDRH reviewer with regard to the PCR assay preclude its inclusion in the PI as well.

8. Safety

The safety of dasatinib was evaluated in Study CA180372, a phase 2 multicenter, historically-controlled study of dasatinib added to the AIEOP-BFM ALL 2000 multiagent chemotherapy backbone, with some supportive data from CA180204 using a different chemotherapy backbone. The safety profile of dasatinib in the proposed indication was consistent with other registrational trials with dasatinib administered as monotherapy, although the incidence and types of adverse reactions seen were also typical of those seen with the various components of the multiagent chemotherapy regimen, which, in the non-randomized setting, renders interpretation challenging.

A summary of the important safety results is listed below.

- The median exposure to dasatinib on CA180372 for the 81 patients who received the tablet formulation exclusively was 23.6 months, with a median dose intensity of 99%, and <20% of patients achieved a dose intensity of <80%.
- Of the 81 patients who received the tablet formulation exclusively on CA180372, 2 patients (3%) died during consolidation, and there were no deaths during the first 60 days of tehrapy. These rates are overall consistent with the rates seen wit the use of multiagent chemotherapy regimens in this population.
- All 3 deaths that occurred within 30 days of the last dose of dasatinib (4%) were due to infection. This is a known complication of myelosuppression associated with dasatinib as well as the other chemotherapy agents that are part of the AIEOP-BFM ALL 2000 regimen.
- SAEs occurred in 98% of patients treated with dasatinib (exclusively tablet formulation) in combination with chemotherapy, and those that occurred in ≥10% of patients included febrile neutropenia, pyrexia, mucositis, diarrhea, sepsis, hypotension, bactermia, hypersensitivity, pneumonia, clostridial infection, renal insufficiency, abdominal pain, musculoskeletal pain, viral infections, dehydration and pleural effusion.
- Of the 81 patients who received exclusively the tablet formulation of dasatinib on Study CA180372, 8 patients (10%) had dasatinib discontinued due to an adverse reaction (AR), of which the most common was infection (fungal sepsis, CMV infection and pneumonia).
- 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), urinary tract infection (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 (≥20%) non-hematologic laboratory abnormalities were transaminase elevation, hypercalcemia, hypocalcemia, hypokalemia, hyponatremia, hypermagnesemia, hypomagenesemia, hypohphosphatemia, hyperbilirubinemia, and elevated creatinine.
- The most common (≥20%) hematologic laboratory abnormalities were neutropenia, anemia, leukopenia, thrombocytopenia and lymphopenia.
- There were no new signals with regard to AESI already established for dasatinib.

9. Advisory Committee Meeting

This efficacy supplement was not presented to the Oncologic Drugs Advisory Committee because the application did not raise significant efficacy or safety issues for the proposed indication.

10. Pediatrics

The application involved exlusively pediatric patients, and together with the sNDA, a request for exclusivity determination was submitted. With regard to effects on bone growth and development, known AESI associated with dasatinib, no new signals were detected in the data submitted as part of this sNDA. However, it is recognized that the approved indication includes a significant percentage of patients who are not expected to be able to swallow tablets, and at present there is no approved pediatric formulation.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues.
- **Exclusivity or Patent Issues of Concern:** The applicant submitted a request for exclusivity determination together with the sNDA submission. See the clinical review, appendix 13.5, for detailed exclusivity determination review. The exclusivity board granted exclusivity on 9/27/2018.
- **Financial Disclosures:** The Applicant submitted financial disclosure information for both CA180372 and CA180204. There were financial conflict of interest information reported from 1 investigator of 1158 total for CA180372, and 2 investigators for whom certificationof due diligence was submitted. For CA180204, the Applicant reported financial conflict of interest information for 4 investigators of 777, and 15 investigators for whom certification of due diligence was submitted. Refer to Clinical Review Appendix (Clinical Investigator Financial Disclosure Review) for details. The impact of financial

conflict of interest on the reported outcome of the pivotal study, CA180372, is mitigated by the multi-center trial design and the small number of patients enrolled at the affected sites.

- **Other GCP Issues:** None
- **Office of Scientific Investigation (OSI) Audits:** OSI conducted inspections for Study CA180372 at site #30 and site #10. A Form 483 was issued at site #30 due to non-compliance with protocol-delineated SAE reporting with regard to the 24-hour time-frame. They did note that the 2 SAEs that were not reported in the required time frame were reported, albeit with a delay. The PI at that site responded adequately to the Form 483 on 9/28/2018. Clinical site #10 did not have any issues. Overall, the findings do not appear to impact reliability of the study results.
- **Other outstanding regulatory issues**: None

12. Labeling

Prescribing Information

- (b) (4)

(b) (4)

[redacted]

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The review teams did not identify a need for a REMS based on the data provided with the application.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Given the issues around the lack of an approved pediatric formulation at this time, the following PMC was issued:
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. Recommended Comments to the Applicant

None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AVIVA C KRAUSS
12/20/2018